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A Novel Series of Orally Active Antiplatelet Agents

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Abstract—A novel series of orally active fibrinogen receptor antagonists has been discovered through structural modification of our lead intravenous (iv) antiplatelet agent, 5-(4-amidinophenyl)pentanoyl-Asp-Phe **1** (SC-52012). The Asp–Phe amide bond was removed through truncation to a 3-substituted β-amino acid aspartate mimetic which resulted in a tripeptide mimetic inhibitor of lower molecular weight (from 482 to the 330–390 g mol^{-1}). The zwitterionic nature of the inhibitor was masked through the preparation of an ethyl ester prodrug. A lead compound from this series, 5-(4-amidinophenyl)pentanoyl-3-(3-pyridyl)propanoic acid **19a**, was found to be a potent inhibitor of canine platelet aggregation *in vitro* (collagen, platelet rich plasma, PRP, IC_{50} = 270 nM). In further canine studies, oral administration of different ester pro-drugs of **19a** at 10 mg kg^{-1} resulted in the following oral systemic activities: pivaloyloxymethyl ester derivative **19p** (5.1 ± 1.5% OSA), cyclohexyl ester derivative **19c** (9.2 ± 1.9% OSA), and ethyl ester derivative **19e** (9.9 ± 2.3% OSA).

Introduction

Platelets and fibrinogen play a major role in vascular hemostasis.[1] The glycoprotein IIb–IIIa (GP IIb–IIIa) receptor, a platelet membrane protein, belongs to a cytoadhesion class of heterodimeric receptors known as the integrins.[2] The GP IIb–IIIa receptor recognizes the Arg–Gly–Asp (RGD) sequence found on matrix proteins (fibrinogen, vitronectin, fibronectin)[3] and snake venom proteins such as echistatin,[4] decorsin,[5] and bitistatin.[6] We[7] and others[8] have demonstrated that tripeptide mimetics of the RGD sequence are capable of effectively inhibiting the binding of fibrinogen to the GP IIb–IIIa receptor which disrupts platelet aggregation.

The linear IV fibrinogen receptor antagonists **1**,[7a] **2**[8a] and **3**[8b] (Fig. 1) have potential for the immediate treatment of a myocardial infarct (MI) when used in combination therapy with a fibrinolytic agent.[8h–j] A chronically administered orally active fibrinogen receptor antagonist may prove useful in the prevention of vascular complications including MI and stroke. Herein, we describe a novel series of orally active fibrinogen receptor antagonists obtained by logical modification of our iv antiplatelet agent **1**.[9]

Results and Discussion

Chemistry

The novel platelet aggregation inhibitors can be prepared following the general synthetic sequence as outlined in Scheme 1. 5-(4-Cyanophenyl)pentanoic acid was prepared as previously described.[7a] The amide bonds were prepared using standard coupling reagents, e.g. *N,N*-disuccinimidyl carbonate (DSC). The benzonitrile was converted to the amidine via the thioimidate in nearly quantitative yield by a simple three step sequence involving treatment with hydrogen

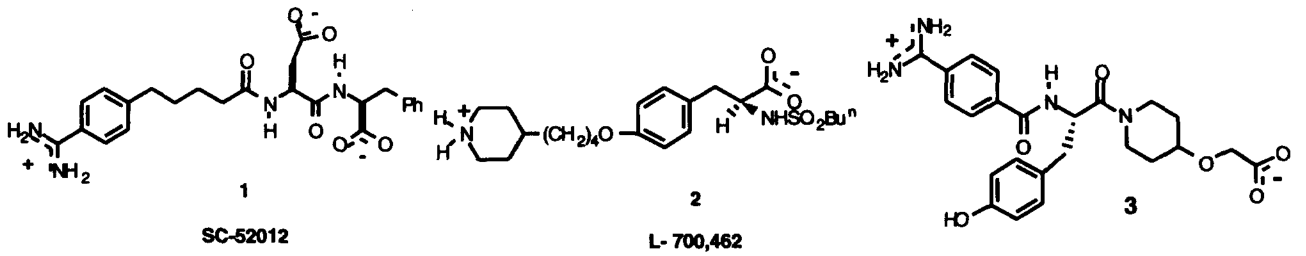

1
SC-52012
2
L-700,462
3

Figure 1. Linear RGD-based antiplatelet agents: Zablocki *et al.*[7a] benzamidine derivative **1**, Hartman *et al.*[8a] piperidine derivative **2**, and Alig *et al.*[8b] benzamidine derivative **3**.

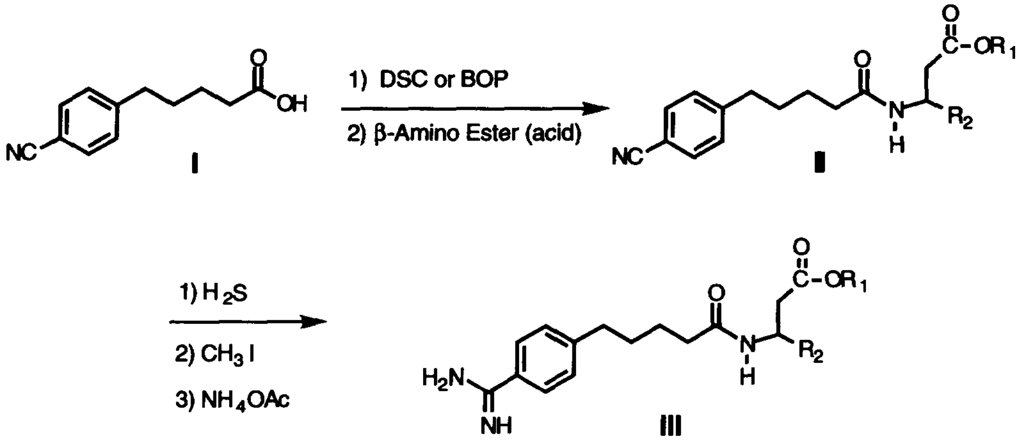
sulfide, methyl iodide, and ammonium acetate. In an alternative sequence (Scheme 2), an appropriately substituted benzonitrile was converted to the benzamidine using lithium bis(trimethylsilyl)amide in ether–hexane solvent mixture.[10] The resultant benzamidine acid was coupled using standard coupling reagents (e.g. DSC) to the appropriately substituted β-amino acid which afforded the platelet aggregation inhibitors in a direct manner. Both sequences afford the platelet aggregation inhibitors in good overall yield. The final compounds for biological testing were obtained by purification by reverse phase high pressure liquid chromatography.[11]

The appropriately substituted β-amino esters of Schemes 1 and 2 can be either purchased or prepared from commercially available starting materials using known methods as illustrated in Scheme 3. The racemic β-aryl β-amino acids were prepared from the appropriate aryl aldehyde, malonic acid, and ammonium acetate utilizing a modified Knoevenagel process[12] as shown in Scheme 3, method 1. The racemic β-alkyl β-amino esters were prepared from the corresponding β-lactam by treatment with anhydrous HCl gas in ethanol. The β-lactams were prepared from the corresponding alkene and chlorosulfonyl isocyanate as shown in Scheme 3, method 2.[13] The Arndt–Eistert reaction,[14] a process known to occur with retention of configuration, was used to homologate both (*R*) and (*S*) alanine to the corresponding β-amino esters as shown in Scheme 3, method 3.

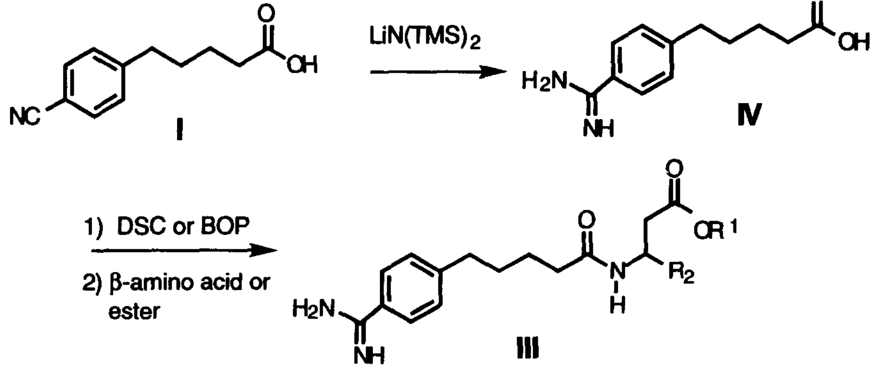
SAR

We have set out to identify a novel orally active series of fibrinogen receptor antagonists through modification of our lead iv antiplatelet agent **1** by following basic concepts to achieving oral activity with a peptide mimetic as outlined by Karali.[15a] Initially, the zwitterion character of compound **1** was removed by preparing the diethyl ester pro-drug (compound **6**, Fig. 2). In all of our *in vivo* screening for oral activity we used beagles of either sex following the administration protocol as outlined in the Experimental section. Oral administration of **6** in canine studies only at high doses (30 mg kg^{-1}) afforded transient and submaximal inhibition of *ex vivo* collagen induced platelet aggregation.

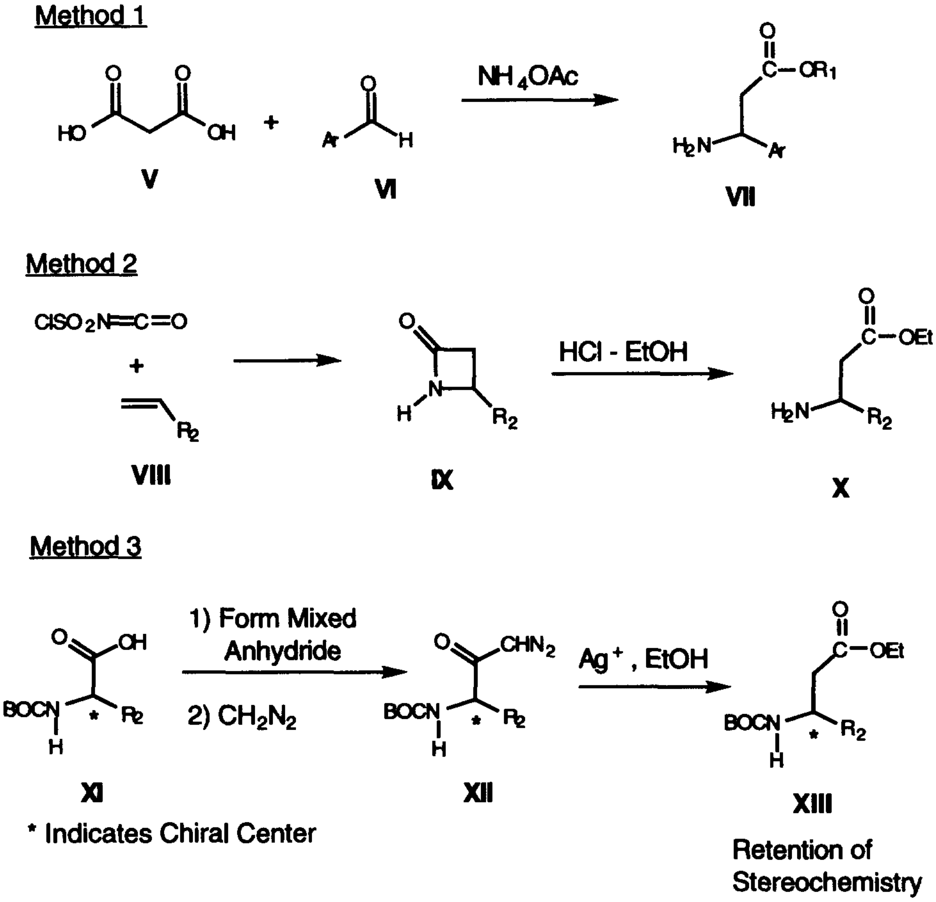
The next concept utilized was to remove or modify one or more peptidic bonds to enhance oral absorption.[15,16] The Asp–Phe amide bond of **1** is readily cleaved *in vivo* contributing to a short half-life for our iv antiplatelet agents.[17] Two strategic opportunities present themselves: (1) stabilize the Asp–Phe amide bond to cleavage *in vivo*, or (2) remove this amide bond and



Scheme 1.

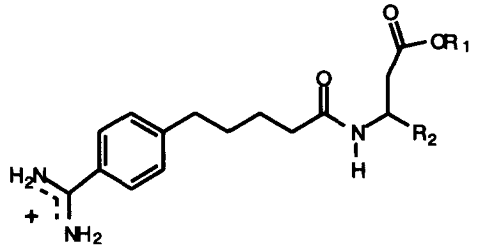


Scheme 2.



Scheme 3.

Table 1. *In vitro* inhibition of platelet aggregation and *ex vivo* inhibition of collagen induced platelet aggregation of *p*-benzamidinopentanoyl (BAP)—derivatives **8** and **9**



Cmpd / Mol. Wt.	R_1	R_2	IC_{50} (μM)[a]	Oral Dose (mg / kg)	Duration[b] Time (h)
8a / 367	H	Ph	4.88 ± 0.42		
8e / 395	Et	Ph		30	> 6 < 24
				10	submaximal
9a / 305	H	Me	2.87 ± 0.38		
9e / 333	Et	Me		30	> 4 < 5.3
				10	> 4 < 6

[a] Dog platelet rich plasma, PRP, collagen, $n = 3$, pooled blood, ± standard error.

[b] Duration of maximal inhibition of *ex vivo* collagen induced platelet aggregation post ig dosing at specified dose.

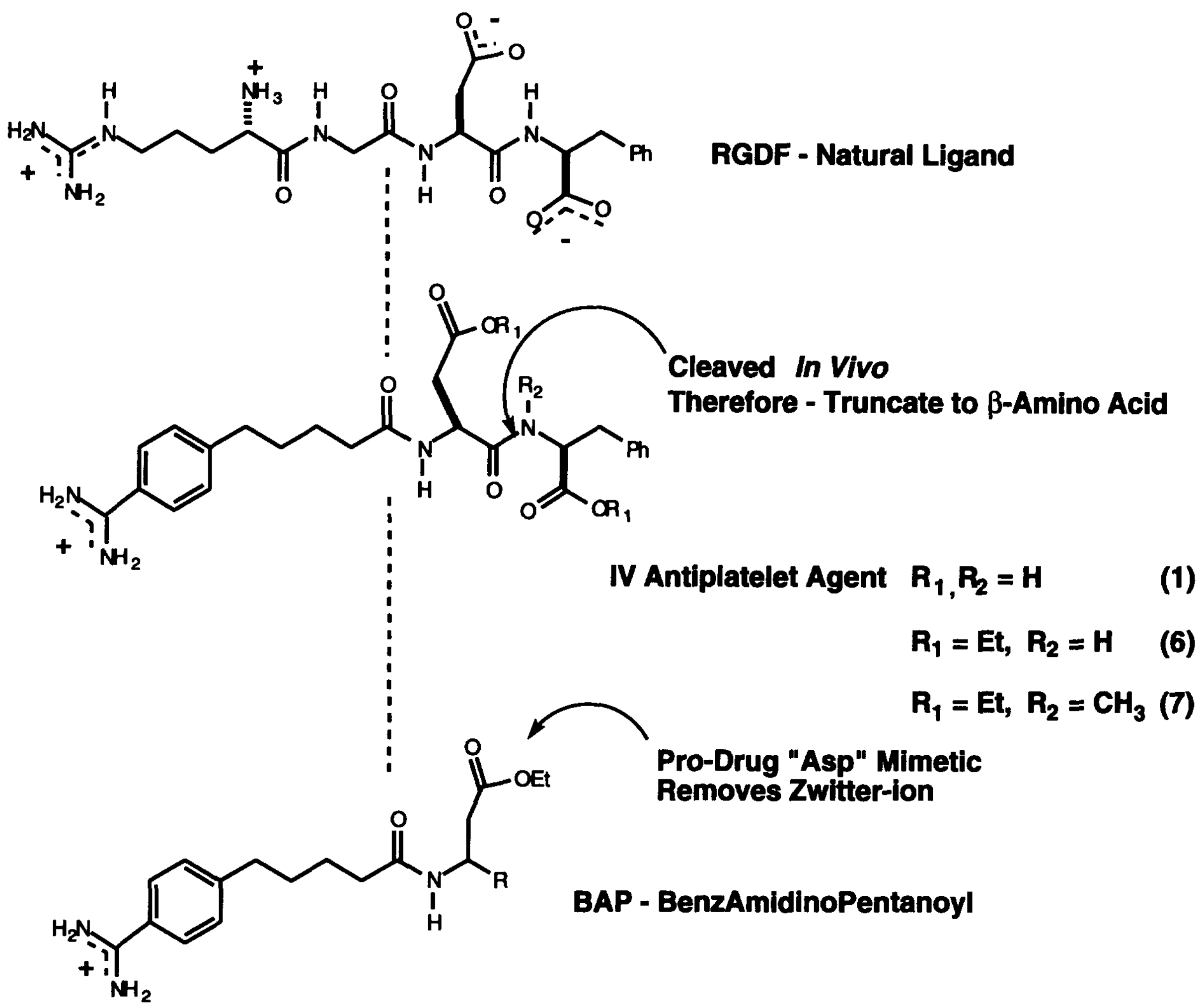


Figure 2. Progression from natural peptide to iv antiplatelet agent **1** to the orally active BAP series.

the Phe residue altogether, since we[7b] and others[8b,8c] have found that the arginine and aspartic acid side chains alone may be sufficient for retaining potency. Regarding the first strategy, the tertiary amide-*N*-methylphenylalanine (**7**) was prepared in an effort to stabilize the Asp–Phe amide bond. Compound **7** exhibited only modest inhibitory potency (1.6 μM, canine platelet rich plasma, PRP[19]) and low oral activity. The second strategy proved more rewarding. The Asp–Phe amide bond was removed completely by truncating to a 3-substituted β-amino ester pro-drug, wherein the key binding elements are mimetics of the crucial basic arginine and aspartic acid side chains;[8b,8c] additionally, the remaining amide bond has been significantly altered to enhance its stability towards peptidases (Fig. 2). Our first substantial oral activity was observed with the ester prodrugs **8e** and **9e** where R = phenyl and methyl, respectively. The respective *in vitro* and *in vivo* activities of the acid/ester pairs, **8a**/**8e** and **9a**/**9e**, are outlined in Table 1. Truncation of the aspartic acid residue to a 3-substituted β-amino acid (ester pro-drug) served two purposes: it decreased the molecular weight from the 482 g mol^{-1} range of **1** to the 395–330 g mol^{-1} range of ester prodrugs **8e** and **9e**. It provided a handle for rapid screening of analogs to improve the potency of the platelet aggregation inhibitors.

In order to probe the stereochemical requirements for activity, both enantiomers of **9a** were prepared as described above. The (*R*)-enantiomer **10a** corresponding to the natural (L)-aspartic acid configuration accounts for nearly all of the antiplatelet activity of the racemic material, since the (*S*)-enantiomer **11a** was found to be inactive at high test concentrations (Table 2). The 3,3-dimethyl β-alanine BAP derivative **12a** was inactive at 100 μM, but the unsubstituted β-alanine BAP derivative **13a** possessed modest inhibitory potency (Table 2). Presumably, the *gem*-dimethyl derivative is inactive due to unfavorable steric interactions with the receptor, since **12a** and **13a** possess similar conformer populations about the β-amino acid.[19]

Since the *in vitro* potencies of our first two orally active compounds **8a** and **9a** (Table 1) were approximately 100 fold less than our lead iv antiplatelet agent **1** (72 ± 11 nM, dog PRP), we undertook efforts to enhance potency through varying the 3-substituent of the β-amino acid. Saturation of the phenyl ring of **8a** resulted in approximately a 3-fold decrease in inhibitory potency

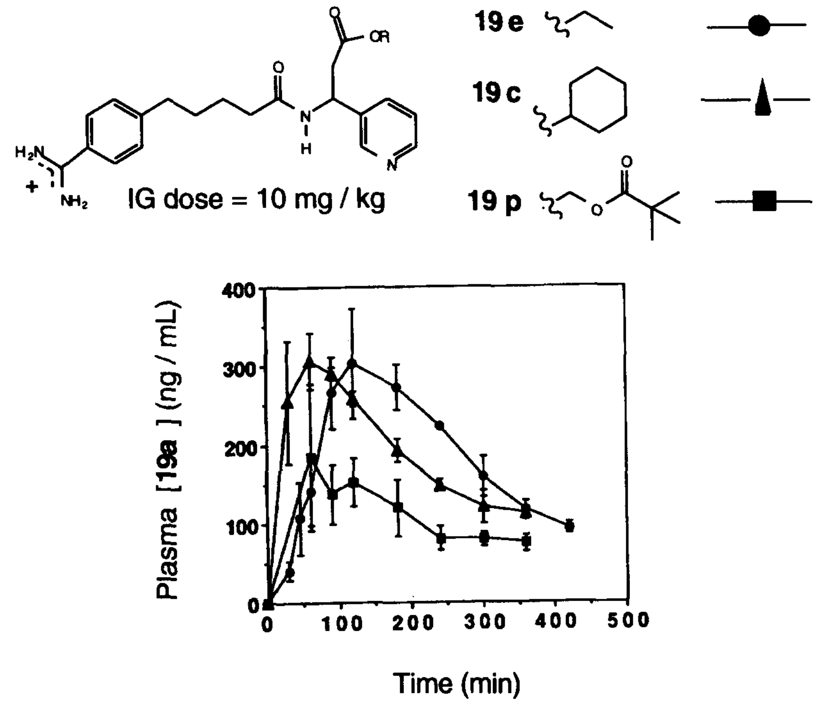


Figure 3. ig Canine studies—the effect of pro-drug on the plasma concentration of active acid **19a**. The oral systemic activity (OSA) for the pro-drugs: **19e** = 9.9 ± 2.3%; **19c** = 9.2 ± 1.9%; **19p** = 5.1 ± 1.5.

(cyclohexyl derivative **14a**, Table 3). The cyclohexenyl derivative **15a** had potency in between the completely saturated **14a** and unsaturated analogs **8a**. The corresponding 3-benzyl **16a** and the 3-phenethyl **17a** β-alanine derivatives had comparable inhibitory potency to the 3-phenyl β-alanine derivative **8a**. SAR of the 3-phenyl β-alanine derivative **8a** was further probed through the preparation and testing of derivatives **18a**–**23a**. Addition of a *para* or *meta* substituted alkoxy group to the phenyl ring of **8a** led to a slight increase in potency (**18a** and **21a**). The phenylmethylenedioxy derivative **22a** represents a combination of both *para* and *meta* alkoxy substitution which led to further enhancement of potency (Table 3). The 3-(3-pyridyl) β-alanine derivative **19a** was found superior to the 3-(2-pyridyl) β-alanine derivative **23a** in inhibitory potency. Addition of a *para* alkoxy substituent to **19a** did not lead to enhanced potency (derivative **20a**). The most potent *in vitro* inhibitor, the 3-(3-pyridyl) β-alanine derivative **19a** (152 ± 15 nM, dog PRP), is approaching the potency of the iv antiplatelet agent **1** (72 ± 11 nM, dog PRP).

The effect of pro-drug on oral activity was briefly investigated for the 3-(3-pyridyl) β-alanine derivative **19a**. The pivaloyloxymethyl (**19p**), ethyl (**19e**), and cyclohexyl (**19c**) ester derivatives were administered orally in a canine study at 10 mg kg^{-1} and plasma concentrations of the active constituent were determined using a bioassay (standard curve, see Experimental).[20] The plasma concentration of the acid **19a** was determined following iv bolus administration to dogs which was used to determine the oral systemic availability.[20] The ethyl ester **19e** and the cyclohexyl ester **19c** had similar oral systemic activities (9.9 ± 2.3% and 9.2 ± 1.9%), and then followed by the pivaloyloxymethyl ester derivative **19p** (5.1 ± 1.5% OSA). All three pro-drugs of **19a** have improved oral duration of activity (> 6 h at 10 mg kg^{-1}) relative to the iv antiplatelet agent **1**, or it's diethyl ester pro-drug **6** (both less than 3 h at substantially higher doses).

Conclusion

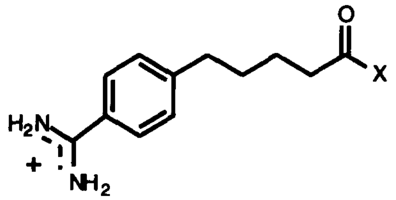
A novel benzamidinylpentanoyl (BAP) series of orally active fibrinogen receptor antagonists has been discovered through modification of our lead iv antiplatelet agent. The most orally-active analogs have a severely truncated C-terminal region compared to the parent iv agent, and they lack natural peptide bonds. Efforts are ongoing to further improve upon the oral systemic activity of **19e** through structural modifications.[22]

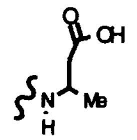
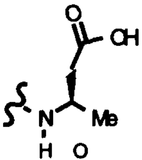
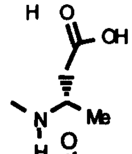
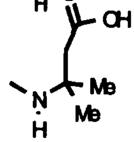
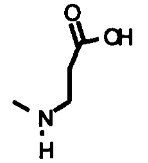
Experimental

Pharmacology. In vitro *inhibition of collagen induced canine platelet aggregation*[21,24]

Thirty mL of whole blood (pooled from ≥ 2 dogs) was collected into 0.129 M buffered sodium citrate (3.8%, 1:10). Platelet-rich plasma (PRP) was prepared by centrifugation at 975 *g* for 3.17 min at room temperature. Platelet poor plasma (PPP) was prepared by centrifuging at 6000 *g* for 8 min at room temperature. The PRP was adjusted with PPP to a count of (2–3) × 10^8 platelets mL^{-1}. PRP (400 μL) was preincubated with 50 μL of the compound to be tested, or saline (control), for 2 min at 37 °C in an aggregometer (PAP-4C, Biodata, Hatboro, PA). Collagen (50 μL, final concentration 33 μg mL^{-1}, Chronolog, Havevertown, PA) was added and the aggregation was monitored for 3 min. Results were calculated as follows: [per cent aggregation (inhibitor)] divided by [maximum per cent aggregation (control)] equals the per cent of control. The per cent inhibition = 100 − (per cent of control). All the compounds were screened at 0.1 μM and 100 μM. The % inhibition values were used to choose a minimum of four doses which were run in duplicate 3 separate times (n = 3). The IC$_{50}$ (mean ± SE) was calculated by linear regression of individual plots of % inhibition (logit) vs concentration (log).

Table 2. *In vitro* platelet aggregation of β-alanine aspartate mimetics



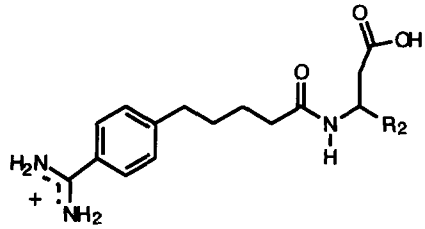
Compound	X	IC$_{50}$ (μM)[a]
9a		2.87 ± 0.38
10a		0.97 ± 1.4
11a		>>100
12a		>>100
13a		5.88 ± 0.39

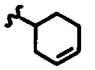
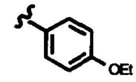
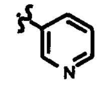
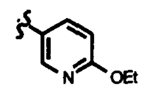
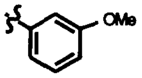
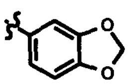
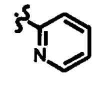
[a] Dog platelet rich plasma, PRP, collagen, n = 3, pooled blood, ± standard error.

Canine model for response to compound administration: determination of % inhibition of ex vivo *collagen induced platelet aggregation*

The ester pro-drugs **19c** and **19p** were administered orally by capsule (**19e** by gavage) to conscious beagle dogs (n = 3, White Eagle, Doylestown, PA; 7–12 kg) at a dose of 10 mg kg^{-1}. The acid **19a** was administered by bolus injection (1 min) into the cephalic vein of dogs at a dose of 2 mg kg^{-1}. Blood samples (2 mL) were withdrawn via venipuncture of the cephalic vein into citrated vacutainers at predetermined times before and after dosing for a period of 24 h or until activity had returned to baseline. PRP was prepared by centrifuging blood samples at 266 g for 6 min. Aggregation was measured and per cent inhibition for individual dogs calculated as described above. The remaining blood samples were centrifuged at 14,000 g to obtain PPP for

Table 3. *In vitro* inhibition of platelet aggregation of *p*-benzamidinopentanoyl (BAP)—SAR of 3-substituted β-alanine derivatives



Compound	R$_2$	IC$_{50}$ (μM)[a]
14a	c-hexyl	18.2 ± 0.17
15a		11.5 ± 0.08
16a	-CH$_2$Ph	4.72 ± 0.29
17a	-CH$_2$CH$_2$Ph	5.0 ± 0.39
18a		1.72 ± 0.05
19a		0.152 ± 0.015
20a		0.222 ± 0.002
21a		1.78 ± 0.29
22a		0.391 ± 0.022
23a		3.81 ± 0.76

[a] Dog platelet rich plasma, PRP, collagen, n = 3, pooled blood, ± standard error.

determination of the plasma concentration of active compound by bioassay. The % *ex vivo* inhibition of collagen induced platelet aggregation upon oral administration for compounds **8e** and **9e** were done in the same manner except at $n = 2$.

Bioassay methods—oral systemic activity (OSA)[20]

The concentration of the active agent in plasma was determined by using plasma from treated dogs to inhibit PRP from donor dogs. Blood was collected in citrate (9:1) from nontreated dogs and centrifuged (500 *g*, 3 min) to yield PRP. The remaining blood sample was centrifuged at 1800 *g* for 10 min to obtain PPP used to standardize the aggregometer and for sample dilution. Plasma (225 μL) from treated dogs was mixed with an equal volume of PRP from donor dogs and incubated for 2 min at 37 °C in an aggregometer. Collagen (as above) was added and aggregation was monitored. Per cent of control was calculated as described above and the concentration of active compound in plasma from treated dogs was obtained by comparison with the inhibition observed in a standard curve of plasma which had been spiked with known amounts of compound (acid form). If the sample plasma from the treated animals produced greater than 80% inhibition, the sample was diluted with PPP to produce inhibition that was within the 20–80% range of the standard curve. Concentration of compound in plasma samples determined by bioassay was plotted vs the time the sample was taken to obtain a curve. The area under the curve (AUC) was calculated. AUCs for IV and oral treatments were corrected for respective doses, and OSA was expressed as the ratio of AUCs (oral / iv).

Chemistry

High field ^{1}H NMR and ^{13}C NMR were recorded on a GE QE-300 spectrometer at 300 MHz and 75 MHz, respectively. Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Microanalyses were performed at the Searle Physical Methodology Department. Final compounds purified by reverse phase HPLC using a Waters LC-3000 and a Waters C-18 column (5 × 30 cm) using a linear gradient (5% CH_3CN / 0.05% TFA in H_2O to 40% CH_3CN / 0.05% TFA in H_2O) over 30 min.

General procedure A

*DL-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-phenyl-β-alanine (8a)*

Section 1

*DL-*N*-[5-(p-Cyanophenyl)pentanoyl]-3-phenyl-β-alanine (24).* To a solution of 5-(*p*-cyanophenyl)pentanoic acid[7a] (1.00g, 4.93 mmol), dimethylformamide (10 mL), and pyridine (2 mL) was added *N,N'*-disuccinimidylcarbonate (1.24 g, 4.85 mmol) and 4-dimethylaminopyridine (60 mg, 0.493 mmol) under an argon atmosphere at 23 °C. After 5 h, D,L-3-amino-3-phenylpropionic acid (0.814 g, 4.93 mmol) was added as a solid, followed immediately by *N,N'*-diisopropylethylamine (0.627 g, 4.85 mmol). After 20 h at 23 °C, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (300 mL), washed with $KHSO_4$ (1N, 2 × 50 mL), washed with brine (1 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (2 liters ethyl acetate:chloroform: acetic acid, 50:50:0.5 followed by 2 liters of ethyl acetate:methanol:acetic acid, 89:10:1) to afford 850 mg (50 %) of (**24**). ^{1}H NMR ($CDCl_3$) δ 1.45–1.63 (*m*, 4H), 2.28 (*br t*, $J = 7$ Hz, CH_2), 2.54 (*br t*, $J = 7$ Hz, CH_2), 2.69–2.92 (*m*, CH_2), 5.39–5.51 (*m*, CH), 7.15–7.28 (*m*, PhH), 7.43 (*d*, $J = 7$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 24.9, 29.9, 35.3, 35.7, 40.5, 49.7, 109.1, 118.9, 126.1, 127.4, 128.5, 129.0, 131.9, 140.5, 147.8, 173.4, 176.4.

Section 2

*DL-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-phenyl-β-alanine (8a).* Hydrogen sulfide was bubbled through a solution of 350 mg (1.00 mmol) of **24** in pyridine:triethylamine (12 mL:1.2 mL) for 3 min at 23 °C (caution: hydrogen sulfide is highly toxic and the reaction should be done in a hood). After 24 h at 23 °C in an enclosed flask, the reaction mixture was concentrated under a steady stream of nitrogen. The residue was diluted with ethyl acetate (200 mL), washed with $KHSO_4$ (2N, 2 × 50 mL), brine (1 × 50 mL), and dried (Na_2SO_4). Concentration *in vacuo* afforded a 94% yield of thioamide **25** as a gummy solid. ^{1}H NMR ($CDCl_3$) δ 1.52–1.68 (*m*, 4H), 2.20 (*br t*, $J = 7$ Hz, CH_2), 2.60 (*br t*, $J = 7$ Hz, CH_2), 2.72–2.89 (*m*, CH_2), 5.37–5.43 (*m*, CH), 7.13 (*d*, $J = 7$ Hz, PhH), 7.21–7.38 (*m*, PhH), 7.79 (*d*, $J = 7$ Hz, PhH); ^{13}C NMR ($CDCl_3$) δ 24.6, 29.8, 35.2, 35.6, 35.7, 39.6, 49.2, 125.8, 126.9, 127.0, 127.8, 128.1, 128.7, 131.7, 140.4, 146.2, 172.8, 172.9, 202.5.

Thioamide **25** (360 mg, 0.937 mmol) was dissolved in a solution of acetone:iodomethane (14 mL:1 mL). The reaction mixture was warmed to achieve reflux for 25 min. Concentration *in vacuo* afforded a quantitative yield of **26** as the HI salt.

A solution of **26** (373 mg, 0.937 mmol) and ammonium acetate (108 mg, 1.40 mmol) in methanol (10 mL) was warmed to achieve reflux for 3.5 h. After cooling to 23 °C, the reaction mixture was concentrated under a steady stream of nitrogen in the hood which afforded a quantitative yield of **8a**. The product was purified on a Waters reverse-phase C-18 microbondapak column (5 cm × 30 cm) using a linear gradient of 5% acetonitrile/water 0.05% trifluoroacetic acid to 40% acetonitrile/water 0.05% trifluoroacetic acid (30 min) with a flow rate of 80 mL min^{-1} to afford **8a**: ^{1}H NMR (CD_3OD) δ 1.62–1.78 (*m*, 4H), 2.25 (*m*, CH_2), 2.64–2.73 (*m*, CH_2), 2.72–2.89 (*m*, CH_2), 5.33–5.43 (*m*, CH), 7.21–7.38 (*m*, PhH), 7.72 (*d*, $J = 7$ Hz, PhH); ^{13}C NMR (CD_3OD) δ 25.0, 30.0, 34.9, 35.3, 40.2, 50.1, 125.4, 126.2, 127.1, 127.5, 128.2, 129.0, 141.5, 149.5, 166.9, 172.8, 173.8. Anal. $C_{21}H_{25}N_3O_3$ plus 0.6 H_2O and 0.7 acetic acid (C, H, N).

Section 3

*DL-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-phenyl β-alanine ethyl ester (8e).* Compound **8a** was esterified in neat ethanol saturated with HCl gas to afford **8e** in a quantitative yield: ^{1}H NMR (CD_3OD) δ 1.16 (*t*, *J* = 7 Hz, CH_3), 1.62–1.78 (*m*, 4H), 2.25 (*m*, CH_2), 2.64–2.73 (*m*, CH_2), 2.72–2.89 (*m*, CH_2), 4.05 (*q*, *J* = 7 Hz, CH_2), 5.33–5.43 (*m*, CH), 7.21–7.38 (*m*, PhH), 7.72 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3OD) δ 14.2, 26.3, 30.7, 35.4, 35.8, 41.0, 47.9, 52.0, 61.4, 126.0, 127.4, 128.5, 128.6, 129.4, 130.1, 141.2, 150.2, 166.9, 171.3, 176.0; CI MS (MH^+ = 396). Anal. $C_{23}H_{29}N_3O_3$ plus 0.5 CF_3CO_2H and 1.0 H_2O (C, H, N).

*DL-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-methyl-β-alanine (9a)* Compound **9a** was prepared in the manner of compound **8a** (Procedure A) with the following modifications: substituting 3-methyl-β-alanine for 3-phenyl-β-alanine: ^{1}H NMR (CD_3OD) δ 1.20 (*d*, *J* = 7 Hz, CH_3), 1.58–1.74 (*m*, 4H), 2.22 (*t*, *J* = 7 Hz, CH_2), 2.38–2.59 (*m*, CH_2), 2.74 (*t*, *J* = 7 Hz, CH_2), 4.23–4.37 (*m*, CH), 7.43 (*d*, *J* = 7 Hz, PhH), 7.78 (*d*, *J* = 7 Hz, PhH) 8.02 (*d*, *J* = 7 Hz, NH), 8.87 and 9.20 (2*s*, NH_2); ^{13}C NMR (CD_3OD) δ 19.7, 25.7, 30.7, 35.6, 36.0, 40.8, 42.9, 126.0, 128.2, 129.7, 150.1, 166.9, 174.1, 174.4; CI MS (MH^+ = 306). Anal. $C_{16}H_{23}N_3O_3$ plus 0.3 H_2O and 1.0 CF_3CO_2H (C, H, N).

*DL-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-methyl-β-alanine ethyl ester (9e).* Compound **9a** was esterified in neat ethanol saturated with HCl gas to afford **9e** in a quantitative yield after concentration *in vacuo*: ^{1}H NMR (CD_3OD) δ 1.20 (*d*, *J* = 7 Hz, CH_3), 1.24 (*t*, *J* = 7 Hz, CH_3), 1.58–1.74 (*m*, 4H), 2.22 (*t*, *J* = 7 Hz, CH_2), 2.38–2.59 (*m*, CH_2), 2.74 (*t*, *J* = 7 Hz, CH_2), 4.05 (*q*, *J* = 7 Hz, CH_2), 4.23–4.37 (*m*, CH), 7.43 (*d*, *J* = 7 Hz, PhH), 7.78 (*d*, *J* = 7 Hz, PhH), 8.02 (*d*, *J* = 7 Hz, NH), 8.87 and 9.25 (2*s*, NH_2); ^{13}C NMR (CD_3OD) δ 13.0, 18.9, 24.9, 29.9, 34.8, 35.0, 40.1, 42.3, 60.0, 126.0, 127.5, 129.0, 149.3, 166.9, 171.1, 173.8; CI MS (MH^+ = 335). Anal. $C_{18}H_{27}N_3O_3$ plus 1.7 H_2O and 1.0 HCl (C, N; H: calcd, 7.90; found, 7.39).

General procedure B

Ethyl-[[[5-[4-(amidino)phenyl]-1-oxopentyl]amino]-4-ethoxybenzenepropanoate

Section 1

5-[4-(Amidino)phenyl]pentanoic acid (5). To a slurry of 4.06 g (20.0 mmol) of 5-(*p*-cyanophenyl)pentanoic acid in 60 mL of anhydrous ether was added 100 mL of lithium bis(trimethylsilyl)amide (1.0 M in hexanes) via cannula. After 20 h at 23 °C, the reaction was quenched through the slow addition of water (25 mL) followed by adjustment of the pH to 7 using 20% HCl (approx 45 mL required). After dilution with acetonitrile (25 mL), the product was collected by filtration, washed with water (50 mL), washed with ether:acetonitrile (7:3, 100 mL), washed with ether (50 mL), and dried *in vacuo* to afford 4.0 g (90%) of the product as the zwitterion. The zwitterion product was converted to the HCl salt by treatment with saturated anhydrous HCl in dioxane. After concentration *in vacuo*, the precipitate was washed with ether and stored in a vacuum desiccator; ^{1}H NMR (CD_3OD) δ 1.44–1.63 (*m*, 2-CH_2), 2.24 (*t*, *J* = 7 Hz, CH_2), 2.64 (*t*, *J* = 7 Hz, CH_2), 7.35 (*d*, *J* = 7 Hz, PhH), 7.68 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3OD) δ 24.0, 29.9, 33.3, 34.8, 127.6, 129.1, 131.8, 159.5, 166.8, 175.8. Anal. $C_{12}H_{16}N_2O_2$ (C, H, N).

Section 2

Ethyl-[[[5-[4-(amidino)phenyl]-1-oxopentyl]amino]-4-ethoxybenzenepropanoate (18e). 4-Ethoxybenzaldehyde (3 g, 20 mmol), malonic acid (2.4 g, 23 mmol) and ammonium acetate (2 g, 28 mmol) were gently refluxed in ethanol (100 mL) overnight. The reaction mixture was allowed to cool down to room temperature and the solid precipitate was collected by filtration and washed with ethanol (2 × 30 mL). The air-dried free acid (FAB-MS: MH^+ = 210) was suspended in the absolute ethanol (100 mL). The solution was cooled in an ice bath and HCl gas was bubbled through the solution for 15 min. The reaction mixture was stirred at room temperature for 20 h, and then the solvent was removed *in vacuo* to afford ethyl 3-amino-3-(4-ethoxyphenyl)propanoate–HCl (**27**). The residue was dried in a vacuum desiccator and was used without any further purification. FAB-MS (MH^+ = 238).

4-Amidinophenylpentanoic acid–HCl (**5**) (0.4 g, 1.66 mmol), disuccinimidyl carbonate (0.5 g, 2 mmol), and 4-dimethylaminopyridine (40 mg) were dissolved in 25 mL of DMF (25 mL) and the solution was stirred at 23 °C for 20 h. To this mixture, a solution of ethyl 3-amino-3-(4-ethoxyphenyl)propanoate–HCl (0.41 g, 1.5 mmol) and *N,N*-diisopropylethylamine (0.14 g, 1.1 mmol) in DMF (10 mL) was added with stirring. After 20 h at 23 °C, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in acetonitrile/water and purified on a Waters Deltapak C-18 HPLC column (30 cm × 5 cm) with a flow rate of 80 mL min^{-1}. A linear gradient (30 min) of 10 to 40% acetonitrile/water/0.05% TFA followed by an increase to 60% acetonitrile in 10 min was used. The ester eluted at an acetonitrile concentration of 42–46% and the desired peak was lyophilized to yield 170 mg of **18e** as a white solid which was converted to its HCl salt; ^{1}H NMR (DMSO-d_6) 1.10 (*t*, *J* = 7 Hz, 3H, CH_3), 1.31 (*t*, *J* = 7 Hz, 3H, Ar-OCH_2CH_3), 1.50 (*br*, 4H, 4-CH_2), 2.10 (*t*, *J* = 7 Hz, 2H, CH_2CO), 2.67 (*m*, 4H, Ar-CH_2 and CH_2CO_2), 3.98 (*m*, 4H, $CO_2CH_2CH_3$ and Ar-OCH_2CH_3), 5.16 (*m*, 1H, CHN), 6.82 (*d*, *J* = 7 Hz, 2H, PhH), 7.2 (*d*, *J* = 7 Hz, 2H, PhH), 7.4 (*d*, *J* = 7 Hz, 2H, PhH), 7.73 (*d*, *J* = 7 Hz, 2H, PhH), 8.3 (*m*, 1H, NH), 9.0 and 9.27 (2*s*, 4H, H_2NCNH_2); FAB-MS (MH^+ = 440). Anal. $C_{25}H_{33}N_3O_4$ plus 1.0 HCl and 1.0 H_2O (N; C: calcd, 60.78; found, 58.12; H: calcd, 7.34; found, 6.22).

Section 3

β-[[5-[4-(Amidino)phenyl]-1-oxopentyl]amino]-4-ethoxybenzene-propanoic acid (18a). The ester **18e** (100 mg) was treated with 1 N LiOH: methanol (5 mL:5mL) for 30 min. The mixture was neutralized with 4 N HCl and diluted with water (25 mL). The product was purified by reverse phase HPLC under the above conditions (**18e**) which afforded after collection and freeze-drying a yield of 65 mg of **18a**. ^{1}H NMR (DMSO-d_6) 1.31 (*t*, 3H, $ArOCH_2CH_3$), 1.50 (*br s*, 4H, $CH_2CH_2CH_2CH_2$), 2.1 (*t*, 2H, CH_2CH_2CO), 2.67 (*m*, 4H, Ar-CH_2 and $CHCH_2CO$), 3.98 (*m*, 2H, Ar-OCH_2CH_3), 5.12 (*q*, 1H, CH), 6.82 and 7.2 (*d*, 4H, Ar), 7.4 and 7.73 (*d*, 4H, Ar), 8.23 (*d*, 1H, CONH), 8.89 and 9.20 (*s*, 4H, H_2NCNH_2); FAB-MS (MH^+ = 412). Anal. $C_{23}H_{29}N_3O_4$ plus 1.0 CF_3CO_2H (C, H, N).

General procedure C

β-[[[5-(p-Amidino)phenyl]-1-oxopentyl]amino]benzenepentanoic acid (17a)

Section 1

3-(Phenethyl)-β-lactam (30). Chlorosulfonyl isocyanate (7.2 mL, 11.7 g, 82.7 mmol) was added to 4-phenyl-1-butene (11.1 g, 84.0 mmol) under a nitrogen atmosphere at 23 °C. After 40 h, the reaction mixture was added dropwise to a rapidly stirring cold (0 °C) solution of $NaHCO_3$ (18 g), $NaHSO_3$ (5 g), and H_2O:CH_2Cl_2 (75 mL:50 mL). After 1 h, the methylene chloride was removed *in vacuo*, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL), washed with H_2O (2 × 50 mL), washed with brine (2 × 50 mL), and dried (Na_2SO_4). After concentration *in vacuo*, the residue was purified by flash chromatography (ethyl acetate:hexane, 1:4 to ethyl acetate:hexane, 1:1) to afford 9.78 g of the beta lactam. The material was recrystallized from ether:hexane to afford 7.50 g of beta lactam **30**: ^{1}H NMR ($CDCl_3$) δ 1.78–1.85 (*m*, CH_2Ph), 2.43–2.52 (*m*, 1H, CHH), 2.51–2.69 (*m*, 2H, CH_2), 2.91–2.98 (*m*, CHH), 3.42–3.55 (*m*, CHN), 7.05 (*br s*, NH), 7.10–7.32 (*m*, PhH); ^{13}C NMR ($CDCl_3$) δ 32.3, 36.7, 43.0, 47.3, 125.8, 128.0, 128.2, 140.6, 168.4. Anal. $C_{11}H_{13}NO$ (C, H, N).

Section 2

Ethyl 3-amino-5-phenylpentanoate (31). The beta lactam **30** was opened by treatment with neat ethanol saturated with HCl gas at 0 °C for 1 h which afforded a quantitative yield of ethyl 3-amino-5-phenylpentanoate (**31**) as the hydrochloride salt after concentration *in vacuo*; ^{1}H NMR ($CDCl_3$) δ 1.18 (*t*, *J* = 7 Hz, CH_3), 1.98–2.32 (*m*, CH_2Ph), 2.71–2.97 (*m*, 4 H, 2-CH_2), 3.65–3.79 (*m*, CHN), 4.10 (*q*, *J* = 7 Hz, CH_2O), 7.12–7.24 (*m*, PhH), 8.65 (*br s*, NH_3+); ^{13}C NMR ($CDCl_3$) δ 14.5, 31.9, 34.6, 37.2, 49.0, 61.8, 126.7, 128.9, 129.0, 140.5, 170.6.

Section 3

Ethyl β-[[[5-(p-amidino)phenyl]-1-oxopentyl]amino]-benzenepentanoate (17e). The title compound was prepared following general procedure A with the following modification: substitution of D,L-ethyl 3-amino-5-phenylpentanoate (**31**) for D,L-3-amino-3-phenylpropionic acid in section 1 of procedure A. ^{1}H NMR (CD_3OD) δ 1.25 (*t*, *J* = 7 Hz, CH_3), 1.57–1.75 (*m*, 2-CH_2), 2.47–2.53 (*m*, 2H, CH_2), 2.53–2.69 (*m*, 2-CH_2), 2.72–2.79 (*m*, 2H, CH_2), 3.95 (*q*, *J* = 7 Hz, CH_2), 4.23–4.44 (*m*, 1H, CHN), 7.00–7.16 (*m*, PhH), 7.30 (*d*, *J* = 7 Hz, PhH), 7.65 (*d*, *J* = 7 Hz, PhH); MS EI (M^+ = 423); ^{13}C NMR (CD_3OD) δ 13.3, 26.2, 30.5, 32.5, 34.9, 35.5, 35.9, 38.8, 47.7, 61.0, 125.5, 126.0, 128.0, 128.5, 128.6, 129.4, 141.2, 149.6, 166.8, 171.9, 176.6.

Section 4

β-[[[5-(p-Amidino)phenyl]-1-oxopentyl]amino]benzenepentanoic acid (17a). The ester **17e** (200 mg, 0.473 mmol) was cleaved to the acid **17a** by treatment with aqueous 6 N HCl (10 mL) and 5 mL of dioxane for 20 h at 23 °C which afforded the acid **17a** in quantitative yield after concentration under a stream of nitrogen. ^{1}H NMR (CD_3OD) δ 1.65–1.94 (*m*, 3-CH_2), 2.47–2.53 (*m*, 2H, CH_2), 2.53–2.69 (*m*, 2-CH_2), 2.72–2.79 (*m*, 2H, CH_2), 4.23–4.44 (*m*, 1H, CHN), 7.13–7.28 (*m*, PhH), 7.47 (*d*, *J* = 7 Hz, PhH), 7.82 (*d*, *J* = 7 Hz, PhH), 8.87 and 9.25 (2*s*, NH_2); ^{13}C NMR ($CDCl_3$) δ 26.0, 30.3, 32.3, 34.7, 35.3, 35.7, 38.9, 47.9, 125.5, 126.2, 128.2, 128.5, 128.6, 129.6, 141.4, 149.8, 166.8, 171.9, 176.6; MS EI (M^+ = 395). Anal. $C_{25}H_{33}N_3O_3$ plus 0.35 H_2O and 1.0 CF_3CO_2H (C, H, N).

5-(p-Amidinophenyl)pentanoyl-(S)-aspartyl-(S)-N-methylphenylalanine (7). Compound **7** was prepared following the general procedure A with the following modifications: 5-(*p*-cyanophenyl)pentanoic acid[7a] was coupled sequentially to (*S*)- β-(*O*-*tert*-butyl)-aspartate followed by (*S*)-(*O*-*tert*-butyl)-*N*-methylphenylalanine to afford 5-(*p*-cyanophenyl)pentanoyl-(*S*)-aspartyl-(*S*)-*N*-methylphenylalanine which was converted to the benzamidine as described in procedure A. Compound **7** was afforded upon deprotection with 90% TFA:water:^{1}H NMR (CD_3OD) δ 1.53–1.72 (*m*, 4H), 2.12–2.34 (*m*, 2-CH_2), 2.73 (*t*, *J* = 7 Hz, CH_2), 2.87–3.17 (*m*, CH_2), 3.38 (s, CH_3), 4.05 (*q*, *J* = 7 Hz, CH_2), 4.92–5.24 (*m*, 2-CHN), 7.15 (*m*, 5H, PhH), 7.43 (*m*, 2H, PhH), 8.73 (*m*, 2H, PhH), 8.87 and 9.25 (2s, NH_2); ^{13}C NMR (CD_3OD) δ 24.8, 30.0, 32.9, 34.0, 34.9, 35.5, 45.6, 46.1, 59.9, 125.5, 126.2, 127.6, 128.1, 128.7, 129.1, 137.4, 149.5, 166.9, 171.6, 172.0, 172.1, 172.3, 173.5, 174.0. Anal. $C_{26}H_{32}N_4O_6$ plus 1.0 CF_3CO_2H and 1 H_2O (C, H, N).

(R)-N-[5-(p-Amidinophenyl)pentanoyl]-3-methyl-β-alanine (10a).

(R)-3-methyl-β-alanine (29). To a solution of N-*t*-Boc-D-alanine (5.05 g, 25.1 mmol) in anhydrous ether (100 mL) was added *N*-methylmorpholine (2.76 mL, 25.1 mmol) at 23 °C. After cooling to −10 °C, isobutyl chloroformate (3.42 g, 25.1 mmol) was added dropwise. The reaction was allowed to warm to 23 °C for 1 h at which point the reaction mixture was filtered. The filtrate was treated with an excess of diazomethane in ether at 0 °C. After 1 h, the reaction was concentrated with a stream of nitrogen in the hood. The residue was dissolved in anhydrous ethanol (125 mL), and a solution of silver benzoate (1.09 eq.) in triethylamine (10 mL) was added slowly (reaction exotherms). After 1 h at 23 °C, the reaction was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient, 1 liter ethyl acetate:hexane, 1:9 to ethyl acetate:hexane 2:8) to afford ethyl *N*-*t*-Boc-(*R*)-3-aminobutyrate (5.04 g, 87%): ^{1}H NMR ($CDCl_3$) δ 1.22 (*d*, *J* = 7 Hz, CH_3), 1.27 (*t*, *J* = 7 Hz, CH_3), 1.43 (s, 12H, Boc), 2.42–2.58 (*m*, 2H, CH_2), 4.16 (*q*, *J* = 7

Hz, CH_2O), 5.01–5.11 (*m*, CH); ^{13}C NMR ($CDCl_3$) δ 15.1, 21.4, 29.2, 41.8, 44.7, 61.3, 80.0, 156.5, 172.7; optical rotation (*c* 1.00, $CHCl_3$) $[\alpha]_D$ +18.7°. Anal. $C_{11}H_{21}NO_4$ (C, H, N).

The ester (535 mg, 2.31 mmol) was hydrolyzed by treatment with 1 N NaOH:methanol (3 mL:2 mL) for 20 h. After removal of the methanol *in vacuo*, the reaction mixture was acidified with 2 N potassium hydrogen sulfate, extracted with ethyl acetate (2 × 80 mL), and dried (Na_2SO_4). The Boc group was removed by treating with 90% TFA–H_2O for 30 min. After concentration *in vacuo*, the residue was lyophilized and subsequently recrystallized (acetone-H_2O) to afford 231 mg of (*R*)-3-aminobutyric acid: ^1H NMR (D_2O) δ 1.38 (*d*, *J* = 7 Hz, CH_3), 2.68–2.86 (*m*, 2H, CH_2), 3.68–3.84 (*m*, CH); ^{13}C NMR (D_2O) δ 17.5, 37.5, 44.4, 173.8; optical rotation (*c* 0.97, H_2O) $[\alpha]_D$ −21.3° (Lit.[23] −35.2°, neat). The title compound was prepared following general procedure A with the following modification: substitution of (*R*)-3-methyl-β-alanine (**29**) for D,L-3-amino-3-phenylpropionic acid in section 1 of procedure A. ^1H NMR, ^{13}C NMR, mass spectroscopy data are identical to those of the racemic material **9a**.

(S)-*N*-[5-(*p*-Amidinophenyl)pentanoyl]-3-methyl-β-alanine (**11a**). The title compound was prepared following the procedure given for compound **10a** with the following substitution: *N*-*t*-Boc-L-alanine was substituted for *N*-*t*-Boc-D-alanine. Ethyl *N*-*t*-Boc-(*S*)-3-aminobutyrate: optical rotation (*c* 1.04, $CHCl_3$) $[\alpha]_D$ −19.4°; (*S*)-3-aminobutyric acid: optical rotation (*c* 0.99, H_2O) $[\alpha]_D$ +22.3° ± 0.701; Lit.[23] (*c* 11.41, H_2O) $[\alpha]^{20}_D$ +35.3° ± 0.2 ; ^1H NMR, ^{13}C NMR, mass spectroscopy data are identical to those of the racemic material **9a**. Anal. $C_{16}H_{23}N_3O_3$ 1.0 CF_3CO_2H (C, H, N).

*Ethyl β-[[[5-(*p*-amidinophenyl)]-1-oxopentyl]amino]-3-methylbutanoate (**12e**).* The title compound was prepared following general procedure C with the following modification: substitution of 2-methylpropene for 4-phenyl-1-butene in section 1 of procedure C. ^1H NMR (CD_3OD) δ 1.15 (*d*, *J* = 7 Hz, CH_3), 1.38 (*s*, 6H, 2-CH_3), 1.53–1.74 (*m*, 4H), 2.15 (*m*, CH_2), 2.54–2.88 (*m*, 2-CH_2), 4.03 (*q*, *J* = 7 Hz, CH_2), 7.43 (*d*, *J* = 7 Hz, PhH), 7.78 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3OD) δ 14.7, 25.7, 27.6, 29.9, 30.8, 34.8, 36.2, 37.2, 44.1, 52.3, 60.5, 126.0, 127.5, 129.0, 149.3, 166.9, 171.1, 173.8; MS EI (M^+ = 347).

*β-[[[5-(*p*-Amidinophenyl)]-1-oxopentyl]amino]-3-methylbutanoic acid (**12a**).* The title compound was prepared by cleaving the ester **12e** to the acid **12a** as described in procedure C section 4. ^1H NMR (CD_3OD) δ 1.38 (*s*, 6H, 2-CH_3), 1.50–1.75 (*m*, 4H), 2.10 (*m*, CH_2), 2.54–2.88 (*m*, 2-CH_2), 7.48 (*d*, *J* = 7 Hz, PhH), 7.75 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3OD) δ 25.3, 27.2, 30.0, 30.4, 34.4, 35.8, 36.8, 43.8, 52.0, 60.1, 126.0, 127.5, 129.0, 149.3, 166.9, 171.1, 174.8; MS EI (M^+ = 319). Anal. $C_{17}H_{25}N_3O_3$ plus 1.5 H_2O and 0.5 CF_3CO_2H (C, H, N).

N-*[5-[4-(Amidinophenyl)]-1-oxopentyl]-β-alanine, phenylmethyl ester (**13e**).* The title compound was prepared following general procedure A with the following modification: substitution of β-alanine benzyl ester for D,L-3-amino-3-phenylpropionic acid in section 1 of procedure A. ^1H NMR (CD_3CO_2D) δ 1.25–1.38 (*m*, 3-CH_2), 1.92–2.02 (*m*, 2H, CH_2), 2.32 (*t*, *J* = 7 Hz, CH_2), 2.35–2.43 (*m*, 2H, CH_2), 3.21 (*t*, *J* = 7 Hz, CH_2), 4.81 (*s*, CH_2Ph), 6.93–7.04 (*m*, PhH), 7.09 (*d*, *J* = 7 Hz, PhH), 7.45 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3CO_2D) δ 24.2, 29.2, 32.7, 34.2, 34.4, 65.6, 124.3, 127.0, 127.1, 127.3, 127.6, 128.4, 135.0, 148.9, 165.6, 171.8, 174.8; CI MS (MH^+ = 382). Anal. $C_{22}H_7N_3O_3$ plus 1.0 CF_3CO_2H (C, H, N).

N-*[5-[4-(Amidino)phenyl]-1-oxopentyl]-β-alanine (**13a**).* A solution of 280 mg (0.735 mmol) of **13e** in 10 mL of ethanol was hydrogenated over 280 mg of 10% Pd/C under a balloon atmosphere of hydrogen over a 20 h period. Filtration and evaporation of the solvent *in vacuo* afforded 180 mg (85%) of the title compound in a pure form. ^1H NMR (CD_3OD) δ 1.49–1.63 (*m*, 2-CH_2), 2.11 (*t*, *J* = 7 Hz, CH_2), 2.38 (*t*, *J* = 7 Hz, CH_2), 2.63 (*t*, *J* = 7 Hz, CH_2), 3.30 (*t*, *J* = 7 Hz, CH_2), 7.35 (*d*, *J* = 7 Hz, PhH), 7.64 (*d*, *J* = 7 Hz, PhH), 8.86 and 9.08 (2*s*, NH_2); ^{13}C NMR (CD_3OD) δ 25.5, 30.6, 33 9, 2C 35.4, 35.5, 35.7, 126.0. 128.1, 129.5, 149.9, 166.9, 174.3, 174.9; CI MS (MH^+ = 292). Anal. $C_{15}H_{21}N_3O_3$ plus 1.3 H_2O and 1.0 CF_3CO_2H (C, H, N).

*β-[[[5-(p-Amidino)phenyl]-1-oxopentyl]amino]cyclohexyl-propanoic acid (**14a**).* The title compound was prepared following general procedure B with the following modification: substitution of 3-amino-3-cyclohexylpropionic acid for ethyl D,L-3-amino-3-(4-ethoxyphenyl)propanoate–HCl in section 3 of procedure B: ^1H NMR (DMSO-d_6) δ 0.80–1.72 (*m*, 10H, 5-CH_2), 1.30 (*m*, 4H, 2-CH_2), 2.10 (*t*, *J* = 7 Hz, 2H, CH_2CO), 2.11–2.40 (*m*, 4H, 2-CH_2), 2.65 (*m*, 1H, CH), 3.96 (*m*, 1H, CH), 7.4 (*d*, *J* = 7 Hz, 2H, PhH), 7.7 (*d*, *J* = 7 Hz, 2H, PhH), 7.60 (*m*, 1H, NH), 8.95– 9.20 (*m*, 4H, H_2NCNH_2); FAB MS (MH^+ = 374). Anal. $C_{21}H_{31}N_3O_3$ plus H_2O and 1.0 CF_3CO_2H (H, N; C: calcd, 54.65; found, 55.09).

*Ethyl β-[[[5-(p-Amidino)phenyl]-1-oxopentyl]amino]-4-phenylbutanoate (**16e**).* The title compound was prepared following general procedure C with the following modification: substitution of 3-phenyl-1-propene for 4-phenyl-1-butene in section 1 of procedure C. ^1H NMR (CD_3OD) δ 1.18 (*t*, *J* = 7 Hz, CH_3), 1.47–1.59 (*m*, 2-CH_2), 2.03 (*m*, 2 H, CH_2), 2.27–2.45 (*m*, 2-CH_2), 2.52–2.59 (*m*, CH_2), 2.61–2.85 (*m*, 2H, CH_2), 3.95 (*q*, *J* = 7 Hz, CH_2), 4.32–4.42 (*m*, H, CHN), 7.03–7.15 (*m*, PhH), 7.29 (*d*, *J* = 7 Hz, PhH), 7.63 (*d*, *J* = 7 Hz, PhH); ^{13}C NMR (CD_3OD) δ 13.8, 25.7, 30.6, 35.7, 36.1, 39.3, 40.7, 48.1, 61. 0, 126.1, 126.9, 128.0, 128.3, 128.7, 129.7, 129.8, 138.7, 150.2, 166.8, 172.2, 174.5. Anal. $C_{24}H_{31}N_3O_3$ plus 1.5 CF_3CO_2H (C, H, N).

*β-[[[5-(p-Amidino)phenyl]-1-oxopentyl]amino]-4-phenylbutanoic acid (**16a**).* The title compound was prepared by cleaving the ester **16e** to the acid **16a** as described in procedure C section 4. ^{1}H NMR (CD_3OD) δ 1.67–1.78 (*m*, 2-CH_2), 2.32–2.38 (*m*, 2H, CH_2), 2.61–2.75 (*m*, 2-CH_2), 2.84–2.92 (*m*, CH_2), 2.93–3.13 (*m*, 2H, CH_2), 4.62–4.73 (*m*, H, CHN), 7.32–7.45 (*m*, PhH), 7.61 (*d*, *J* = 7 Hz, PhH), 7.93 (*d*, *J* = 7 Hz, PhH), 9.04 and 9.38 (2*s*, NH_2); ^{13}C NMR (CD_3OD) δ 25.5, 30.4, 35.5, 35.9, 38.8, 40.4, 48.4, 126.1, 126.7, 128.1, 128.6, 129.5, 129.7, 138.7, 150.1, 167.6, 174.0, 174.5; CI MS (MH^+ = 382). Anal. $C_{22}H_{27}N_3O_3$ plus 1.1 H_2O and 1.0 CF_3CO_2H (C, H, N).

*Ethyl β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-3-pyridylpropanoate (**19e**).* Anhydrous HCl was bubbled through a solution of 3-amino-3-(3-pyridyl)propanoic acid (1.0 g, 60 mmol) in 100 mL of absolute ethanol for 2 h. After concentration *in vacuo*, the residue was suspended in 20 mL of absolute ethanol. The suspension was filtered and the filter cake was washed once with ethanol and dried to afford ethyl 3-amino-3-(3-pyridyl)propanoate–HCl: ^{1}H NMR (DMSO-d_6) 1.10 (*t*, *J* = 7 Hz, CH_3), 3.32 (*m*, 2H, CH_2), 4.02 (*m*, 2H, CH_2), 4.88 (*m*, 1H, CHN), 7.97–8.04 (*m*, 1H, ArH), 8.69–8.74 (*m*, 1H, ArH), 8.85–8.89 (*m*, 1H, ArH), 9.08–9.20 (*m*, 4H, ArH and $CHNH_3^+$); FAB-MS (MH^+ = 167).

The title compound was prepared following general procedure B with the following modification: substitution of ethyl D,L-3-amino-3-pyridylpropanoate for ethyl D,L-3-amino-3-(4-ethoxyphenyl)propanoate–HCl in section 3 of procedure B and a 5 to 50% acetonitrile/water/0.05% TFA in 40 min was used for the reverse phase HPLC purification and the ester eluted at 24% acetonitrile concentration. Fractions containing the desired peak were lyophilized to give a white solid. The product was then dissolved in four equivalents of 0.1 M HCl in water and lyophilized: ^{1}H NMR (DMSO-d_6) δ 1.10 (*t*, *J* = 7 Hz, 3H, CH_3), 1.50 (*m*, 4H, 2-CH_2), 2.12 (*t*, *J* = 7 Hz, 2H, CH_2), 2.63 (*t*, *J* = 7 Hz, 2H, CH_2), 2.83 (*m*, 2H, CH_2), 3.99 (*q*, *J* = 7 Hz, 2H, CH_2), 5.25 (*m*, 1H, NCH), 7.39 (*d*, *J* = 7 Hz, 2H, PhH), 7.72 (*d*, *J* = 7 Hz, 2H, PhH), 7.52–7.56 (*m*, 1H, ArH), 7.96 (*m*, 1H, NH), 8.50–8.66 (*m*, 3H, ArH), 9.08 and 9.22 (2 *br s*, 4H, $H_2NCNH_2^+$); FAB-MS (MH^+ = 397).

*Cyclohexyl β-[[[5-(*p*-amidino)phenyl]-1-oxopentyl]-amino]-3-pyridylpropanoate (**19c**).* Compound **19c** was prepared in the manner of **19e** substituting cyclohexanol for ethanol: ^{1}H NMR (DMSO-d_6) δ 1.15–1.70 (*m*, 10H, 5-CH_2), 1.45 (*m*, 4H, 4-CH_2), 2.06 (*t*, *J* = 7 Hz, 2H, CH_2CO), 2.64 (*t*, *J* = 7 Hz, 2H, $ArCH_2$), 2.83 (*m*, 2H, CH_2CO_2), 4.6 (*m*, 1H, CH), 5.13 (*m*, 1H, NCH), 7.35 (*d*, *J* = 7 Hz, 2H, PhH), 7.67 (*d*, *J* = 7 Hz, 2H, PhH), 7.55 (*m*, 1H, Pyr), 7.91 (*m*, 1H, NH), 8.43–8.58 (*m*, 3H, Pyr), 9.02 and 9.18 (2 *br s*, 4H, $H_2NCNH_2^+$); FAB-MS (MH^+ = 451). Anal. $C_{29}H_{24}N_4O_3$ plus 2 HCl (N, H; C: calcd, 55.14; found, 55.60).

*β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-3-pyridylpropanoic acid (**19a**).* Ethyl 3-[[[5-(*p*-amidino)phenyl]-1-oxopentyl]amino]-3-pyridylpropanoic acid (**19e**) (30 mg, 0.055 mmol), ethanol (4 mL), and 2 N LiOH in water (4 mL) were stirred for 2.5 h. The solution was acidified to pH 3 with 2 N HCl and concentrated *in vacuo*. The residue was dissolved in acetonitrile/water and purified by HPLC on a Waters Deltapak C-18 column (30 cm × 5 cm). A gradient of 2 to 60% acetonitrile/water/0.05% TFA over 30 min was used and the acid **19a** eluted at an acetonitrile concentration of 28%. Fractions containing the desired peak were lyophilized to give a white solid: ^{1}H NMR (DMSO-d_6) δ 1.43 (*m*, 4H, 2-CH_2), 2.06 (*t*, *J* = 7 Hz, 2H, CH_2), 2.63 (*t*, *J* = 7 Hz, 2H, CH_2), 2.83 (*m*, 2H, CH_2), 5.15 (*m*, 1H, NCH), 7.33 (*d*, *J* = 7 Hz, 2 H, PhH), 7.66 (*d*, *J* = 7 Hz, 2H, PhH), 7.48–7.56 (*m*, 1H, ArH), 7.93 (*m*, 1H, NH), 8.38–8.45 (*m*, 1H, ArH), 8.48–8.53 (*m*, 1H, ArH), 8.58 (*br s*, 1H, ArH), 9.01 and 9.18 (2 *br s*, 4H, $H_2NCNH_2^+$); FAB-MS (MH^+ = 369).

*Pivaloyloxymethyl [[5-(*p*-amidinophenyl)]-1-oxopentyl]-amino-pyridylpropanoate (**19p**).* Boc-3-amino-3-pyridylpropionic acid (3.99 g, 15 mmol) and chloromethylpivalate (2.16 mL, 15 mmol) were combined in 50 mL acetone with tetrabutylammonium bromide (1.61 g, 5 mmol) and the solution was warmed to achieve reflux for 8 h. After concentration *in vacuo*, the residue was purified by reverse phase HPLC (linear gradient 5 to 50% acetonitrile/H_2O/0.05% TFA over 30 min). The Boc group was removed by treatment with 4 N HCl/dioxane for 30 min and the pivaloyloxymethyl [3-amino-3-pyridylpropionate]–HCl salt was obtained by ethyl ether precipitation: 5-(*p*-amidinophenyl)pentanoic acid–HCl (4.20 g, 16.5 mmol) was activated towards coupling by treatment with *N,N′*-disuccinimidylcarbonate (5.00 g, 19.5 mmol) and 4-dimethylaminopyridine (0.25 g, mmol) in 25 mL of DMF for 20 h. Then, the above active ester solution was added to a solution of pivaloyloxymethyl [3-amino-3-pyridylpropionate] in 25 mL of DMF which had been titrated to neutral pH with diisopropylethylamine. After 16 h at 23 °C, the mixture was stripped to afford an oil which was purified on reverse phase HPLC as above to yield 1.96 g of **19p** (27% overall yield): ^{1}H NMR (DMSO-d_6) δ 1.10 (*s*, 9H, $C(CH_3)_3$), 1.40 (*m*, 4H, 2-CH_2), 2.06 (*t*, *J* = 7 Hz, 2H, CH_2CO), 2.64 (*t*, *J* = 7 Hz, 2H, $ArCH_2CH_2$), 2.83 (*m*, 2H, $CHCH_2CO_2$), 5.10 (*m*, 1H, NHCH), 5.6 (*s*, 2H, O-CH_2-O), 7.35 (*d*, *J* = 7 Hz, 2H, PhH), 7.67 (*d*, *J* = 7 Hz, 2H, PhH), 7.45 (*m*, 1H, Pyr), 8.20 (br d, 1H, NHCH), 7.89-8.58 (*m*, 3H, ArH), 8.95 and 9.18 (*m*, 4H, $H_2NCNH_2^+$); FAB-MS (MH^+ = 483.7). Anal. $C_{26}H_{34}N_4O_5$ plus 2 CF_3CO_2H (C, H, N).

*β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-3-(4-ethoxypyridyl)propanoic acid (**20a**).* The title compound was prepared following general procedure A with the following modification: substitution of D,L-(*O-tert*-butyl)-3-amino-3-(4-ethoxypyridyl)propionate for D,L-3-amino-3-phenylpropionic acid in section 1 of general procedure A followed by deprotection by treatment with 90% TFA/water: ^{1}H NMR (CD_3OD) δ 1.51 (*t*, *J* = 7 Hz, CH_3), 1.61–1.78 (*m*, 2-CH_2), 2.28–2.38 (*m*, 2 H, CH_2), 2.64–2.78 (*m*, 2H, CH_2), 2.92–3.11 (*m*, 2H, CH_2), 4.51 (*q*, *J* = 7 Hz, CH_2), 5.42–5.48 (*m*, H, CHN), 7.41–7.51 (*m*, 3H, ArH), 7.76 (*d*, *J* = 7 Hz, PhH), 8.38–8.51 (*m*, 2H, ArH), 8.93 and 9.15 (2*s*, NH_2); ^{13}C NMR (CD_3OD) δ 13.7, 14.6, 25.9, 30.9, 35.8, 36.2, 42.0, 48.4, 61.0, 67.7, 111.1, 126.2, 128.5, 130.0, 130.7, 138.6, 146.0, 150.2, 164.0, 166.8, 170.5, 174.4.

*β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-3-methoxybenzenepropanoic acid (21a).* The title compound was prepared following general procedure B with the following modification: substitution of D,L-3-amino-3-(3-methoxyphenyl)propionic acid for ethyl D,L-3-amino-3-(4-ethoxyphenyl)propanoate–HCl in section 3 of procedure B: ^1H NMR (DMSO-d_6) δ 1.0 (*m*, 4H, 2-CH_2), 2.10 (*t*, *J* = 7 Hz, 2H, CH_2), 2.62 (*m*, 4H, Ar-CH_2 and $CHCH_2CO$), 3.71 (s, 3H, $ArOCH_3$), 5.10 (*m*, 1H, CHN), 6.82–7.23 (*m*, 4H, ArH), 7.40 (*d*, *J* = 7 Hz, 2H, PhH), 7.70 (*d*, *J* = 7 Hz, 2H, PhH), 8.23 (*m*, 1H, NH), 8.95 and 9.20 (2*s*, 4H, H_2NCNH_2); FAB-MS (MH^+ = 398). Anal. $C_{22}H_{27}N_3O_4$ plus 1.0 H_2O and 1.0 CF_3CO_2H (C, N, H: calcd, 4.78; found, 4.10).

*β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-1,3-benzodioxole-5-propanoic acid (22a).* The title compound was prepared following general procedure B with the following modification: substitution of D,L-3-amino-3-(1,3-benzodioxole)-5-propanoic acid for ethyl D,L-3-amino-3-(4-ethoxyphenyl)propanoate–HCl in section 3 of procedure B; ^1H NMR (DMSO-d_6) 1.50 (*m*, 4H, 2-CH_2), 2.10 (*t*, *J* = 7 Hz, 2H, CH_2CO), 2.63 (*m*, 4H, Ar-CH_2 and $CHCH_2CO$), 5.05 (*m*, 1H, CHN), 5.97 (s, 2H, OCH_2O), 6.71–6.92 (*m*, 3H, PhH), 7.40 (*d*, *J* = 7 Hz, 2H, PhH), 7.70 (*d*, *J* = 7 Hz, 2H, PhH), 8.27 (*m*, 1H, NH), 8.85 and 9.15 (*br s*, 4H, H_2NCNH_2); FAB-MS (MH^+ = 412). Anal. $C_{22}H_{29}N_3O_5$ plus 1 H_2O and 1 CF_3CO_2H (H, N, C: calcd, 54.65; found, 55.09).

*β-[[[5-(*p*-Amidino)phenyl]-1-oxopentyl]amino]-2-pyridylpropanoic acid (23a).* The title compound was prepared following general procedure C with the following modification: substitution of D,L-3-amino-2-pyridylpropionic acid for ethyl D,L-3-amino-3-(4-ethoxyphenyl)propanoate–HCl in section 3 of procedure B: ^1H NMR (DMSO-d_6) 1.50 (*br*, 4H, 2-CH_2), 2.16 (*t*, *J* = 7 Hz, 2H, CH_2) 2.64 (*m*, 2H, CH_2) 2.84 (*q*, *J* = 7 Hz, 2H, CH_2) 5.28 (*m*, 1H, NCH), 7.38–7.49 (*m*, ArH), 7.39 (*d*, *J* = 7 Hz, 2H, PhH), 7.75 (*d*, *J* = 7 Hz, 2H, PhH), 7.85–7.93 (*m*, ArH), 8.48 (*d*, 1H, CONH), 8.55 (*m*, ArH), 9.02 and 9.27 (2*s*, 4H, H_2NCNH_2); FAB-MS (MH^+ = 369.0). Anal. $C_{20}H_{24}N_4O_3$ plus 1.9 CF_3CO_2H and H_2O (C, H, N).

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