Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 4, pp 693–705, 1997

Published by Elsevier Science Ltd
Printed in Great Britain
0968-0896/97 $17.00 + 0.00

PII: S0968-0896(97)00013-8

Design, Synthesis, and In Vitro Activities of Benzamide-Core Glycoprotein IIb/IIIa Antagonists: 2,3-Diaminopropionic Acid Derivatives as Surrogates of Aspartic Acid

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Abstract—In an effort to discover novel nonpeptide glycoprotein IIb/IIIa (GPIIb/IIIa, $\alpha_{IIb}/\beta 3$) inhibitors, we investigated RGD mimetics featuring a 3-substituted benzoic acid as the core, benzamidine as the basic moiety, and a series of β- and α-substituted β-alanine derivatives as aspartic acid surrogates. It was found that the use of β-methyl β-alanine slightly improved the anti-aggregant potency in human platelet-rich plasma over the unsubstituted β-alanine compound, while β-substitution with a trifluoromethyl group resulted in considerable loss in activity. Significant enhancement (up to 100-fold) in potency was obtained when the β-alanine was replaced with N^2-substituted L-2,3-diaminopropionic acid derivatives. Among the three types of α-substituents (carbamate, amide, and sulfonamide) investigated, no apparent preference was observed with respect to in vitro potency. However, alkyl groups were more favorable than arylalkyl groups (Cbz) in the carbamate analogues. We also investigated piperidine, piperazine, and *N*-formamidinopiperidine as replacements for the benzamidine moiety. The former two replacements led to a drop in potency while the latter replacement resulted in maintenance of activity as compared with the corresponding benzamidine analogue. © 1997 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd.

Introduction

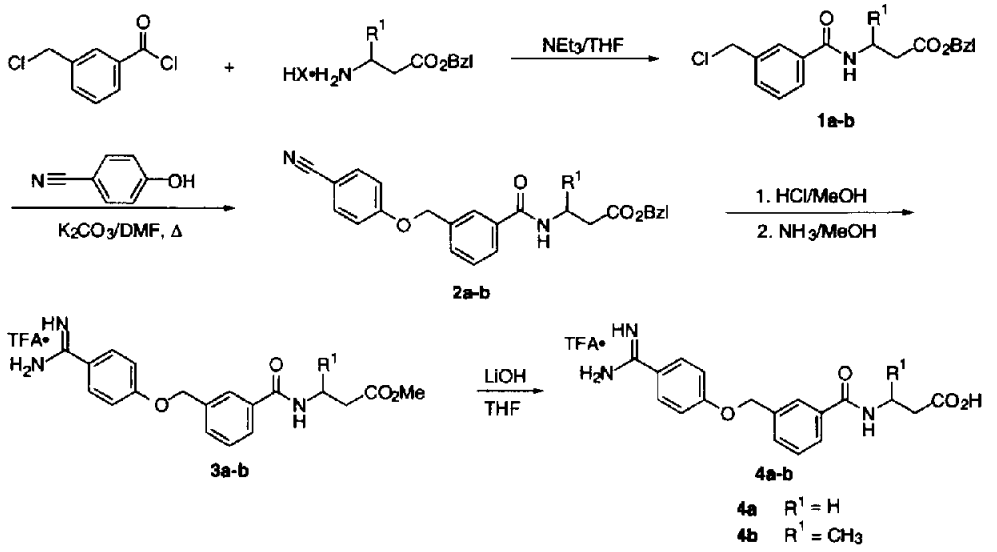
Glycoprotein IIb/IIIa is a heterodimeric membrane protein present on the surface of platelets, which mediates platelet adherence and aggregation.[1] In response to platelet stimulation by a variety of agonists, such as ADP, thrombin, and collagen, this protein undergoes a substantial conformational change that results in an increased affinity for fibrinogen, a multivalent plasma protein.[2,3] The binding of multiple GPIIb/IIIa molecules to a single molecule of fibrinogen leads to crosslinking of the platelets and thrombus formation, resulting in myocardial infarction, unstable angina, and ischemic stroke.[4,5] Thus, inhibition of platelet aggregation by selectively blocking the association of fibrinogen with GPIIb/IIIa represents an attractive antithrombotic strategy.

The interaction of GPIIb/IIIa and fibrinogen is mediated, at least in part, by the recognition by the activated receptor of a tripeptide motif present on fibrinogen,[6,7] the Arg-Gly-Asp (RGD) sequence, as evidenced by the inhibition of platelet aggregation in the presence of small RGD-containing peptides.[8–12] Thus, the RGD sequence has provided a starting point for the successful development of highly potent antagonists of GPIIb/IIIa, and a number of potent cyclic RGD-containing peptides and nonpeptide RGD mimetics have been reported as potential antithrombotics.[13] Although the nonpeptide inhibitors are structurally varied, they have in common a basic moiety that mimics the guanidine group of the arginine residue and a carboxylic acid that mimics the side-chain carboxylic acid of the aspartic acid residue.[14–22] Common surrogates of the guanidine residue include benzamidine and piperidine, while a β-alanine or β-substituted β-alanine have been used to replace the aspartic acid.

Since the discovery of the orally active cyclic peptide DMP 728,[23–25] we have focused our efforts on the identification of potent nonpeptide fibrinogen receptor antagonists. As part of our efforts, we were interested in novel surrogates of the aspartic acid residue of RGD. In this paper we report the synthesis and structure–activity relationships of a series of benzamide fibrinogen receptor antagonists featuring 2,3-diaminopropionic acid derivatives as surrogates of aspartic acid.

Chemistry

Compounds **4a** and **4b** were prepared using the method described in Scheme 1. Reaction of 3-chloromethylbenzoyl chloride with β-alanine benzyl ester or benzyl DL-3-aminobutyrate produced the intermediates **1a** and **1b**, respectively. Alkylation of 4-cyanophenol with **1a–b** using potassium carbonate in DMF at 80 °C yielded the ether compounds **2a–b**. Compounds **2a–b** were subjected to a Pinner reaction using saturated anhydrous HCl in methanol. Treatment of the resulting imidates

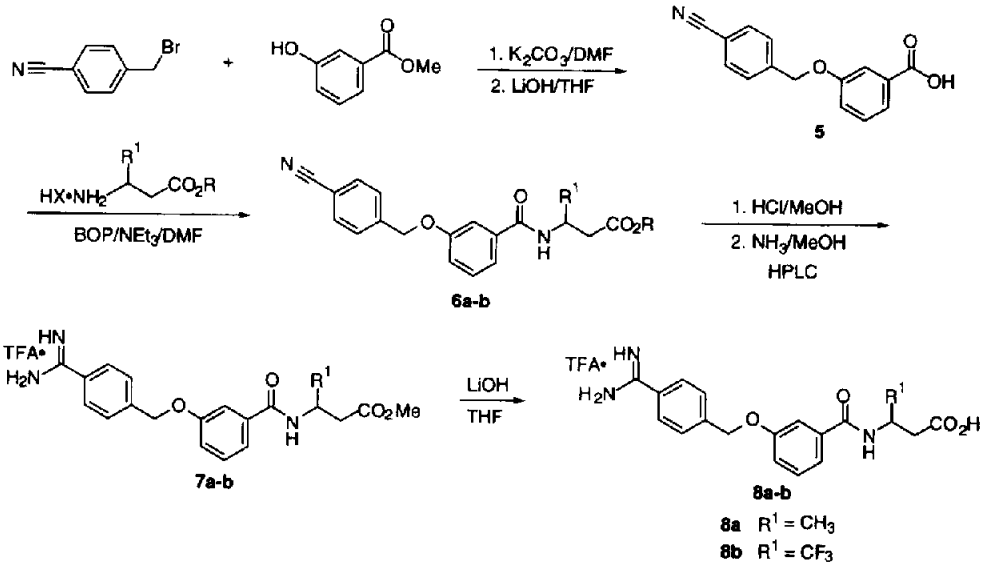


Scheme 1.

with anhydrous ammonia in methanol provided the benzamidine compounds **3a–b**. Under these conditions, the benzyl ester was transesterified with solvent methanol to give the methyl ester, as revealed by proton NMR. Saponification of **3a–b** afforded the carboxylic acid **4a–b**, which were isolated as TFA salts after reversed-phase HPLC purification.

Compounds **8a** and **8b** were synthesized using the procedures outlined in Scheme 2. Alkylation of methyl 3-hydroxybenzoic acid with 4-cyanobenzyl bromide followed by saponification yielded the carboxylic acid **5**. Coupling of **5** with benzyl 3-amino-DL-butyrate or methyl 3-amino-4,4,4-trifluoro-DL-butyrate gave the intermediates **6a** and **6b**, respectively. The cyano group was converted to an amidino group by a Pinner sequence to give the benzamidine compounds **7a–b**, which were isolated as TFA salts after purification by reversed-phase HPLC. Saponification of **7a–b** using LiOH produced the racemic products **8a–b**.

The synthesis of compounds containing diaminopropionic acid derivatives is shown in Scheme 3. Reaction of 3-chloromethylbenzoyl chloride with methyl N^2-benzyloxy-carbonyl-L-2,3-diaminopropionate **17a** (see Scheme 4) yielded the intermediate **9**, which was reacted with 4-cyanophenol to give **10**. The cyano group of **10** was converted to an amidine **11** using a Pinner sequence. We found that the Cbz group was removed under the acidic conditions necessary to form the imidate. Compound **11** was used as a common intermediate to synthesize a variety of analogues. Saponification of **11** produced the α-amino acid **12**. Selective acylation of **11** with alkyl chloroformate or di-*t*-butyl dicarbonate was achieved using sodium bicarbonate as base in a mixture solvent of water and acetonitrile to give carbamates

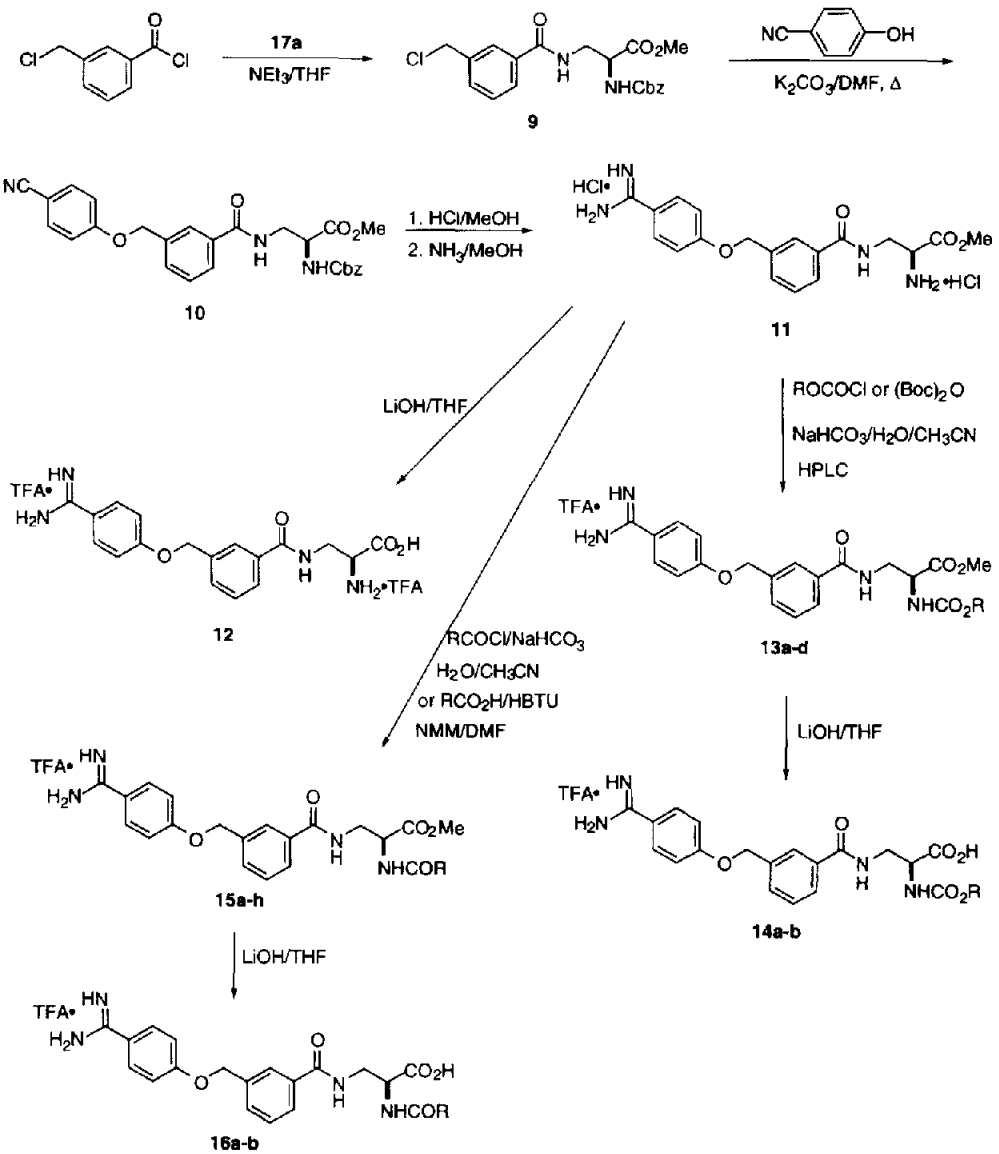


Scheme 2.

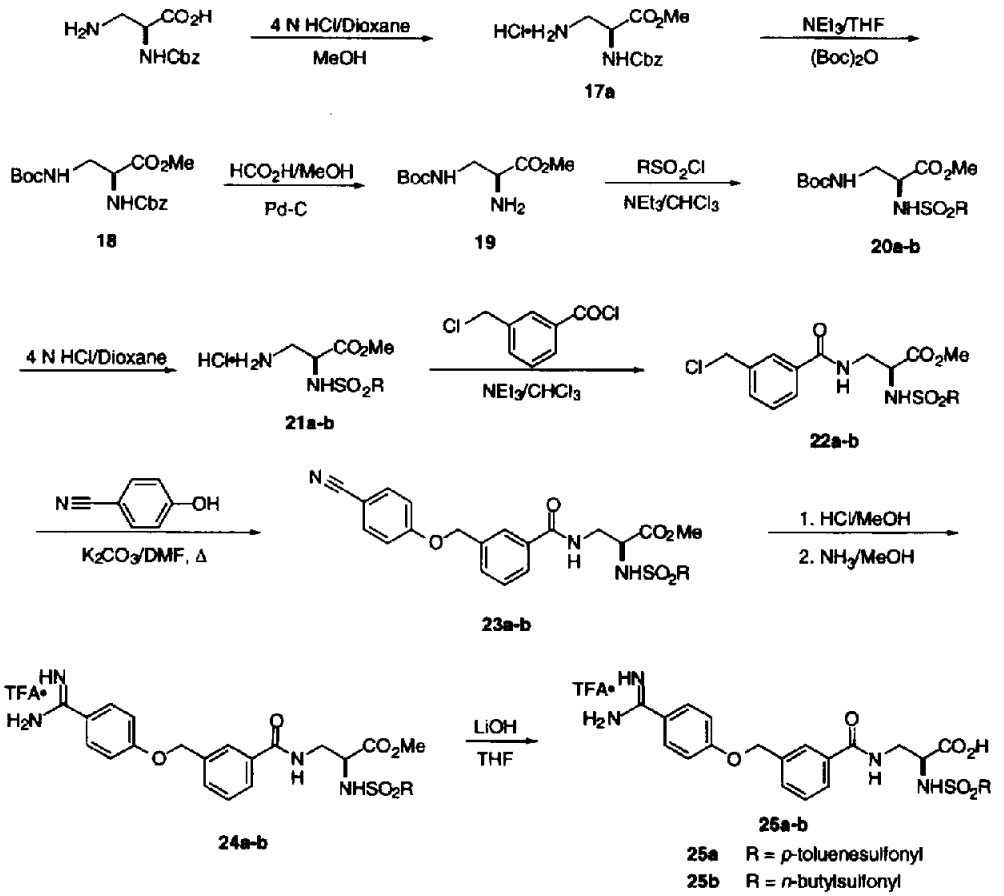
derivative **13a–d**. Under these conditions, the amidine is protonated and acylation at the amidine is blocked. Saponification of **13a–b** gave **14a–b**. Alternatively, compound **11** was selectively acylated using acyl chlorides under the same conditions or by using carboxylic acids in the presence of a coupling agent such as HBTU to give compounds **15a–h**. Saponification of **15a–b** afforded **16a–b**.

The toluenesulfonamide **25a** could be prepared from intermediate **11** using conditions similar to those shown in Scheme 3. However, attempts to synthesize the *n*-butyl-sulfonamide analogue **25b** using these conditions failed. Thus, a new synthetic route, depicted in Scheme 4, was developed for the synthesis of the sulfonamides. Commercially available N^2-Cbz-L-2,3-diaminopropionic acid was converted to its methyl ester **17a** using a Fisher esterification. The 3-amino group was protected using Boc anhydride to give **18**. Hydrogenation of **18** yielded **19**, which was reacted with *p*-toluenesulfonyl chloride or *n*-butanesulfonyl chloride to give **20a** and **20b**, respectively. The Boc group of **20a–b** was removed using HCl in dioxane and the resulting amines **21a–b** were coupled with 3-chloromethylbenzoyl chloride to afford amides **22a–b**, which were reacted with 4-cyanophenol to give **23a–b**. Amidine synthesis using the Pinner sequence, followed by saponification produced the final products **25a–b**.

The nonbenzamidine analogues **29a–b** and **30** were prepared using the procedures given in Scheme 5. Protection of the secondary amine of hydroxyalkyl piperidine or piperazine using di-*t*-butyl-di-carbonate yielded compounds **26a–c**. Alkylation of **26a–c** with ethyl 3-chloromethyl-benzoate, prepared by treatment of 3-chloromethylbenzoyl chloride with ethanol, gave the ether intermediates **27a–c**. Saponification of **27a–c** produced the carboxylic acids **28a–c**. Coupling of **28a–c** with methyl or ethyl N^2-Cbz-L-2,3-diaminopropionate followed by acidic deprotection of the Boc group



Scheme 3.



Scheme 4.

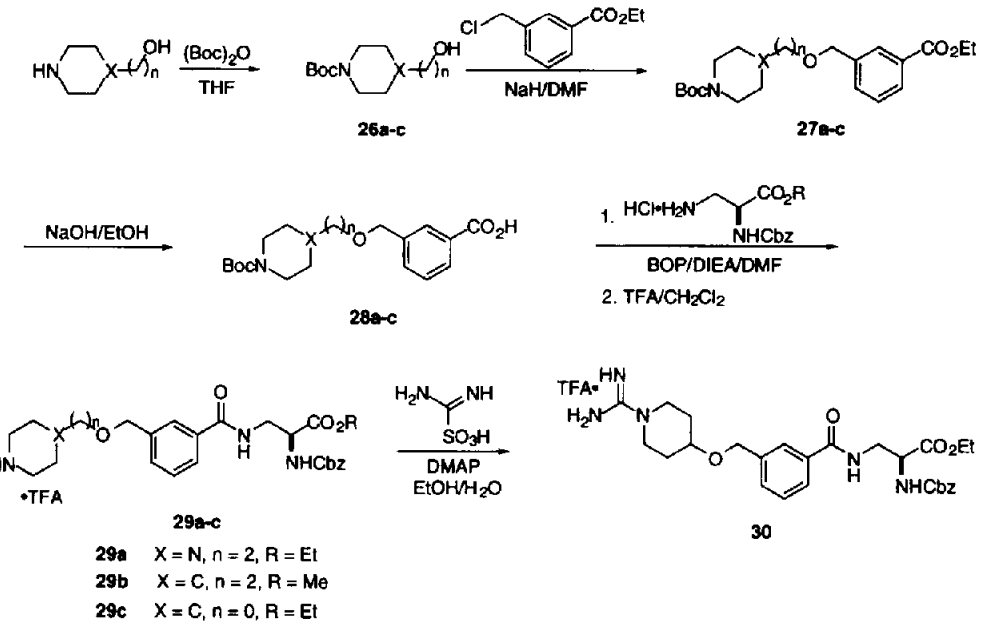
afforded compounds **29a–c**. Piperidine **29c** was converted to the *N*-amidino analogue using formamidinosulfonic acid to give compound **30**.

Results and Discussion

The cyclic RGD peptide DMP 728 is a potent GPIIb/IIIa inhibitor with oral activity in animal models of thrombosis.[23–25] Molecular modeling studies based on the conformation[26] of DMP 728 revealed that a rigid core such as a 1,3-disubstituted phenyl ring might be a good replacement of the arginine-glycine amide residue. Thus we targeted structure **I**[27] (Fig. 1) and compound **4a**, in which the linker between the benzamidine and the benzoic acid is an oxymethylene group, was prepared. Compound **4a** has weak activity in the human platelet-rich plasma (PRP) aggregation assay, with an IC_{50} of 4.4 ± 0.5 μM (Table 1). Our goal was to optimize compound **4a** (structure **II**, Fig. 1). Thus, replacement of the β-alanine in **4a** with a 3-amino-DL-butyric acid afforded the racemic compound **4b**, which is about threefold more potent than **4a**. Exchanging the oxygen with the methylene between the benzamidine and the benzamide core in **4b** provided compound **8a**, which possessed activity comparable to **4b**, indicating that the oxygen might not be involved in significant interaction with the fibrinogen receptor. Interestingly, replacement of the β-methyl group in **8a** with a trifluoromethyl group (**8b**) resulted in a 40-fold loss in activity.

The discovery by the Merck group of the significant improvement in activity resulting from the α-substituent in tyrosine derivative MK-383[28,29] attracted our interest. The effect of the α-substitution was suggested to be a result of an interaction of the substituent with an exosite in the receptor. We initiated our modifications at the α-position by incorporating an amino group into the β-alanine residue, which gave rise to a 2,3-diaminopropionic acid (structure **III**, Fig. 2).

The first diaminopropionic acid structure prepared was the free α-amine **12**, which demonstrated an activity fourfold greater than **4a**. Substitution of the α-amine with a benzyloxycarbonyl (Cbz) group resulted in compound **14a**, which is threefold more potent than compound **12**. Replacement of the Cbz group in **14a** with a *n*-butyloxycarbonyl group led to **14b**, which is 10-fold more potent than **14a** and approximately 100-fold more potent than parent compound **4a**. The *n*-butylcarbamate **14b** and the corresponding methyl ester **13b** showed comparable potency in the human PRP assay after incubation of the ester with pig liver esterases at 37 °C for 2 h, indicating that the ester was completely hydrolyzed to its free acid by the esterase prior to the assay. The conversion rate of **13b** to **14b** was also followed by HPLC analysis and it was



Scheme 5.

found that **13b** was completely hydrolyzed to **14b** within 30 min under those conditions. Thus, many of the analogues were assayed in the human PRP assay as methyl or ethyl esters following esterase treatment for 2 h. Two additional carbamate analogues, the *i*-butyl carbamate **13c** (methyl ester) and the *t*-butyl carbamate **13d**, demonstrated activity comparable to that of the corresponding *n*-butyl carbamate. Comparison of the inhibitory activities among the four carbamate compounds **14a**, **14b**, **13c**, and **13d** revealed the superiority of alkyl groups over arylalkyl group (Cbz).

In order to investigate if the oxygen of the alkyloxy group in the cabamate analogues is required for activity, *N*-acyl amide analogues were prepared. The preference for alkyl versus arylalkyl groups found in the carbamates was not observed in the amide analogues. Replacement of the oxygen of the benzyloxy group in **14a** with a methylene was accompanied by a twofold increase in potency (**16a**, IC_{50} = 0.23 ± 0.10 μM). However, no significant potency improvement arose from replacement of the phenylpropanoyl group with alkyl acyl groups, for example, butyroyl (**16b**, IC_{50} = 0.16 ± 0.04 μM) or pentanoyl (**15b**, IC_{50} = 0.10 ± 0.02 μM). In an attempt to enhance additional binding from the α-substituent, six carboxamide compounds (**15c–15h**) containing a pyridine ring were synthesized. The 2-pyridine carboxamide (**15c**), 3-pyridinecarboxamide

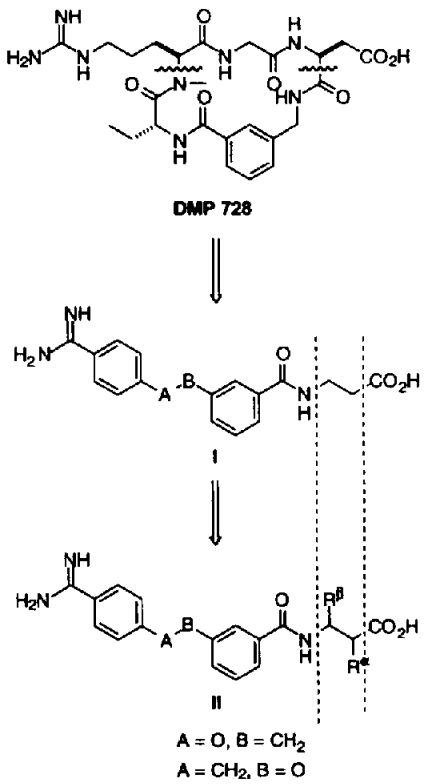


Figure 1.

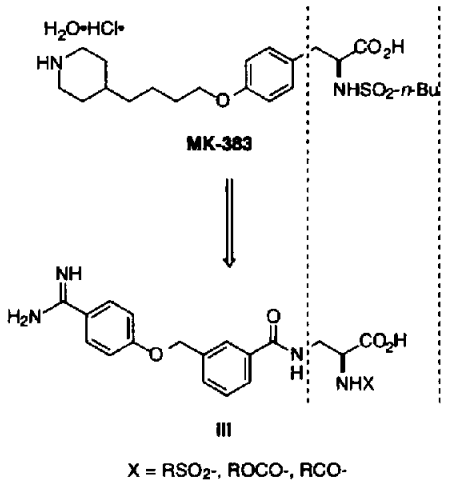


Figure 2.

(**15d**), and 4-pyridylacetamide (**15h**) were comparable in potency to the pentanoylamide **15b**. The remaining pyridine analogues **15e**, **15f**, and **15g** showed diminished activity as compared with **15b**. These results imply that no additional binding from the pyridine ring was obtained. However, a hydrophilic group is tolerated.

We synthesized two sulfonamide analogues, the *p*-toluenesulfonamide **25a**, and the *n*-butylsulfonamide **25b** (Table 1). The *p*-toluenesulfonamide **25a** was comparable in in vitro potency to the alkylcarbamates **13b–13d** while the *n*-butylsulfonamide **25b** was slightly less active than **25a**.

In order to determine the importance of the benzamidine moiety, attempts were made to replace the benzamidine with other basic groups at the *N*-terminus (Table 2). Using a Cbz group as the α-nitrogen substituent of the diaminopropionate, three nonbenzamidine moieties were evaluated. Replacement of the benzamidine with a piperazinoethyl group (**29a**, IC_{50} = 3.9 ± 0.43 μM) resulted in a 10-fold drop in potency as compared with **14a**. The piperidin-4-ylethyl analogue **29b** exhibited a slight improvement over **29a** but was still sixfold less active than **14a**. Potency was restored when an *N*-amidinopiperidin-4-yl group (**30**) was used as the replacement of the benzamidine. Thus, in this series, it appears that benzamidine and *N*-amidinopiperidine represent the optimal guanidine surrogates.[30]

Conclusions

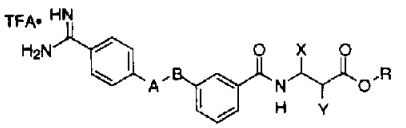
Using a 3-substituted benzoic acid as the core and a benzamidine as the basic moiety of the nonpeptide template, we have successfully employed L-2,3-diaminopropionic acid derivatives as surrogates of aspartic acid. The use of N^2-alkyloxycarbonyl L-2,3-diaminopropionic acid derivatives resulted in an approximately 100-fold improvement in in vitro potency over the β-alanine parent. No apparent preference among the three types of α-substituents (carbamate, amide, and sulfonamide) investigated was observed in terms of in vitro potency. However, a shape preference was observed among the carbamates evaluated, with the alkyl groups demonstrating higher potency than the arylalkyl (Cbz) group. The use of N^2-alkyloxycarbonyl-L-2,3-diaminopropionic acid derivatives as Asp surrogates in other series of nonpeptide GPIIb/IIIa receptor antagonists has recently been investigated in these laboratories[31-33] and will be described in more detail in the near future.

Experimental

General experimental

Proton NMR data were obtained on a Varian Unity 300 spectrometer and are referenced to TMS. Mass spectra were recorded on VG Trio 2000 (ESI) or VG 70-VSE (high resolution) mass spectrometers. Combustion

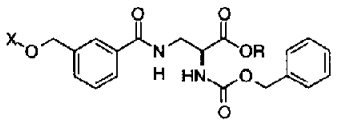
Table 1. Compounds with phenyl ring as the core and benzamidine as the basic moiety

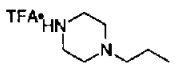
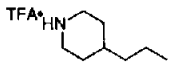
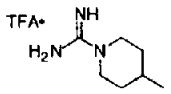


Compd	A	B	X	Y	R[a]	Human PRP IC_{50} ± SEM (μM)[b]
4a	O	CH_2	H	H	H	4.4 ± 0.5
4b	O	CH_2	CH_3	H	H	1.3 ± 0.2
8a	CH_2	O	CH_3	H	H	1.0 ± 0.2
8b	CH_2	O	CF_3	H	H	40 ± 1
12	O	CH_2	H	NH_2	H	1.0 ± 0.2
13b	O	CH_2	H	$NHCO_2(CH_2)_3CH_3$	Me	0.032 ± 0.005
13c	O	CH_2	H	$NHCO_2CH_2CH(CH_3)_2$	Me	0.042 ± 0.010
13d	O	CH_2	H	$NHCO_2C(CH_3)_3$	Me	0.07 ± 0.01
14a	O	CH_2	H	NHCbz	H	0.32 ± 0.04
14b	O	CH_2	H	$NHCO_2(CH_2)_3CH_3$	H	0.04 ± 0.01
15b	O	CH_2	H	$NHCO(CH_2)_3CH_3$	Me	0.10 ± 0.02
15c	O	CH_2	H	NHCO-2-Py	Me	0.11 ± 0.03
15d	O	CH_2	H	NHCO-3-Py	Me	0.075 ± 0.030
15e	O	CH_2	H	NHCO-4-Py	Me	0.38 ± 0.02
15f	O	CH_2	H	$NHCOCH_2$-2-Py	Me	0.25 ± 0.05
15g	O	CH_2	H	$NHCOCH_2$-3-Py	Me	0.59 ± 0.05
15h	O	CH_2	H	$NHCOCH_2$-4-Py	Me	0.10 ± 0.05
16a	O	CH_2	H	$NHCO(CH_2)_2Ph$	H	0.23 ± 0.10
16b	O	CH_2	H	$NHCO(CH_2)_2CH_3$	H	0.16 ± 0.04
25a	O	CH_2	H	$NHSO_2$-*p*-Toluene	H	0.055 ± 0.010
25b	O	CH_2	H	$NHSO_2(CH_2)_3CH_3$	H	0.19 ± 0.08

[a]Esters were treated with liver esterases (pigs) prior to the platelet aggregation test. See Experimental for detail.
[b]Inhibition of ADP-induced platelet aggregation was determined in three donors. See Experimental for assay protocol.

Table 2. Compounds with nonbenzamidine as the basic moiety



Compd	X	R[a]	Human PRP IC_{50} ± SEM (μM)[b]
29a		Et	3.9 ± 0.4
29b		Me	2.5 ± 0.8
30		Et	0.53 ± 0.13

[a]See footnote a in Table 1.
[b]See footnote b in Table 1.

analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Analytical HPLC were run on a HP 1090 system using a Vydac C_{18} column and a gradient of water (0.05% TFA) and acetonitrile (0.05% TFA). Preparative HPLC were performed on a Rainin system using a Vadac C_{18} column and a gradient of water (0.05% TFA) and acetonitrile (0.05% TFA).

Benzyl *N*-(3-chloromethylbenzoyl)-3-aminopropionate (1a). To a solution of 3-chloromethylbenzoyl chloride (3 mmol, 0.426 mL) and benzyl 3-aminopropionate toluenesulfonic acid salt (3.2 mmol, 1.12 g) in 10 mL of chloroform cooled in an ice bath was added triethylamine (7 mmol, 0.98 mL) and the solution was stirred for 2 h and then concentrated. The residue was taken up in ethyl acetate and washed with dilute citric acid, brine, sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated. Crystallization from ether–petroleum ether gave 0.9 g (90%) of the title compound as a crystalline solid. ^{1}H NMR (DMSO-d_6) δ 8.62 (t, 1H), 7.88 (s, 1H), 7.78 (d, 1H), 7.46 (t, 1H), 7.32 (m, 5H), 5.10 (s, 2H), 4.80 (s, 2H), 3.52 (m, 2H), 3.65 (t, 2H). Anal. calcd for $C_{18}H_{18}NO_3Cl$: C, 65.16; H, 5.48; N, 4.22. Found: C, 64.91; H, 5.29; N, 3.99.

Benzyl *N*-(3-(4-cyanophenyloxymethyl)benzoyl)-3-aminopropionate (2a). A mixture of **1a** (2.5 mmol, 829 mg), 4-cyanophenol (2.5 mmol, 298 mg), and potassium carbonate (5 mmol, 691 mg) in 15 mL of DMF was stirred at 80 °C for 5 h and then cooled to room temperature. Dilute citric acid solution was added followed by ethyl acetate. The organic phase was separated, washed with dilute citric acid, brine, sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated to give 1 g (97%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) δ 8.62 (t, 1H), 7.92 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.50 (t, 1H), 7.32 (m, 5H), 7.20 (d, 2H), 5.24 (s, 2H), 5.10 (s, 2H), 3.52 (m, 2H), 2.66 (t, 2H). Anal. calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.77. Found: C, 72.28; H, 5.21; N, 6.60.

Methyl *N*-(3-(4-amidinophenyloxymethyl)benzoyl)-3-aminopropionate TFA salt (3a). Dry HCl gas was bubbled through a solution of compound **2a** (2 mmol, 830 mg) in 20 mL of methanol for 1 h in an ice bath. The solution was stirred for 1 h at room temperature and then concentrated. The residue was taken up in 20 mL of 2 M ammonia in methanol and the solution was stirred for 5 h and then concentrated. The residue was taken up in methanol and water. The solution was filtered and purified on reversed-phase HPLC to give 650 mg (69%) of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.18 (s, 2H), 8.90 (s, 2H), 8.62 (t, 1H), 7.85 (s, 1H), 7.82 (d, 2H), 7.80 (d, 1H), 7.61 (d, 1H), 7.50 (t, 3H), 7.24 (d, 2H), 5.30 (s, 2H), 3.60 (s, 3H), 3.50 (m, 2H), 2.60 (t, 2H). Anal. calcd for $C_{21}H_{22}N_3O_6F_3 \cdot H_2O$: C, 51.74; H, 4.96; N, 8.62. Found: C, 51.93; H, 4.70; N, 8.49.

***N*-(3-(4-Amidinophenyloxymethyl)benzoyl)-3-aminopropionic acid TFA salt (4a).** Compound **3a** (0.21 mmol, 100 mg) was dissolved in 2 mL of THF and 2 mL of 1 N LiOH and after 1 h the solution was acidified with TFA to pH 3. Purification on reversed-phase HPLC gave 85 mg (88%) of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.18 (s, 2H), 8.90 (s, 2H), 8.62 (t, 1H), 7.85 (s, 1H), 7.82 (d, 2H), 7.80 (d, 1H), 7.61 (d, 1H), 7.50 (t, 3H), 7.24 (d, 2H), 5.30 (s, 2H), 3.45 (m, 2H), 2.50 (t, 2H). ESI–MS $(M + H)^+$: calcd 342.2; found 342.2. Anal. calcd for $C_{20}H_{20}N_3O_6F_3 \cdot 0.3TFA$: C, 50.53; H, 4.18; N, 8.58. Found: C, 50.50; H, 4.30; N, 8.63.

Benzyl *N*-(3-chloromethylbenzoyl)-DL-3-aminobutyrate (1b). To a solution of 3-chloromethylbenzoyl chloride (10 mmol, 1.42 mL) and benzyl DL-3-aminobutyrate toluenesulfonic acid salt (10.5 mmol, 3.84 g) in 30 mL of chloroform cooled in an ice bath was added triethylamine (21 mmol, 2.93 mL) and the solution was stirred for 2 h and then concentrated. The residue was taken up in ethyl acetate and washed with dilute citric acid, brine, sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated. Crystallization from ether–petroleum ether gave 2.9 g (84%) of the title compound as a crystalline solid. ^{1}H NMR (DMSO-d_6) δ 8.41 (d, 1H), 7.88 (s, 1H), 7.78 (d, 1H), 7.59 (d, 1H), 7.48 (t, 1H), 7.32 (m, 5H), 5.06 (s, 2H), 4.80 (s, 2H), 4.42 (m, 1H), 2.62 (m, 2H), 1.20 (d, 3H). Anal. calcd for $C_{19}H_{20}NO_3Cl$: C, 65.99; H, 5.84; N, 4.05. Found: C, 65.61; H, 5.82; N, 4.10.

Benzyl *N*-(3-(4-cyanophenyloxymethyl)benzoyl)-DL-3-aminobutyrate (2b). A solution of **1b** (5 mmol, 1.73 g), 4-cyanophenol (5 mmol, 596 mg), and potassium carbonate (10 mmol, 1.38 g) in 10 mL of DMF was heated at 60 °C for 18 h and then cooled to room temperature. Dilute citric acid solution was added followed by ethyl acetate. The organic phase was separated, washed with dilute citric acid, brine, sodium

bicarbonate, and brine, dried ($MgSO_4$), and concentrated to give 2.1 g (98%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) δ 8.40 (d, 1H), 7.90 (s, 1H), 7.78 (m, 3H), 7.61 (d, 1H), 7.48 (t, 1H), 7.28 (m, 5H), 7.20 (d, 2H), 5.23 (s, 2H), 5.04 (s, 2H), 4.41 (m, 1H), 2.62 (m, 2H), 1.20 (d, 3H). Anal. calcd for $C_{26}H_{24}N_2O_4 \cdot 0.3H_2O$: C, 71.96; H, 5.71; N, 6.45. Found: C, 71.85; H, 5.52; N, 6.35.

Methyl *N*-(3-(4-amidinophenyloxymethyl)benzoyl)-DL-3-aminobutyrate TFA salt (3b). Compound **2b** (2 mmol, 857 mg) was dissolved in 20 mL of methanol and 20 mL of 4 N HCl in dioxane. The mixture was stirred for 24 h and then concentrated. The residue was taken up in 20 mL of 2 M ammonia in methanol and the solution was stirred overnight and then concentrated. The residue was dissolved in DMF and the solution was filtered, diluted with water, and purified by reversed-phase HPLC to give 100 mg of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 2H), 8.94 (s, 2H), 8.40 (d, 1H), 7.90 (s, 1H), 7.81 (d, 2H), 7.80 (d, 1H), 7.61 (d, 1H), 7.50 (t, 1H), 7.25 (d, 2H), 5.30 (s, 2H), 4.38 (m, 1H), 3.59 (s, 3H), 2.58 (m, 2H), 1.20 (d, 3H). Anal. calcd for $C_{22}H_{24}N_3O_6F_3$: C, 54.66; H, 5.00; N, 8.69. Found: C, 54.79; H, 5.08; N, 8.61.

***N*-(3-(4-Amidinophenyloxymethyl)benzoyl)-DL-3-aminobutyric acid TFA salt (4b).** Compound **3b** (40 mg) was dissolved in 1 mL of THF and 1 mL of 1 N LiOH and after 2 h, the solution was acidified with HCl to pH 3. Purification on reversed-phase HPLC gave 30 mg of the title compound as a powder after lyophilization. δ 9.16 (s, 2H), 8.94 (s, 2H), 8.40 (d, 1H), 7.90 (s, 1H), 7.81 (d, 2H), 7.80 (d, 1H), 7.61 (d, 1H), 7.50 (t, 1H), 7.25 (d, 2H), 5.30 (s, 2H), 4.30 (m, 1H), 2.45 (m, 2H), 1.20 (d, 3H). ESI–MS $(M + H)^+$: calcd 356.2; found 356.2. Anal. calcd for $C_{21}H_{22}N_3O_6F_3 \cdot 0.5H_2O$: C, 52.72; H, 4.94; N, 8.78. Found: C, 52.71; H, 4.68; N, 8.65.

3-(4-Cyanobenzyloxy)benzoic acid (5). A mixture of 4-cyanobenzyl bromide (40 mmol, 7.84 g), methyl 3-hydroxybenzoate (40 mmol, 6.08 g), and potassium carbonate (60 mmol, 8.29 g) in 50 mL of DMF was stirred at 60 °C overnight and the solution was cooled to room temperature. To it was added dilute citric acid followed by ethyl acetate. The organic layer was separated, washed with brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give a solid. The solid was washed with ether twice and dissolved in 50 mL of THF, and to it was added 30 mL of 1 N LiOH. The solution was stirred for 5 h and acidified with 1 N HCl to give a solid. The solid was isolated by filtration and washed with water to give 5.8 g (60%) of the title compound. ^{1}H NMR (DMSO-d_6) δ 7.88 (d, 2H), 7.68 (d, 2H), 7.58 (m, 2H), 7.43 (t, 1H), 7.30 (dd, 1H), 5.32 (s, 2H). Anal. calcd for $C_{15}H_{11}NO_3 \cdot 1.7HCl$: C, 57.13; H, 4.05; N, 4.44. Found: C, 57.08; H, 3.71; N, 4.23.

Benzyl *N*-(3-(4-cyanobenzyloxy)benzoyl)-DL-3-aminobutyrate (6a). To a solution of **5** (4 mmol, 1.01 g) and benzyl DL-3-aminobutyrate toluenesulfonic acid salt (4.2 mmol, 1.53 g) in 10 mL of DMF were added BOP (4.2 mmol, 1.53 g) and triethylamine (15 mmol, 2.1 mL) and the solution was stirred overnight. Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with dilute citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to give 1.6 g (94%) of the desired product as an oil. ^{1}H NMR (DMSO-d_6) δ 8.35 (d, 1H), 7.86 (d, 2H), 7.65 (d, 2H), 7.18–7.45 (m, 9H), 5.26 (s, 2H), 5.08 (s, 2H), 4.40 (m, 1H), 2.64 (m, 2H), 1.18 (d, 3H). Anal. calcd for $C_{26}H_{24}N_2O_4 \cdot 0.5H_2O$: C, 71.37; H, 5.76; N, 6.40. Found: C, 71.22; H, 5.72; N, 6.31.

Methyl *N*-(3-(4-amidinobenzyloxy)benzoyl)-DL-3-aminobutyrate TFA salt (7a). Dry HCl gas was bubbled through a solution of **6a** (2 mmol, 857 mg) in 30 mL of methanol in an ice bath for 1 h and the solution was stirred overnight at room temperature and then concentrated. The residue was taken up in 30 mL of methanol through which ammonia gas was bubbled in an ice bath for 1 h. The mixture was stirred overnight at room temperature and then concentrated. The solid was washed with ether and dissolved in DMF and water. Purification on reversed-phase HPLC gave 240 mg of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 2H), 9.02 (s, 2H), 8.31 (d, 1H), 7.82 (d, 2H), 7.68 (d, 2H), 7.18–7.45 (m, 4H), 5.30 (s, 2H), 4.34 (m, 1H), 3.58 (s, 3H), 2.58 (m, 2H), 1.18 (d, 3H). Anal. calcd for $C_{22}H_{24}N_3O_6F_3$: C, 54.66; H, 5.00; N, 8.69. Found: C, 54.87; H, 5.15; N, 8.73.

***N*-(3-(4-amidinobenzyloxy)benzoyl)-DL-3-aminobutyric acid TFA salt (8a).** Compound **7a** (50 mg) was dissolved in 2 mL of THF and 2 mL of 1 N LiOH and after 1 h, the solution was acidified with TFA to pH 3. Purification by reversed-phase HPLC gave 40 mg of the desired product as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.30 (s, 2H), 9.02 (s, 2H), 8.31 (d, 1H), 7.82 (d, 2H), 7.68 (d, 2H), 7.18–7.45 (m, 4H), 5.30 (s, 2H), 4.30 (m, 1H), 2.50 (m, 2H), 1.16 (d, 3H). ESI–MS $(M + H)^+$: calcd 356.2; found 356.2. Anal. calcd for $C_{21}H_{22}N_3O_6F_3 \cdot H_2O$: C, 51.74; H, 4.96; N, 8.62. Found: C, 51.78; H, 4.63; N, 8.64.

Methyl *N*-(3-(4-cyanobenzyloxy)benzoyl)-DL-3-amino-4,4,4-trifluorobutyrate (6b). DL-3-Amino-4,4,4-trifluorobutyric acid (19.1 mmol, 3 g) was dissolved in 20 mL of methanol and 20 mL of 4 N HCl in dioxane. The solution stood at room temperature overnight and then concentrated to give 4.2 g (100%) of the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 9.58 (b, 3H), 4.50 (m, 1H), 3.68 (s, 3H), 3.02 (m, 2H).

The above ester was coupled with compound **5** using the procedure as described for **6a**. ^{1}H NMR (DMSO-d_6) δ 8.92 (d, 1H), 7.88 (d, 2H), 7.68 (d, 2H), 7.5 (m, 3H), 7.24 (dd, 1H), 5.28 (s, 2H), 5.18 (m, 1H), 3.61 (s, 1H), 2.95 (d, 2H). Anal. calcd for $C_{20}H_{17}N_2O_4F_3$: C, 59.12; H, 4.22; N, 6.89. Found: C, 59.07; H, 4.09; N, 6.76.

***N*-(3-(4-Amidinobenzyloxy)benzoyl)-DL-3-amino-4,4,4-trifluorobutyric acid TFA salt (8b).** This compound

was prepared from **6b** using the procedure as described for **8a**. ^{1}H NMR (DMSO-d_6) δ 9.32 (s, 2H), 9.12 (s, 2H), 8.88 (d, 1H), 7.84 (d, 2H), 7.70 (d, 2H), 7.48 (m, 3H), 7.24 (d, 1H), 5.32 (s, 2H), 5.12 (m, 1H), 2.82 (d, 2H). ESI–MS $(M + H)^+$: calcd 410.2; found 410.2. Anal. calcd for $C_{21}H_{19}N_3O_6F_6 \cdot 0.8H_2O$: C, 46.89; H, 3.86; N, 7.81. Found: C, 46.70; H, 3.60; N, 7.57.

Methyl N^2-Cbz-L-2,3-diaminopropionate HCl salt (17a). N^2-Cbz-L-2,3-diaminopropionic acid (10 mmol, 2.39 g) was dissolved in 20 mL of methanol and 20 mL of 4 N HCl in dioxane and the solution was stirred for 2 h and then concentrated to give 2.74 g (95%) of the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 8.38 (b, 3H), 7.96 (d, 1H), 7.38 (m, 5H), 5.05 (s, 2H), 4.44 (m, 1H), 3.66 (s, 3H), 3.14 (m, 2H). Anal. calcd for $C_{12}H_{17}N_2O_4Cl$: C, 49.92; H, 5.93; N, 9.70. Found: C, 49.63; H, 5.84; N, 9.68.

Methyl N^2-Cbz-N^3-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (9). To a solution of 3-chloromethylbenzoyl chloride (5 mmol, 0.71 mL) and **17a** (5.3 mmol, 1.53 g) in 20 mL of chloroform cooled in an ice bath was added triethylamine (11 mmol, 1.53 mL). The solution was stirred for 3 h and then concentrated. The residue was taken up in ethyl acetate and the solution was washed with citric acid, brine, sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated to give 2.1 g (100%) of the title compound as an oil. ^{1}H NMR (DMSO-d_6) δ 8.62 (t, 1H), 7.86 (s, 1H), 7.79 (d, 1H), 7.60 (d, 1H), 7.48 (t, 1H), 7.34 (m, 5H), 5.02 (s, 2H), 4.82 (s, 2H), 4.35 (m, 1H), 3.62 (s, 3H), 3.55 (m, 2H). Anal. calcd for $C_{20}H_{21}N_2O_5Cl \cdot 0.1H_2O$: C, 59.06; H, 5.25; N, 6.89. Found: C, 58.91; H, 5.15; N, 6.73.

Methyl N^2-Cbz-N^3-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (10). A solution of **9** (5 mmol, 2.0 g), 4-cyanophenol (5 mmol, 596 mg), and potassium carbonate (8 mmol, 1.1 g) in 10 mL of DMF was heated at 80 °C for 16 h and then cooled to room temperature. Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with citric acid, brine, sodium bicarbonate, and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column using ethyl acetate/hexane gave 1.35 g (55%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) δ 8.61 (t, 1H), 7.91 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.34 (m, 5H), 7.20 (d, 2H), 5.25 (s, 2H), 5.02 (s, 2H), 4.34 (m, 1H), 3.61 (s, 3H), 3.60 (m, 2H). Anal. calcd for $C_{27}H_{25}N_3O_6$: C, 66.52; H, 5.18; N, 8.63. Found: C, 66.62; H, 5.17; N, 8.47.

Methyl N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate di-HCl salt (11). Dry HCl gas was bubbled through a solution of compound **10** (22.5 mmol, 11 g) in 100 mL of methanol in an ice bath for 1 h. The solution was stirred overnight at room temperature and concentrated. The residue was taken up in 100 mL of methanol through which ammonia gas was bubbled at 0 °C for 30 min. The solution was stirred for 5 h and concentrated to give 12 g of crude product which was used as described below.

N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid di-TFA salt (12). Compound **11** (100 mg) was treated with 1 mL of THF and 0.5 mL of 1 N LiOH for 1 h and then acidified with acetic acid. Purification using reversed-phase HPLC gave 15 mg of the title compound as a powder after lyophilization. ESI–MS $(M + H)^+$: calcd 357.2; found 357.1. Anal. calcd for $C_{22}H_{22}N_4O_8F_6 \cdot 0.5H_2O$: C, 44.65; H, 3.91; H, 9.44. Found: C, 44.65; H, 4.03; N, 9.56.

Methyl N^2-Cbz-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (13a). Compound **11** (2 mmol, 860 mg) was dissolved in 3 mL of water and 3 mL of acetonitrile and the solution was cooled in an ice bath. To it was added sodium bicarbonate (5 mmol, 160 mg) followed by benzyl chloroformate (2 mmol, 340 mg) and the solution was stirred for 2 h and acidified with acetic acid. Purification on reversed-phase HPLC gave 345 mg (28%) of the desired product as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 2H), 8.92 (s, 2H), 7.91 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.34 (m, 5H), 7.22 (d, 2H), 5.30 (s, 2H), 5.02 (s, 2H), 4.35 (m, 1H), 3.61 (s, 3H), 3.60 (m, 2H). Anal. calcd for $C_{29}H_{29}N_4O_8F_3 \cdot 0.5H_2O$: C, 55.49; H, 4.82; N, 8.93. Found: C, 55.29; H, 4.80; N, 8.79.

N^2-Cbz-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (14a). Compound **13a** (50 mg) was dissolved in 2 mL of THF and 2 mL of 1 N LiOH, and after 1 h the solution was acidified with HCl. Purification on reversed-phase HPLC gave 30 mg of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 2H), 8.92 (s, 2H), 7.91 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.34 (m, 5H), 7.22 (d, 2H), 5.30 (s, 2H), 5.00 (s, 2H), 4.30 (m, 1H), 3.54 (m, 2H). ESI–MS $(M+H)^+$: calcd 491.2; found 491.2. Anal. calcd for $C_{28}H_{27}N_4O_8F_3 \cdot 0.2TFA$: C, 54.37; H, 4.37; N, 8.93. Found: C, 54.10; H, 4.23; N, 9.17.

Methyl N^2-*n*-butyloxycarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (13b). This compound was synthesized in a similar way as for compound **13a**.^{1}H NMR (DMSO-d_6) δ 9.15 (s, 2H), 8.92 (s, 2H), 8.62 (t, 1H), 7.92 (s, 1H), 7.81 (d, 2H), 7.79 (d, 1H), 7.62 (d, 1H), 7.57 (d, 1H), 7.50 (t, 1H), 7.24 (d, 2H), 5.30 (s, 2H), 4.28 (m, 1H), 3.95 (t, 2H), 3.60 (s, 3H), 3.59 (m, 2H), 1.50 (m, 2H), 1.30 (m, 2H), 0.86 (t, 3H). Anal. calcd for $C_{26}H_{31}N_4O_8F_3 \cdot 0.2TFA$: C, 52.20; H, 5.18; N, 9.22. Found: C, 52.56; H, 5.01; N, 8.88.

N^2-*n*-butyloxycarbonyl-N^3-(3-(4-amidinophenyloxymethyl)-benzoyl)-L-2,3-diaminopropionic acid TFA salt (14b). This compound was prepared from saponification of **13b** using LiOH and purification on HPLC. ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 2H), 8.92 (s, 2H), 8.62 (t, 1H), 7.92 (s, 1H), 7.81 (d, 2H), 7.79 (d, 1H), 7.62 (d, 1H), 7.57 (d, 1H), 7.50 (t, 1H), 7.24 (d, 2H), 5.30 (s, 2H), 4.19 (m, 1H), 3.92 (t, 2H), 3.57 (m, 2H), 1.50 (m, 2H), 1.30 (m, 2H), 0.86 (t, 3H). ESI–MS

$(M + H)^+$: calcd 457.3; found 457.2. Anal. calcd for $C_{25}H_{29}N_4O_8F_3 \cdot 0.2H_2O$: C, 52.72; H, 4.94; N, 8.78. Found: C, 52.71; H, 4.68; N, 8.65.

Methyl N^2-*i*-butyloxycarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (13c). This compound was prepared in a manner analogous to that for compound **13a**. ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 2H), 8.92 (s, 2H), 8.62 (t, 1H), 7.92 (s, 1H), 7.81 (d, 2H), 7.79 (d, 1H), 7.62 (d, 1H), 7.57 (d, 1H), 7.50 (t, 1H), 7.24 (d, 2H), 5.30 (s, 2H), 4.28 (m, 1H), 3.75 (d, 2H), 3.60 (s, 3H), 3.59 (m, 2H), 1.80 (m, 1H), 0.86 (d, 6H). ESI–MS $(M + H)^+$: calcd 471.2; found 471.2. Anal. calcd for $C_{26}H_{31}N_4O_8F_3 \cdot 0.1TFA$: C, 53.42; H, 5.35; N, 9.58. Found: C, 52.78; H, 5.26; N, 9.40. Found: C, 52.80; H, 5.16; N, 9.50.

Methyl N^2-*t*-butyloxycarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (13d). This compound was prepared in a manner analogous to that for compound **13a**. High-resolution ESI–MS $(M + H)^+$: calcd 471.2257; found 471.2264. Anal. calcd for $C_{26}H_{31}N_4O_8F_3 \cdot 0.8TFA \cdot H_2O$: C, 47.78; H, 4.91; N, 8.08. Found: C, 47.41; H, 4.94; N, 8.04.

Methyl N^2-(3-phenylpropionyl)-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (15a). This compound was synthesized using a similar procedure as for **13a** from reaction of **11** with 3-phenylpropionyl chloride. ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 2H), 8.90 (s, 2H), 8.64 (t, 1H), 8.35 (d, 1H), 7.91 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.63 (d, 1H), 7.52 (t, 1H), 7.20 (m, 7H), 5.30 (s, 2H), 4.50 (m, 1H), 3.59 (s, 3H), 3.56 (m, 2H), 2.80 (m, 2H), 2.44 (m, 2H). Anal. calcd for $C_{30}H_{31}N_4O_7F_3 \cdot 0.3H_2O$: C, 57.92; H, 5.12; N, 9.00. Found: C, 57.62; H, 4.91; N, 8.72.

N^2-(3-Phenylpropionyl)-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (16a). This compound was prepared from saponification of **15a** and purification on HPLC. ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 2H), 8.90 (s, 2H), 8.64 (t, 1H), 8.35 (d, 1H), 7.91 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.63 (d, 1H), 7.52 (t, 1H), 7.20 (m, 7H), 5.30 (s, 2H), 4.43 (m, 1H), 3.52 (m, 2H), 2.80 (m, 2H), 2.44 (m, 2H). ESI–MS $(M + H)^+$: calcd 489.3; found 489.2. Anal. calcd for $C_{29}H_{29}N_4O_7F_3 \cdot 0.4TFA$: C, 55.21; H, 4.57; N, 8.64. Found: C, 55.11; H, 4.59; N, 8.62.

N^2-Butyryl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (16b). This compound was synthesized using a similar procedure as for compound **16a**. ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 2H), 8.93 (s, 2H), 8.63 (t, 1H), 8.24 (d, 1H), 7.92 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.22 (d, 2H), 5.30 (s, 2H), 4.40 (m, 1H), 3.56 (m, 2H), 2.08 (t, 2H), 1.50 (m, 2H), 0.82 (t, 3H). ESI–MS $(M + H)^+$: calcd 427.2; found 427.1. Anal. calcd for $C_{24}H_{27}N_4O_7F_3 \cdot 0.6H_2O$: C, 49.70; H, 4.59; N, 9.20. Found: C, 49.83; H, 4.66; N, 8.93.

N^2-Pentanoyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15b). This compound was prepared using a manner analogous to that for **15a**. ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 2H), 8.93 (s, 2H), 8.63 (t, 1H), 8.24 (d, 1H), 7.92 (s, 1H), 7.80 (d, 2H), 7.78 (d, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.22 (d, 2H), 5.30 (s, 2H), 4.42 (m, 1H), 3.54 (m, 2H), 2.07 (t, 2H), 1.50–1.40 (m, 4H), 0.81 (t, 3H). ESI–MS $(M + H)^+$: calcd 455.2; found 455.2.

Methyl N^2-2-pyridinecarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15c). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the desired product as a powder, which was over 99% pure. High resolution ESI–MS $(M + H)^+$: calcd 476.1933; found 476.1931.

Methyl N^2-3-pyridinecarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15d). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the title compound as a powder which was over 99% pure on HPLC. High-resolution ESI–MS $(M + H)^+$: calcd 476.1933; found 476.1932.

Methyl N^2-4-pyridinecarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15e). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the title compound as a powder, which was over 99% pure. High-resolution ESI–MS $(M + H)^+$: calcd 476.1933; found 476.1932.

Methyl N^2-2-pyridineacetyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15f). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the desired product as a powder, which was over 98% pure. High resolution ESI–MS $(M + H)^+$: calcd 490.2090; found 490.2093.

Methyl N^2-2-pyridinecarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15g). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the title compound as a powder, which was over 98% pure. High-resolution ESI–MS $(M+H)^+$: calcd 490.2090; found 490.2089.

Methyl N^2-2-pyridinecarbonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionic acid TFA salt (15h). This compound was synthesized using a similar procedure as for compound **15a**. Purification on reversed-phase HPLC gave the title compound as a powder, which was over 98% pure. High resolution ESI–MS $(M + H)^+$: calcd 490.2090; found 490.2072.

Methyl N^2-Cbz-N^3-Boc-L-2,3-diaminopropionate (18). To a solution of **17a** (13.9 mmol, 4 g) and di-*t*-butyl dicarbonate (13.9 mmol, 3.03 g) in 30 mL of THF cooled in an ice bath was added triethylamine (15 mmol, 2.1 mL) and the solution was stirred for 4 h.

Dilute citric acid solution was added followed by ethyl acetate. The organic layer was separated, washed with dilute citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Crystallization from ether–petroleum ether gave 4.68 g (96%) of the title compound as a crystalline solid. ^{1}H NMR (DMSO-d_6) δ 7.60 (d, 1H), 7.35 (m, 5H), 6.88 (t, 1H), 5.02 (s, 2H), 4.14 (m, 1H), 3.60 (s, 3H), 3.28 (m, 2H), 1.37 (s, 9H). Anal. calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.87; N, 7.96. Found: C, 57.95; H, 6.76; N, 7.96.

Methyl N^3-Boc-L-2,3-diaminopropionate HCl salt (19). A mixture of **18** (12.2 mmol, 4.32 g), concentrated HCl (0.87 mL) and 10% Pd/C (432 mg) in 30 mL of methanol was hydrogenated at atmospheric pressure for 4 h. The catalyst was filtered off and the solution was concentrated. Ether was added and the solid was filtered, washed with ether to give 2.46 g (80%) of the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 8.55 (b, 3H), 7.13 (t, 1H), 3.96 (m, 1H), 3.70 (s, 3H), 3.44 (m, 2H), 1.38 (s, 9H). Anal. calcd for $C_9H_{19}N_2O_4Cl$: C, 42.44; H, 7.52; N, 11.00. Found: C, 42.58; H, 7.76; N, 11.22.

Methyl N^2-*p*-toluenesulfonyl-N^3-Boc-L-2,3-diaminopropionate (20a). To a solution of **19** (3 mmol, 767 mg) in 10 mL of THF was added *p*-toluenesulfonyl chloride (3 mmol, 572 mg) followed by triethylamine (7 mmol, 0.98 mL) and the solution was stirred for 4 h. Ethyl acetate was added and the solution was washed with dilute citric acid, brine, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Crystallization from ether–petroleum ether gave 890 mg (79%) of the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 8.20 (d, 1H), 7.64 (d, 2H), 7.38 (d, 2H), 6.84 (t, 1H), 3.90 (m, 1H), 3.38 (s, 3H), 3.10 (m, 2H), 2.39 (s, 3H), 1.32 (s, 9H). Anal. calcd for $C_{16}H_{24}N_2O_6S$: C, 51.60; H, 6.50; N, 7.52. Found: C, 51.73; H, 6.72; N, 7.56.

Methyl N^2-*p*-toluenesulfonyl-L-2,3-diaminopropionate HCl salt (21a). Compound **20a** (2.37 mmol, 880 mg) was treated with 10 mL of 4 N HCl in dioxane for 1 h and the solution was concentrated. The residue was triturated with ether–petroleum ether to give 700 mg (96%) of the desired product as a solid. ^{1}H NMR (DMSO-d_6) δ 8.52 (d, 1H), 8.08 (b, 3H), 7.66 (d, 2H), 7.40 (d, 2H), 4.16 (m, 1H), 3.36 (s, 3H), 3.10 (m, 1H), 2.90 (m, 1H), 2.38 (s, 3H). Anal. calcd for $C_{11}H_{17}N_2O_4SCl{\cdot}0.1HCl$: C, 42.28; H, 5.51; N, 8.97. Found: C, 42.17; H, 5.43; N, 8.98.

Methyl N^2-*p*-toluenesulfonyl-N^3-(3-chloromethylbenzoyl)-L-2,3-diaminopropionate (22a). This compound was synthesized in a similar way as described for **1a** from 3-chloromethylbenzoyl chloride (1.5 mmol, 0.21 mL), **21a** (1.6 mmol, 621 mg), and triethylamine (3.5 mmol, 0.49 mL). Yield 638 mg (100%). ^{1}H NMR (DMSO-d_6) δ 8.56 (t, 1H), 8.35 (d, 1H), 7.80 (s, 1H), 7.62 (m, 4H), 7.46 (t, 1H), 7.26 (d, 2H), 4.80 (s, 2H), 4.08 (m, 1H), 3.50 (m, 2H), 3.40 (s, 3H), 2.30 (s, 3H). Anal. calcd for $C_{19}H_{21}N_2O_5ClS$: C, 53.70; H, 4.98; N, 6.59. Found: C, 53.88; H, 5.02; N, 6.73.

Methyl N^2-*p*-toluenesulfonyl-N^3-(3-(4-cyanophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate (23a). This compound was synthesized in a similar way as described for **2a** from **22a** (1.5 mmol, 637 mg), 4-cyanophenol (1.5 mmol, 179 mg), and potassium carbonate (3 mmol, 415 mg). Purification on a silica gel column using ethyl acetate/hexane gave 340 mg (45%) of the title compound as a solid. ^{1}H NMR (DMSO-d_6) δ 8.56 (t, 1H), 8.35 (d, 1H), 7.84 (s, 1H), 7.80 (d, 2H), 7.70 (d, 1H), 7.61 (m, 3H), 7.50 (t, 1H), 7.28 (d, 2H), 7.20 (d, 2H), 5.26 (s, 2H), 4.06 (m, 1H), 3.50 (m, 1H), 3.38 (m, 1H), 3.39 (s, 3H), 2.30 (s, 3H). Anal. calcd for $C_{26}H_{25}N_3O_6S{\cdot}0.5EtOAc$: C, 60.96; H, 5.29; N, 7.61. Found: C, 60.74; H, 4.99; N, 7.46.

Methyl N^2-*p*-toluenesulfonyl-N^3-(3-(4-amidinophenyloxymethyl)benzoyl)-L-2,3-diaminopropionate TFA salt (24a). This compound was synthesized from **23a** (0.63 mmol, 320 mg) using a similar procedure as described for **3a**. Purification on reversed-phase HPLC gave 125 mg (31%) of the desired product as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 2H), 8.94 (s, 2H), 8.59 (t, 1H), 8.35 (d, 1H), 7.86 (s, 1H), 7.81 (d, 2H), 7.70 (d, 1H), 7.60 (m, 3H), 7.50 (t, 1H), 7.28 (d, 2H), 7.25 (d, 2H), 5.30 (s, 2H), 4.08 (m, 1H), 3.44 (m, 2H), 3.38 (s, 3H), 2.30 (s, 3H). Anal. calcd for $C_{28}H_{29}N_4O_8F_3{\cdot}0.6TFA$: C, 49.60; H, 4.30; N, 7.92. Found: C, 49.59; H, 4.36; N, 7.94.

N^2-*p*-Toluenesulfonyl-N^3-(3-(4-amidinophenyloxymethyl)-benzoyl)-L-2,3-diaminopropionic acid TFA salt (25a). This compound was synthesized by saponification of **24a** with LiOH and then purification on reversed-phase HPLC. ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 2H), 8.94 (s, 2H), 8.59 (t, 1H), 8.35 (d, 1H), 7.86 (s, 1H), 7.81 (d, 2H), 7.70 (d, 1H), 7.60 (m, 3H), 7.50 (t, 1H), 7.28 (d, 2H), 7.25 (d, 2H), 5.30 (s, 2H), 4.04 (m, 1H), 3.42 (m, 2H), 2.30 (s, 3H). ESI–MS $(M + H)^+$: calcd. 511.2; found 511.2. Anal. calcd for $C_{27}H_{27}N_4O_8SF_3{\cdot}0.2TFA$: C, 50.83; H, 4.24; N, 8.65. Found: C, 50.95; H, 4.52; N, 8.88.

N^2-*n*-Butanesulfonyl-N^3-(3-(4-amidinophenyloxymethyl)-benzoyl)-L-2,3-diaminopropionic acid TFA salt (25b). This compound was synthesized using a procedure similar to that for the synthesis of compound **25a**. ^{1}H NMR (DMSO-d_6) δ 9.16 (s, 2H), 8.92 (s, 2H), 8.64 (t, 1H), 7.86 (s, 1H), 7.81 (m, 4H), 7.62 (d, 1H), 7.54 (t, 1H), 7.24 (d, 2H), 5.30 (s, 2H), 4.12 (m, 1H), 3.58 (m, 2H), 2.95 (t, 2H), 1.60 (m, 2H), 1.28 (m, 2H), 0.80 (t, 3H). ESI–MS $(M + H)^+$: calcd 477.2; found 477.3. Anal. calcd for $C_{22}H_{26}N_4O_8SF_3{\cdot}0.75TFA$: C, 45.30; H, 4.43; N, 8.29. Found: C, 45.10; H, 4.70; N, 8.28.

N^4-*t*-Butyloxycarbonyl-N^1-(2-hydroxyethyl)piperazine (26a). To a solution of *N*-(2-hydroxyethyl)piperazine (25 mmol, 3.25 g) in 50 mL of THF in an ice bath was added di-*t*-butyl-di-carbonate (25 mmol, 5.45 g) and after stirring for 3 h, the solution was concentrated. The residue was triturated with petroleum ether three times and left in a refrigerator overnight to get 5.9 g (100%) of the desired product. ^{1}H NMR ($CDCl_3$) δ 3.64 (t, 2H), 3.45 (t, 4H), 2.81 (b, 1H),

2.58 (t, 2H), 2.48 (t, 4H), 1.45 (s, 9H). Anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.36; H, 9.63; N, 12.16. Found: C, 57.49; H, 9.71; N, 11.90.

Ethyl 3-[2-(4-*t*-butyloxycarbonylpiperazin-1-yl)ethyloxymethyl]benzoate (27a). 3-Chloromethylbenzoyl chloride (10 mmol, 1.8 g) was treated with 20 mL of ethanol and the solution was concentrated and dried. To a solution of **26** (10 mmol, 2.3 g) in 10 mL of DMF in an ice bath was added NaH (15 mmol, 0.6 g) and after stirring for 1 h, a solution of ethyl 3-chloromethylbenzoate prepared above in 10 mL of DMF was added dropwise. The mixture was stirred overnight and quenched with 25 mL of ethanol. The solvents were removed under vacuum and the residue was taken up in ethyl acetate which was washed with $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Purification on a silica gel column using methanol (1%):chloroform as eluent gave 2.01 g (51%) of the desired product. ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 7.96 (d, 1H), 7.52 (d, 1H), 7.41 (t, 1H), 4.58 (s, 2H), 4.38 (q, 2H), 3.63 (b, 2H), 3.48 (b, 4H), 2.66 (b, 2H), 2.48 (b, 4H), 1.44 (s, 9H), 1.39 (t, 3H). A small amount of the product was further purified on reversed-phase HPLC. Anal. calcd for $C_{23}H_{33}N_2O_7F_3 \cdot 0.7$TFA: C, 49.98; H, 5.79; N, 4.78. Found: C, 50.21; H, 5.58; N, 4.74.

3-[2-(4-*t*-Butyloxycarbonyl-1-piperazino)ethyloxymethyl]benzoic acid (28a). Compound **27a** (2.55 mmol, 1 g) was dissolved in 10 mL of ethanol and 5 mL of 1 N NaOH was added. The solution was stirred for 2.5 h, acidified with dilute HCl and concentrated. The residue was taken up in ethanol and insoluble material (NaCl) was filtered off. The ethanol solution was concentrated and the residue was purified on reversed-phase HPLC to give 0.99 g (66%) of the title compound as a powder after lyophilization. ^{1}H NMR (DMSO-d_6) δ 11.2 (b, COOH), 7.88 (s, 1H), 7.84 (d, 1H), 7.60 (d, 1H), 7.44 (t, 1H), 4.57 (s, 2H), 3.91 (m, 2H), 3.80 (t, 2H), 3.40 (m, 2H), 3.32 (m, 2H), 3.00 (m, 2H), 1.38 (s, 9H). Anal. calcd for $C_{21}H_{29}N_2O_7F_3 \cdot 0.65$TFA: C, 48.47; H, 5.40; N, 5.07. Found: C, 48.59; H, 5.19; N, 4.81.

Ethyl N^2-benzyloxycarbonyl-N^3-[3-(2-piperazinoethyloxymethyl)benzoyl]-L-2,3-diaminopropionate (29a). Ethyl N^2-benzyloxycarbonyl-L-2,3-diaminopropionate **17b** was prepared in a similar manner to that for **17a**. To a solution of compound **28a** (1 mmol, 0.364 g) and compound **17b** (1 mmol, 0.302 g) in 5 mL of DMF cooled in an ice bath was added diisopropylethylamine (4 mmol, 0.516 g) followed by HBTU (1 mmol, 0.321 g). The mixture was stirred overnight and concentrated. The residue was taken up in ethyl acetate and the solution was washed with citric acid, brine, $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was taken up in 20 mL of 25% TFA/CH_2Cl_2 and after 30 min, solvents were removed under vacuum. The residue was washed with ether to give 0.41 g (67%) of the desired product which was over 98% pure as judged by reversed-phase HPLC. ESI–MS $(M + H)^+$: calcd 513.3; found 513.3.

Methyl N^2-benzyloxycarbonyl-N^3-{3-[2-(piperidin-4-yl)-ethyloxymethyl]benzoyl}-L-2,3-diaminopropionate TFA salt (29b). This compound was synthesized in a manner analogous to that for compound **29a**. Purification on reversed-phase HPLC gave the title compound as a powder which was over 99% pure. ESI–MS $(M + H)^+$: calcd 498.3; found 498.3. Anal. calcd for $C_{29}H_{36}N_3O_8F_3 \cdot 0.45$TFA: C, 54.16; H, 5.55; N, 6.34. Found: C, 53.96; H, 5.64; N, 6.69.

Ethyl N^2-benzyloxycarbonyl-N^3-{3-[(*N*-amidinopiperidin-4-yl)oxymethyl]benzoyl}-L-2,3-diaminopropionate TFA salt (30). Ethyl N^2-benzyloxycarbonyl-N^3-{3-[(piperidin-4-yl)oxymethyl]benzoyl}-L-2,3-diaminopropionate TFA salt (**29c**) was prepared in a similar manner to that for **29a**. To a solution of **29c** (0.1 mmol, 60 mg) and 4-dimethylaminopyridine (0.2 mmol, 20 mg) in 1 mL of ethanol:water (3:1) was added formamidine sulfonic acid (0.1 mmol, 12.4 mg) and the mixture was stirred overnight. Purification on reversed-phase HPLC gave 7 mg of desired product as a powder which was over 99% pure. ESI–MS $(M + H)^+$: calcd 526.3; found 526.3. Anal. calcd for $C_{29}H_{36}N_5O_8F_3$: C, 54.46; H, 5.67; N, 10.95. Found: C, 54.60; H, 5.76; N, 10.61.

Conversion of esters to acids. Esters were treated with pig liver esterases prior to the human PRP assay. Each ester was added with 100 IU/mL pig liver esterases and incubated at 37 °C in phosphate buffer at pH 7.4 for 2 h. To ensure complete hydrolysis of ester to its corresponding acid, the conversion rate of compound **13b** to **14b** was followed by HPLC analysis. The hydrolysis reaction was stopped at various times by addition of 2 vol of methanol. After centrifugation, the supernatant was analyzed for the ester **13b** and its free acid **14b** using HPLC. It was found that **13b** was completely hydrolyzed to **14b** within 30 min.

Human PRP assay

Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin-free for at least two weeks prior to blood collection. Blood was collected into 10-mL citrated vacutainer tubes. The blood was centrifuged for 15 min at 150 *g* at room temperature, and platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 min at 1500 *g* at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on an aggregometer (PAP-4 platelet aggregation profiler), using PPP as the blank (100% transmittance). PRP (200 μL) was added to each micro test tube, and transmittance was set to 0%. Agonist ADP (10 μM) was added to each tube, and the aggregation profiles were plotted (percent transmittance versus time). The results were expressed as percent inhibition of agonist-induced platelet aggregation. For the IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

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(*Received in U.S.A.* 1 *August* 1996; *accepted* 24 *December* 1996)