Rational Design and Synthesis of Novel, Potent Bis-phenylamidine Carboxylate Factor Xa Inhibitors

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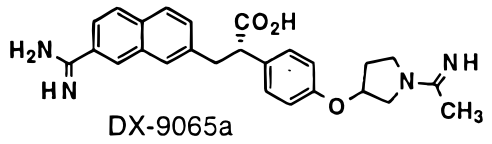
The molecular modeling studies, rational design, and synthesis of a novel series of bis-phenylamidine carboxylate compounds which are inhibitors of factor Xa in the blood coagulation cascade are described. Inhibition of blood coagulation has been proposed to have several potential therapeutic utilities (Kaiser and Hauptmann, *Cardiovasc. Drug Rev.* **1994**, *12*, 225−236). Factor Xa (fXa) holds a central position in the coagulation cascade (Coleman et al. in *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 1994, pp 3−18). Its major role is the generation of thrombin by the proteolytic cleavage of prothrombin. Inhibition of fXa would serve to reduce the formation of platelet clots. The fXa dimer crystal structure (Tulinsky et al., *J. Mol. Biol.* **1993**, *232*, 947−966) was used in our molecular modeling studies to design a novel series of fXa inhibitors. We initially docked and minimized isolated small molecule fragments in the S1 and S4 aryl-binding subsites. Subsequently, these fragments were connected with a tether, so as not to disturb the orientation of the fragments in their respective pockets. These modeling studies led to the initial compound (**1**) which was found to have significant inhibitory potency for fXa (K_i = 34 nM). The synthesis of the core structure, structure−activity relationships (SAR), and proposed binding orientation based on molecular modeling for this novel bis-phenylamidine series of fXa inhibitors are described.

Introduction

Factor Xa (fXa) holds a central position in the coagulation cascade that links the intrinsic and extrinsic activation mechanisms. The major biological role of fXa is the generation of thrombin by the proteolysis of prothrombin. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, is amplified by formation of a prothrombinase complex (factor Xa, factor V, Ca^{2+}, and phospholipid). Since it is calculated that one molecule of fXa can generate 138 molecules of thrombin,[4] inhibition of fXa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system. Therefore, we have targeted this enzyme in our efforts to develop novel antithrombotic agents.

There are several examples of dibasic fXa inhibitors disclosed in the literature.[5] Of these the bis-amidine DX-9065a is the most selective fXa inhibitor with an IC_{50} of 41 nM.[6] DX-9065a was proposed to bind to the



DX-9065a

receptor site with the naphthyl amidine hydrogen bonding to Asp189 in the S1 site, the carboxylic acid functionality hydrogen bonding to Gln192 in fXa, and the acetimidoyl pyrrolidine group presumably binding in the aryl-binding pocket (Figure 1). This binding motif has been confirmed by Bode's group.[7] The fXa−DX-9065a crystal structure complex shows the pyrrolidine in the aryl-binding pocket with the acetimidoyl functionality hydrogen bonding in a cation hole created by the carbonyl groups of Lys96 and Glu97 together with the Glu97 side chain. The Daiichi scientists found that the carboxylic acid was important for fXa selectivity: specificity for fXa versus thrombin is >28000-fold with the carboxylic acid compared to 280-fold with the corresponding methyl ester. The specificity for fXa over thrombin is proposed to stem from the interaction between the carboxylate of DX-9065a and Gln192 in fXa. The corresponding residue in thrombin (Glu192) is expected to be deprotonated which would cause a strong repulsive interaction between the DX-9065a carboxylate and this residue.

Since there were no inhibitor-bound fXa crystal structures reported at the time this work was done, the X-ray coordinates of fXa structural dimer[3] served as the starting point for our molecular modeling studies. The fXa dimer crystal structure has the C-terminal arginine of the light chain of one monomer bound in the S1 pocket of the other. We envisioned a phenylamidine group binding in the S1 site, hydrogen bonding to the Asp189 residue analogous to the trypsin−phenylamidine complex.[8] The lowest energy orientation[9] for the phenylamidine residue in the S1 pocket is shown in Figure 2. Subsequently, we attempted to find a fragment which would be compatible to the S4 aryl-binding pocket.[7] The aryl-binding pocket is outlined with three aromatic residues: Phe174, Tyr99, and Trp215. Initially we modeled a phenyl ring into the S4 aryl-binding pocket to find an optimal binding orientation. This

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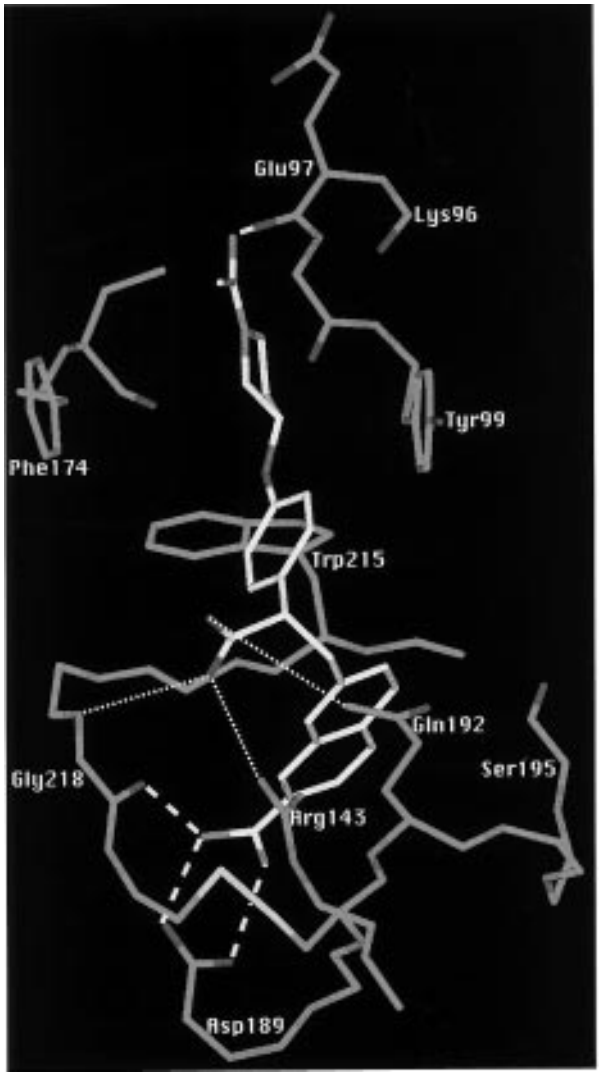


Figure 1. Binding model of DX-9065a to the fXa active site. For clarity, only the residues closest to the ligand are displayed. The ligand's 3-point pharmacophore comprises (1) the naphthyl amidino moiety forming hydrogen bonds with Asp189 and Gly218 in the S1 pocket (long white dashed lines); (2) the carboxylate in the region of positive electrostatic potential defined by Arg143, Gln192, and Gly218−NH (short white dashed lines); and (3) the acetimidoyl pyrrolidine which fills the S4 pocket (Phe174, Trp215, Tyr99) and puts a positive charge in the region of negative electrostatic potential defined by the backbone carbonyls of Lys96, Glu97, and Thr98 and the side chain of Glu97.

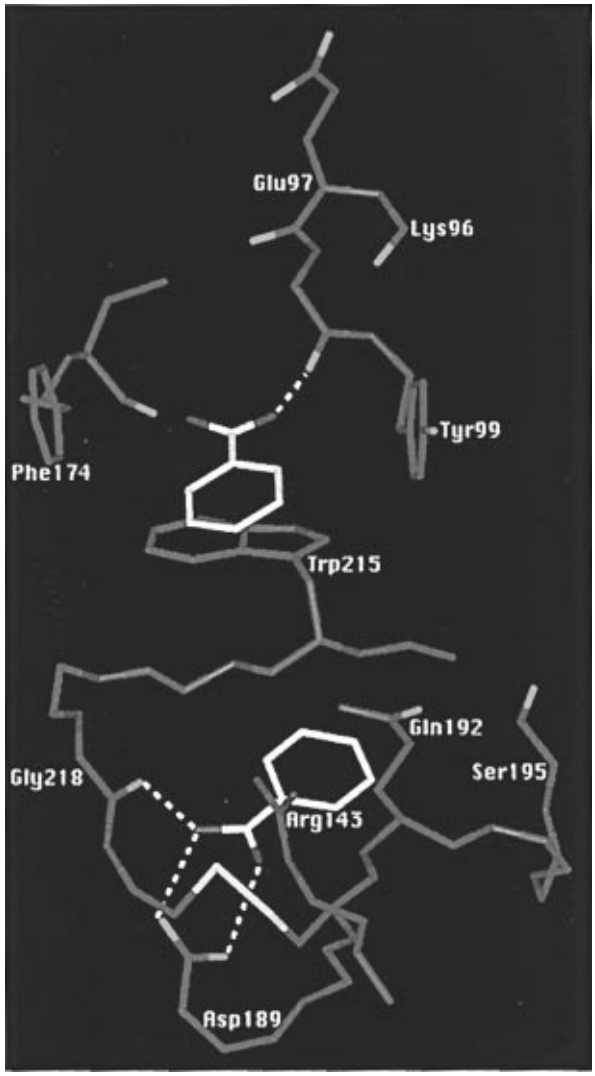
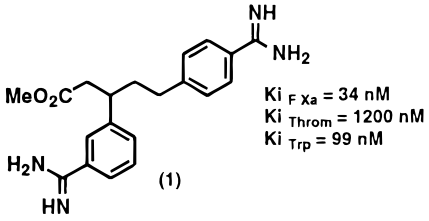


Figure 2. Optimum binding modes of phenylamidino moieties in the fXa S1 and S4 pockets, accounting for two of the three points of the pharmacophore model defined in Figure 1. The phenylamidine in the S4 pocket does not go as deep as the equivalent acetimidoyl pyrrolidine of DX-9065a and may interact directly with the Thr98 carbonyl rather than with Glu97.

phenyl ring fragment was then substituted with an amidine group to try and take advantage of the binding into the cation hole that the Daiichi group had found with their acetimidoyl group. We found that a phenylamidine residue placed into various positions in this pocket consistently minimized to the same position (Figure 2) with the amidine stacked over residue Trp215 and protons pointing toward the phenyl rings.[10] This orientation of the phenylamidine in the S4 pocket is different from the position of the acetimidoyl group for the Daiichi compound. Assuming the orientation of the phenylamidine in S1 and the phenylamidine in aryl-binding pocket to be preferred, the next step was to connect these fragments so as not to disrupt their respective orientations. We found that a 3-atom spacer connecting the meta position of the P1 phenylamidine to the para position of the P4 phenylamidine satisfied these requirements as shown in Figure 3. Finally we needed to tether a carboxylate group off this framework toward the Gln192 interaction, similar to the Daiichi pharmacophore. This was best achieved by functionalizing the benzylic methylene of the P1 phenylamidine.

The initial bis-phenylamidine carboxylate compound (**1**) was found to have good binding affinity in the fXa assay[11] (K_i = 34 nM). A subsequent set of compounds was prepared to confirm the 3-point pharmacophore, confirm the regio position of the amidines, and optimize the distal phenylamidine.



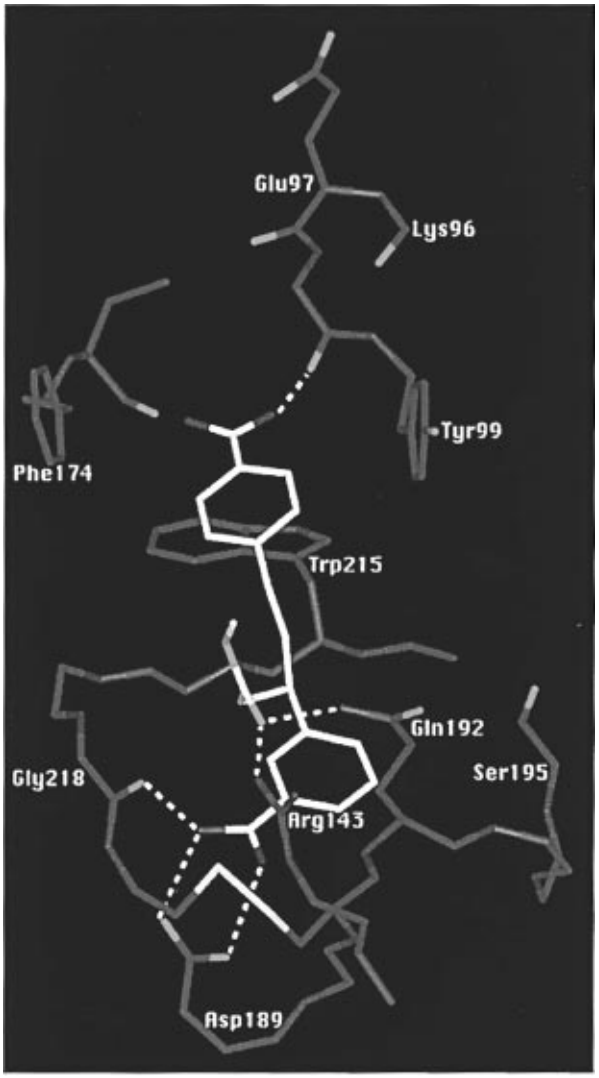
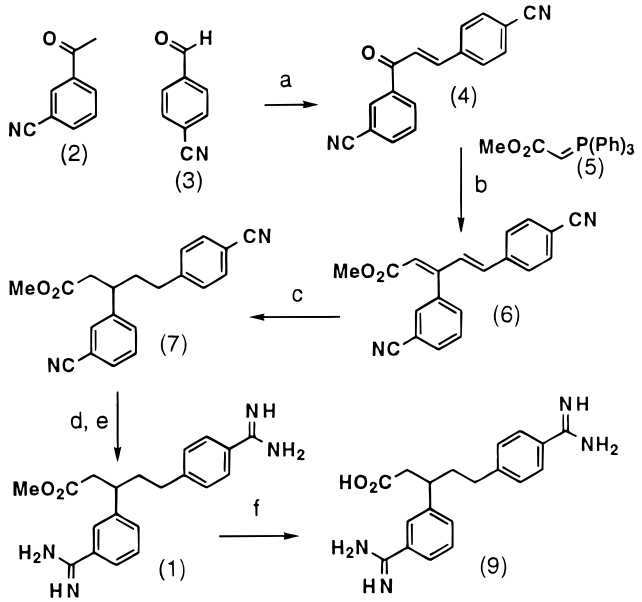


Figure 3. Binding model of **1** to the fXa active site. All three aspects of the pharmacophore defined in Figure 1 are present. Both phenylamidines are in almost identical positions as their optimum binding mode shown in Figure 2. The methyl ester is shown to interact with Arg143 and Gln192 simultaneously. Most likely only one of these interactions actually occurs because simultaneous hydrogen bonding would bring the terminal side chain nitrogens of those residues too close together.

Chemistry

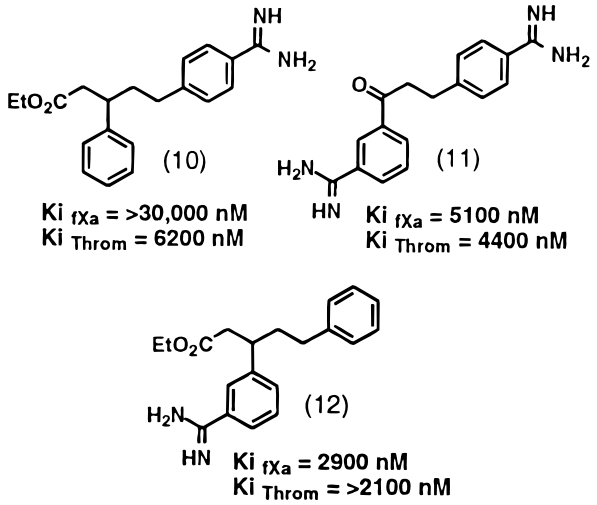
The bis-phenylamidine carboxylate compounds such as **1** were prepared as described in Scheme 1. The aldol condensation product **4** was prepared from *m*-cyanoacetophenone (**2**) and *p*-cyanobenzaldehyde (**3**) with sodium methoxide in methanol to give a mixture of *E* and *Z* isomers. The dienone ester **6** was prepared by reaction of methyl (triphenylphosphoranyldiene)acetate (**5**) in toluene at reflux with the enone **4**. The diene was reduced to the saturated ester **7** by hydrogenation over palladium on carbon under Parr shaker conditions. The bis-phenylamidine carboxylate **1** was prepared from the bis-nitrile **7** using modified Pinner[12] conditions to prepare the imidate and reaction with ammonium carbonate to give the bis-amidine **1**. The bis-phenylamidine carboxylates were purified by preparative HPLC using an acetonitrile/water/TFA gradient on a Vydac C-18 semipreparative column. The free acid **9** was prepared by treating the ester **1** with 6 N HCl.

Scheme 1[a]



[a] Reagents: (a) NaOMe, methanol, room temperature; (b) toluene, reflux; (c) 10% Pd/carbon, 50 psi H_2, THF; (d) HCl gas, methanol, room temperature; (e) $(NH_4)_2CO_3$, methanol; (f) 6 N HCl.

Chart 1



Discussion

To confirm the critical functional groups in the pharmacophore of compound **1**, it was necessary to prepare a series of deletion analogues (Chart 1). The elimination of the P1 *m*-amidine group (**10**) was found to have the most critical effect on activity. The resulting compound (**10**) was totally devoid of fXa activity, while compounds with elimination of the distal P4 *p*-amidine group (**12**) or the ester group (**11**) still retained some micromolar activity. These analogues thus confirmed that all functional groups were important to achieve nanomolar activity.

The other regio isomers of the amidine groups were also prepared to confirm the optimum substitution pattern for the basic centers (Chart 2). Moving the P1 *m*-amidine group to the para position (**13**) completely eliminated activity in the fXa assay. However, moving the P4 *p*-amidine to the meta position reduced inhibitory activity for fXa by 90-fold. The double-reposition isomer (**15**) was found to have micromolar activity (K_i = 1642

Chart 2

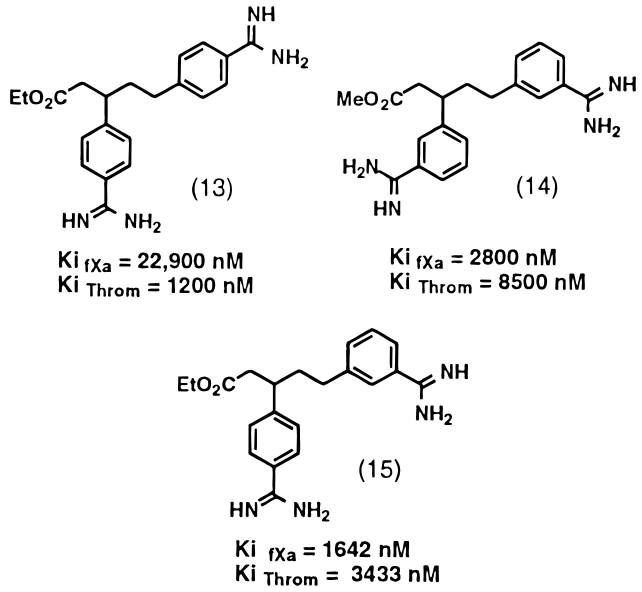
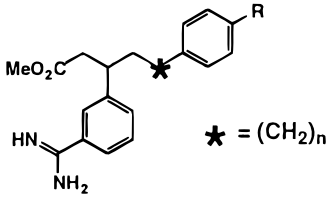


Table 1. Effect on in Vitro Activity by Substitution of the P4 *p*-Amidine



compd	*n*	R	K_i, nM fXa[a]	throm[b]	Trp[c]
1	1	*p*-amidine	34	1200	99
16	1	*p*-CO_2CH_3	2800	3600	330
17	1	*p*-$NHSO_2CH_3$	654	3100	110
18	1	*p*-$NHSO_2Ph$	1100	1750	610
19	1	*p*-C(=O)NH_2	550	6500	870
20	1	*p*-NH_2	5000	7700	1200
21	1	*p*-guanidine	9	3100	96
23	3	*p*-guanidine	57	3300	760

[a] In vitro inhibition of factor Xa K_i.[11] [b] In vitro inhibition of thrombin K_i.[11] [c] In vitro inhibition of trypsin K_i.[11]

nM), better than either compound **13** or **14**. These data may suggest that analogue **15** is binding in the reverse direction compared to **1**, with the *m*-amidine in the S1 pocket and the *p*-amidine in the S4 pocket. This reverse orientation for **15** was confirmed by modeling experiments, but it puts the ester side chain in a nonoptimal position, resulting in the reduced affinity but more activity than the ester deletion analogue **11**. The amidine regio isomer arrangement in **1** was confirmed to be the most active analogue.

The distal P4 *p*-amidine was replaced with a variety of modifications to explore the important polar and lipophilic binding interactions in the S4 pocket (Table 1). When the P4 *p*-amidine was replaced with a methyl ester (**16**), fXa activity was the same as having no substitution in the para position (**12**). The methyl sulfonamide **17** was 20-fold less active than compound **1**, and the larger phenyl sulfonamide **18** was less active then the methyl sulfonamide. The primary amide **19** was almost 20-fold less active than compound **1** but was more active than the methyl ester **10**. The aniline

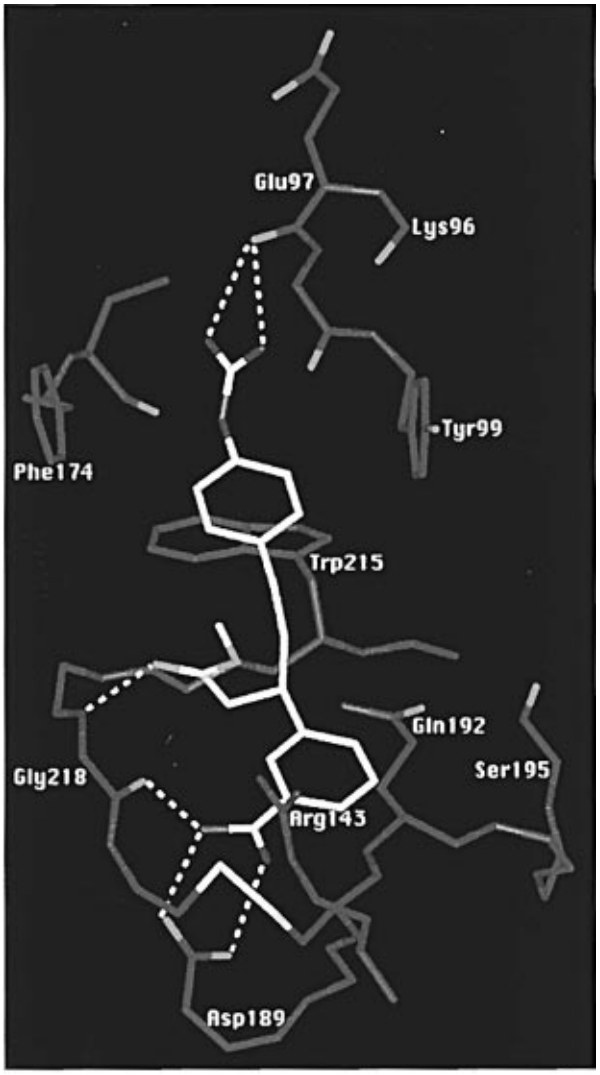


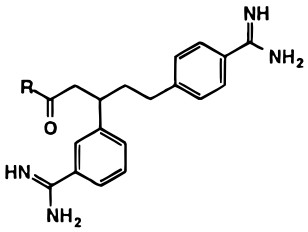
Figure 4. Binding model of **21** to the fXa active site. The phenylguanidine moiety sits deeper in the S4 pocket than the equivalent phenylamidine of **1** (see Figure 3) and potentially interacts with the same residues as DX-9065a (see Figure 1). The methyl ester is shown to interact with Gly218−NH rather than Arg143 or Gln192. The ester can, in principle, form any of those three hydrogen bonds.

compound **20** was more than 100-fold less active than the amidine. Introducing the guanidine compound **21** significantly improved inhibitory potency for fXa (K_i = 9 nM) while decreasing the inhibition of thrombin (K_i = 3100 nM).

These combinations suggest that the S4 pocket prefers a basic charged group. We believe the protonated *p*-amidinophenyl residue is located in the S4 aryl-binding pocket where it engages in cation−π[10] and lipophilic interactions with the surrounding Phe174, Tyr99, and Trp215 and also possibly hydrogen bonds with the carbonyl of Thr98 (Figure 3). The anilino group (**20**) on the other hand is not very basic and is too small to fill this binding pocket. The guanidine analogue **21** would fill the aryl-binding pocket more completely than the amidino group and would also extend deeper into the S4 pocket to interact with the putative "cation hole", the Glu97 backbone carbonyl (Figure 4).

Subsequently, we attempted to extend even deeper into the S4 pocket by extending the 3-atom spacer of

Table 2. Effect on in Vitro Activity by Substitution of the Methyl Ester



		K_i, nM		
compd	R	fXa[a]	throm[b]	Trp[c]
1	OCH_3	34	1200	99
24	OH	1400	>4200	>1200
25	OCH_2CH_3	42	1100	110
26	O-isopropyl	192	1535	140
27	$NHCH_3$	940	8000	820
28	pyrrole	1150	2800	440
29	$NHCH_2CO_2CH_3$	2400	12600	nt
30	$NHOCH_3$	2400	19600	nt

[a] In vitro inhibition of factor Xa K_i.[11] [b] In vitro inhibition of thrombin K_i.[11] [c] In vitro inhibition of trypsin K_i.[11]

21 to a 5-atom spacer (**23**). The fXa activity for this analogue was 5-fold less active than the shorter guanidine modification (**21**). It appears that the preferred distance is close to the 3-atom spacer with guanidine, and no advantage is gained with the longer 5-atom spacer.

The ester group was shown earlier (Chart 1, compound **11**) to be vital for fXa binding. Surprisingly the free acid compound **24** is 50-fold less active than the corresponding ester **1**, although its thrombin activity is also significantly reduced by at least 30-fold (Table 2). This is contrary to what was found in the Daiichi work and what we had predicted from our modeling experiments. We further explored functional group changes for the ester to determine where this group may be interacting in fXa. As the ester alkyl is substituted with increasing size, the fXa activity tends to decrease. Replacing the methyl ester with a methyl amide, compound **27**, reduces the fXa activity significantly. Extending the chain length to the ester compound **29** or using an *O*-methyl hydroxamate greatly reduced activity for fXa. It is unclear where the ester binds, but an alternative binding mode in which the ester is hydrogen bonding to the N−H of Gly218 and less solvent-exposed might help to explain these observations (Figure 4).

Conclusion

Molecular modeling experiments using the active site coordinates of the fXa dimer enabled us to rationally design a series of novel bis-phenylamidine carboxylate compounds which are very potent fXa inhibitors. The proposed 3-point pharmacophore was confirmed by a series of deletion analogues and regio isomer analogues. It still remains to cocrystallize these inhibitors with fXa to confirm the binding orientation of the bis-phenylamidines and to determine the critical interaction for the ester group. The initially designed targets with a carboxylic acid did not have the activity or selectivity we had predicted from our modeling studies. However, these studies have led to a very active fXa inhibitor compound (**21**) (K_i = 9 nM) which has shown 400-fold selectivity versus thrombin (K_i = 3100 nM) and 10-fold selectivity versus trypsin (K_i = 96 nM).

Experimental Section

All reactions detailed below were performed using reagent-grade materials and solvents under a dry atmosphere. All solvents were distilled prior to use or stored over 4-Å molecular sieves. The phrase "flash chromatography" and related phrases refer to the separation methods reported by Still et al.[13] Melting points were determined in an open capillary on a Thomas Scientific melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian VXR-300A spectrometer, and chemical shifts are reported in ppm (δ) using tetramethylsilane as reference. Mass spectra were obtained on a Hewlett-Packard 5988A MS spectrometer. Microanalyses were determined by Quantitative Technologies, Inc., Bound Brook, NJ.

Preparation of (±)-Methyl 4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Bis-(trifluoroacetate) (1). Part A: Preparation of 3-[3-(4-Cyanophenyl)-1-oxo-2-propenyl]benzonitrile (4). Sodium methoxide (25% in MeOH, 1.5 mL, 6.8 mmol) was added dropwise to a solution of 3-acetylbenzonitrile (0.987 g, 6.8 mmol) and 4-cyanobenzaldehyde (0.891 g, 6.8 mmol) in dry methanol. Within 5 min, a precipitate began to form. The mixture was stirred at room temperature for 4 h and was diluted with methanol. The solids were filtered off, washed with cold methanol, and dried to give 3-[3-(4-cyanophenyl)-1-oxo-2-propenyl]benzonitrile as a white solid (1.7 g, 97%): MS $(M + H)^+$ 259; ^{1}H NMR ($CDCl_3$) 7.55 (d, 1H), 7.65 (t, 1H), 7.75 (s, 4H), 7.85 (m, 2H), 8.25 (d, 1H), 8.30 (s, 1H).

Part B: Preparation of Methyl 3-(3-Cyanophenyl)-5-(4-cyanophenyl)-2,4-pentadienoate (6). The 3-[3-(4-cyanophenyl)-1-oxo-2-propenyl]benzonitrile (**4**) (2 g, 7.75 mmol) was suspended in dry toluene and methyl (triphenylphosphoranylidene)acetate (2.59 g, 7.75 mmol) added. The mixture was then heated at 100 °C for 24 h and cooled and the solvent removed under vacuum. The residue was chromatographed on silica gel eluting ethyl acetate/hexanes (25:75, v:v) to give methyl 3-(3-cyanophenyl)-5-(4-cyanophenyl)-2,4-pentadienoate (**6**) as an oil (2.1 g, 87%): MS $(M + H)^+$ 315; ^{1}H NMR ($CDCl_3$) 3.60 (s, 3H), 3.80 (s, 3H), 5.90 (s, 1H), 6.23 (m, 2H), 6.45 (d, 1H), 7.15 (d, 1H), 7.55 (m, 16H), 8.60 (d, 1H).

Part C: Preparation of Methyl 4-Cyano-β-(3-cyanophenyl)benzenepentanoate (7). The methyl 3-(3-cyanophenyl)-5-(4-cyanophenyl)-2,4-pentadienoate (**6**) (0.328 g, 1.04 mmol) was dissolved in ethyl acetate/THF (1:1) and degassed with N_2. A catalytic amount of 10% Pd on carbon was added, and the flask was placed on a Parr shaker for 1 h at 45 psi. The contents of the flask were filtered through Celite, and the filtrate was concentrated under vacuum. The residue was chromatographed on silica gel eluting with ethyl acetate/hexanes (25:75, v:v) to give methyl 4-cyano-β-(3-cyanophenyl)-benzenepentanoate (**7**) as an oil (0.190 g, 57%): MS $(M + NH_4)^+$ 336; ^{1}H NMR ($CDCl_3$) 1.95 (m, 1H), 2.05 (m, 1H), 2.55 (m, 2H), 2.65 (dd, 2H), 3.15 (m, 1H), 3.60 (s, 3H), 7.20 (d, 2H), 7.45 (d, 2H), 7.50 (s, 1H), 7.55 (m, 3H).

Part D: Hydrogen chloride gas was bubbled through a solution of methyl 4-cyano-β-(3-cyanophenyl)benzenepentanoate (**7**) (0.058 g, 0.185 mmol) dissolved in 10 mL of ethanol under a nitrogen atmosphere and cooled to 0 °C in an ice bath for 15 min. The reaction flask was stoppered and allowed to warm to ambient temperature. The reaction mixture was stirred for 24 h and was concentrated in vacuo to give a semisolid residue. The crude imidate was taken up in 10 mL of ethanol, and the ammonium carbonate (0.142 g, 1.48 mmol) was added. The reaction flask was stoppered and stirred at ambient temperature for 28 h, and then the mixture was concentrated in vacuo to give the crude product as a solid residue. The title compound **1** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 21 min), as a white solid (0.051 g, 78%): mp >200 °C; MS $(M + H)^+$ 353; ^{1}H NMR (DMSO-d_6)

2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 7.40 (d, 2H), 7.55 (m, 2H), 7.75 (m, 4H), 9.1 (d, 4H), 9.25 (d, 4H). Anal. ($C_{20}H_{24}N_4O_2(CF_3CO_2H)_{2.0}$) C, H, N.

Preparation of (±)-Methyl 4-(Aminoiminomethyl)-β-phenylbenzenepentanoate Mono(trifluoroacetate) (10). Employing methods similar to example **1**, above, the title compound **10** was prepared and isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 25 min), as a white powder (0.07 g, 56%): mp 202 °C; MS $(M + H)^+$ 311; HRMS calcd 311.1759, found 311.1740; ^{1}H NMR (DMSO-d_6) 9.2 (s, 2H), 9.0 (2,2H), 7.7 (d, 2H), 7.2−7.4 (m, 7H), 3.5 (s, 3H), 3.4 (s, 2H), 3.0 (m, 1H), 2.8 (m, 1H), 2.6 (m, 1H), 2.0 (m, 2H). Anal. ($C_{19}H_{22}N_2O_2(CF_3CO_2H)_{1.0}$) C, H, N.

Preparation of 3-[3-[4-(Aminoiminomethyl)phenyl]-1-oxopropyl]benzenecarboximidamide Bis(trifluoroacetate) (11). Part A: 3-[3-(4-Cyanophenyl)-1-oxo-2-propenyl]benzonitrile was dissolved in THF and degassed with N_2. A catalytic amount of 10% Pd/C was added and the solution placed on a Parr shaker for 45 min at 10 psi. The solution was filtered through Celite and the filtrate concentrated. The residue was chromatographed on silica gel (20% ethyl acetate/toluene) to give 3-(4-cyanophenyl)propio(3-cyano)phenone as a white solid (0.200 g, 66%): MS $(M + NH_4)^+$ 278; ^{1}H NMR ($CDCl_3$) 3.15 (t, 2H), 3.35 (t, 2H), 7.40 (d, 2H), 7.6 (d, 3H), 7.85 (d, 1H), 8.15 (d, 1H), 8.20 (s, 1H).

Part B: Employing methods similar to example **1**, part D, but using 3-(4-cyanophenyl)propio(3-cyano)phenone (0.150 g, 0.576 mmol), the title compound **11** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 18 min), as a semisolid (0.018 g, 10%): MS $(M + H)^+$ 295; ^{1}H NMR (DMSO-d_6) 3.10 (t, 2H), 3.50 (t, 2H), 7.55 (d, 2H), 7.80 (m, 3H), 8.05 (d, 1H), 8.30 (d, 1H), 8.40 (s, 1H), 8.90 (s (broad), 2H), 9.20 (d (broad), 4H), 9.40 (s (broad), 2H). Anal. ($C_{17}H_{18}N_4O(CF_3CO_2H)_{2.1}$) C, H, N.

Preparation of (±)-Methyl β-[3-(Aminoiminomethyl)-phenyl]benzenepentanoate Mono(trifluoroacetate) (12). Part A: Employing methods similar to example **1**, part A, but using benzaldehyde, methyl 3-(3-phenyl-1-oxo-2-propenyl)-benzonitrile was isolated as an oil: MS 234 $(M + H)^+$.

Part B: Employing methods similar to example **1**, part B, but using methyl 3-(3-phenyl-1-oxo-2-propenyl)benzonitrile (1.1 g, 4.7 mmol), methyl 3-(3-cyanophenyl)-5-phenyl-2,4-pentadienoate was obtained as a mixture of *E* and *Z* isomers. This was purified by flash chromatography on silica gel eluting with methylene chloride to give a mixture of isomers (0.59 g, 44%): MS 290 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) 3.8 (s, 3H), 6.45 (d, 2H), 7.2−7.8 (m, 9H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-5-phenyl-2,4-pentadienoate (0.55 g, 1.90 mmol), methyl 3-(3-cyanophenyl)benzenepentanoate was isolated as an oil (0.52 g, 93%): MS 311 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) 1.90−2.10 (m, 2H), 2.45 (t, 2H), 2.55−2.75 (m, 2H), 3.1−3.2 (m, 1H), 3.58 (s, 3H), 7.08 (d, 2H), 7.15−7.60 (m, 7H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)benzenepentanoate (0.30 g, 1.02 mmol), the title compound **13** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 14.3 min), as a white powder (0.12 g): mp 248−249 °C; MS 311 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) 9.3 (s, 2H), 9.0 (s, 2H), 7.85 (s, 1H), 7.8 (m, 2H), 7.4 (t, 1H), 7.2−7.4 (m, 5H), 3.50 (s, 3H), 3.15 (m, 1H), 2.85 (dd, 1H), 2.7 (dd, 1H), 2.5 (m, 2H), 2.0 (m, 2H). Anal. ($C_{19}H_{22}N_2O_2(CF_3CO_2H)_{1.0}$) C, H, N.

Preparation of (±)-Ethyl 4-(Aminoiminomethyl)-β-[4-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (13). Part A: Employing methods similar to example **1**, part A, but using 4-cyanobenzaldehyde (1.80 g, 13.8 mmol) and 4-acetylbenzonitrile (1.0 g, 6.89 mmol), 4-[3-(4-cyanophenyl)-1-oxo-2-propenyl]benzonitrile was isolated as a pale yellow powder (0.4 g, 20%): MS 259 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) 7.78 (d, 2H), 7.6 (t, 1H), 7.5−7.0 (m, 7H).

Part B: Employing methods similar to example **1**, part B, but using 4-[3-(4-cyanophenyl)-1-oxo-2-propenyl]benzonitrile (0.3 g, 1.16 mmol), methyl 3-(4-cyanophenyl)-5-(4-cyanophenyl)-2,4-pentadienoate was obtained as a mixture of *E* and *Z* isomers. This was purified by flash chromatography on silica gel eluting with methylene chloride to a give mixture of isomers (0.31 g, 85%): MS 332 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) 8.5 (d, 1H), 7.75 (d, 2H), 7.65 (d, 2H), 7.56 (d, 2H), 7.45 (d, 2H), 6.47 (d, 2H), 3.82 (s, 3H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(4-cyanophenyl)-5-(4-cyanophenyl)-2,4-pentadienoate (0.5 g, 1.59 mmol), methyl 3-(4-cyanophenyl)-5-(4-cyanophenyl)pentanoate was isolated as an oil (0.3 g, 99%): MS 319 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) 7.65 (d, 2H), 7.55 (d, 2H), 7.45 (d, 2H), 7.17 (d, 2H), 3.7 (s, 3H), 3.2 (m, 1H), 2.65 (m, 2H), 2.50 (t, 2H), 2.1−1.90 (m, 2H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(4-cyanophenyl)-5-(4-cyanophenyl)pentanoate (0.30 g, 0.94 mmol), the title compound **13** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 14.3 min), as a white powder (0.12 g, 35%): mp 248−249 °C; MS 367 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) 9.27 (s, 2H), 9.25 (s, 2H), 9.17 (s, 2H), 9.15 (s, 2H), 7.78 (d, 2H), 7.75 (d, 2H), 7.55 (d, 2H), 7.37 (d, 2H), 3.90 (m, 2H), 3.15 (m, 1H), 2.85 (dd, 1H), 2.7 (dd, 1H), 2.6−2.4 (m, 2H), 1.95 (m, 2H), 1.1 (t, 3H). Anal. ($C_{21}H_{26}N_4O_2(CF_3CO_2H)_{2.2}$) C, H, N.

Preparation of (±)-Methyl 3-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (14). Part A: Employing methods similar to example **1**, part A, but using 3-acetylbenzonitrile (1 g, 6.8 mmol) and 3-cyanobenzaldehyde (2.76 g, 17 mmol), 3-[3-(3-cyanophenyl)-1-oxo-2-propenyl]benzonitrile was isolated as a solid (0.285 g, 15%): MS $(M + H)^+$ 259; ^{1}H NMR ($CDCl_3$) 7.6 (t, 2H), 7.7 (m, 2H), 7.85 (m, 3H), 7.95 (s, 1H), 8.25 (d, 1H), 8.35 (s, 1H).

Part B: Employing methods similar to example **1**, part B, but using 3-[3-(3-cyanophenyl)-1-oxo-2-propenyl]benzonitrile (0.280 g, 1.08 mmol), methyl 3-(3-cyanophenyl)-5-(3-cyanophenyl)-2,4-pentadienoate as a mixture of the *E*/*Z* isomers was prepared as an oil (0.297 g, 87%): MS $(M + NH_4)^+$ 332; ^{1}H NMR ($CDCl_3$) 3.60 (s, 3H), 3.80 (s, 3H), 5.85 (s, 1H), 6.23 (t, 2H), 6.45 (d, 1H), 7.15 (d, 1H), 7.55 (m, 16H), 8.60 (d, 1H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-5-(3-cyanophenyl)-2,4-pentadienoate (0.297 g, 0.945 mmol) methyl 3-(3-cyanophenyl)-5-(3-cyanophenyl)pentanoate was prepared as an oil (0.250 g, 83%): MS $(M + NH_4)^+$ 336; ^{1}H NMR ($CDCl_3$) 1.9 (m, 2H), 2.45 (m, 2H), 2.65 (m, 2H), 3.15 (m, 1H), 3.6 (s, 3H), 7.5 (m, 8H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)-5-(3-cyanophenyl)pentanoate (0.250 g, 0.786 mmol), the title compound **14** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 22 min), as a solid (0.030 g, 11%): MS $(M + H)^+$ 353; ^{1}H NMR (DMSO-d_6) 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 7.5 (s, 2H), 7.55 (m, 2H), 7.6 (t, 2H), 7.7 (d, 1H), 7.75 (s, 1H), 9.2 (s (v broad), 6H). Anal. ($C_{20}H_{24}N_4O_2(CF_3CO_2H)_{2.1}$) C, H, N.

Preparation of (±)-Ethyl 3-(Aminoiminomethyl)-β-[4-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (15). Part A: Employing methods similar to example **1**, part A, but using *m*-cyanobenzaldehyde (0.91 g, 6.89 mmol) and 4-acetylbenzonitrile (1.0 g, 6.89 mmol), 4-[3-(3-cyanophenyl)-1-oxo-2-propenyl]benzonitrile was isolated as a pale yellow powder (1.4 g, 79%): ^{1}H NMR ($CDCl_3$) 8.53 (s, 1H), 8.35 (d, 2H), 8.15−8.20 (m, 3H), 7.92 (d, 1H), 7.82 (d, 1H), 7.67 (t, 1H).

Part B: Employing methods similar to example **1**, part B, but using 4-[3-(3-cyanophenyl)-1-oxo-2-propenyl]benzonitrile (0.5 g, 1.95 mmol), methyl 3-(4-cyanophenyl)-5-(3-cyanophenyl)-2,4-pentadienoate was prepared as mixture of isomers as a semisolid (0.52 g, 85%): MS 332 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) 8.55−7.0 (m, 10H), 6.45−6.15 (m, 1H), 3.8 (s, 3H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(4-cyanophenyl)-5-(3-cyanophenyl)-2,4-pentadienoate (0.5 g, 1.59 mmol), methyl 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoate was isolated after flash chromatography on silica gel (100 mL) eluting with toluene/ethyl acetate (95:5) to give a viscous oil (0.43 g, 85%): MS 319 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) 7.65 (d, 2H), 7.48 (d, 1H), 7.4−7.15 (m, 5H), 3.7 (s, 3H), 3.2 (m, 1H), 2.67 (m, 2H), 2.42 (t, 2H), 2.1−1.9 (m, 2H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoate (0.31 g, 0.97 mmol) and ethanol, the title compound **15** was isolated after HPLC purification on a Vydac C-18 column, eluting with solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 15 min), as a white powder (0.146 g, 41%): mp 180−185 °C; MS 367 $(M + H)^+$; HRMS calcd 367.2134, found 367.2136; ^{1}H NMR (DMSO-d_6) 9.27 (s, 4H), 9.22 (s, 2H), 9.21 (s, 2H), 7.8 (d, 2H), 7.65−7.47 (m, 6H), 3.92 (m, 2H), 3.18 (m, 1H), 2.8 (dd, 1H), 2.67 (dd, 1H), 2.6−2.33 (m, 2H), 2.0 (m, 2H). Anal. ($C_{21}H_{26}N_4O_2(CF_3CO_2H)_{2.1}$) C, H, N.

(±)-Methyl *β*-[3-(Aminoiminomethyl)phenyl]-4-(methoxycarbonyl)benzenepentanoate Mono(trifluoroacetate) (16). Part A: Employing methods similar to example **1**, part A, but using 3-acetylbenzonitrile (1.0 g, 6.8 mmol) and methyl 4-formylbenzoate (3.12 g, 17 mmol), the residue was chromatographed on silica gel eluting with methylene chloride to give 3-[3-(methyl 4-benzoate)-1-oxo-2-propenyl]benzonitrile (0.340 g, 20%): ^{1}H NMR ($CDCl_3$) 3.95 (s, 3H), 7.55 (d, 1H), 7.7 (m, 3H), 7.85 (t, 2H), 8.1 (d, 2H), 8.25 (d, 1H), 8.3 (s, 1H).

Part B: Employing methods similar to example **1**, part B, but using 3-[3-(methyl 4-benzoate)-1-oxo-2-propenyl]benzonitrile (0.192 g, 0.655 mmol), methyl 3-(3-cyanophenyl)-5-(methyl 4-benzoate)-2,4-pentadienoate was prepared as a mixture of *E* and *Z* isomers as an oil (0.215 g, 95%): MS $(M + H)^+$ 348; ^{1}H NMR ($CDCl_3$) 3.6−3.9 (m, 6H), 7.1−8.0 (m, 11H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-5-(methyl 4-benzoate)-2,4-pentadienoate (0.200 g, 0.574 mmol), methyl 3-(3-cyanophenyl)-5-(methyl 4-benzoate)pentanoate was prepared as an oil (0.150 g, 75%): MS $(M + NH_4)^+$ 369; ^{1}H NMR ($CDCl_3$) 2.0 (m, 2H), 2.5 (t, 2H), 2.7 (m, 2H), 3.15 (m, 1H), 3.6 (s, 3H), 3.9 (s, 3H), 7.15 (d, 2H), 7.5 (m, 4H), 7.95 (d, 2H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)-5-(methyl 4-benzoate)-pentanoate (0.151 g, 0.43 mmol), the title compound **16** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 24 min), as a solid (0.017 g, 10%): mp >200 °C; MS $(M + H)^+$ 369; ^{1}H NMR (DMSO-d_6) 1.95 (m, 2H), 2.5 (m, 2H), 2.65 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.55 (s, 3H), 3.8 (s, 3H). Anal. ($C_{21}H_{24}N_2O_4(CF_3CO_2H)_{1.1}$) C, H, N.

Preparation of (±)-Methyl *β*-[3-(Aminoiminomethyl)-phenyl]-4-[(methylsulfonyl)amino]benzenepentanoate Mono(trifluoroacetate) (17). Part A: Methyl 3-(3-cyanophenyl)-5-(4-aminophenyl)pentanoate (0.100 g, 0.325 mmol) was dissolved in 3 mL of benzene and treated with methanesulfonic anhydride (0.062 g, 0.357 mmol). The solution was stirred for 0.5 h, and the solvent was removed under vacuum. The residue was chromatographed on silica gel eluting (ethyl acetate/methylene chloride/toluene, v:v:v, 20:40:40) to give methyl *β*-(3-cyanophenyl)-4-[(methylsulfonyl)amino]benzenepentanoate as an oil (0.038 g, 30%): ^{1}H NMR ($CDCl_3$) 1.9 (m, 2H), 2.4 (t, 2H), 2.6 (m, 2H), 3.0 (s, 3H), 3.15 (m, 1H), 3.6 (s, 3H), 6.25 (s (broad), 1H), 7.1 (q, 4H), 7.5 (m, 4H).

Part B: Employing methods similar to example **1**, part D, but using methyl *β*-(3-cyanophenyl)-4-[(methylsulfonyl)amino]-benzenepentanoate (0.038 g, 0.098 mmol), the title compound **17** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 21 min), as a white solid (0.030 g, 76%): mp >200 °C; MS $(M + H)^+$ 404; ^{1}H NMR (DMSO-d_6) 1.95 (m, 2H), 2.4 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 2.95 (s, 3H), 3.55 (s, 3H), 7.05 (q, 4H), 7.65 (m, 4H), 8.9 (s (broad), 2H), 9.25 (s (broad), 2H), 9.55 (s, 1H). Anal. ($C_{20}H_{25}N_3O_4S(CF_3CO_2H)_{1.2}$) C, H, N.

Preparation of (±)-Methyl *β*-[3-(Aminoiminomethyl)-phenyl]-4-[(phenylsulfonyl)amino]benzenepentanoate Mono(trifluoroacetate) (18). Part A: methyl 3-(3-cyanophenyl)-5-(4-aminophenyl)pentanoate (0.100 g, 0.325 mmol) was dissolved in dioxane, and 0.5 mL of 1 N NaOH was added followed by benzenesulfonyl chloride. The solution was stirred for 1 h, quenched in 1 N HCl, and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was chromatographed on silica gel eluting with ethyl acetate/toluene (20:80, v:v) to give methyl *β*-(3-cyanophenyl)-4-[(phenylsulfonyl)amino]benzenepentanoate as an oil (0.060 g, 41%): MS $(M + NH_4)^+$ 466; ^{1}H NMR ($CDCl_3$) 1.9 (m, 2H), 2.35 (m, 2H), 2.6 (m, 2H), 3.15 (m, 1H), 3.55 (s, 3H), 6.95 (s, 4H), 7.45 (m, 5H), 7.55 (m, 2H), 7.75 (d, 2H).

Part B: Employing methods similar to example **1**, part D, but using methyl *β*-(3-cyanophenyl)-4-[(phenylsulfonyl)amino]-benzenepentanoate (0.060 g, 0.135 mmol), the title compound **18** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 25 min), as a white powder (0.015 g, 24%): mp >200 °C; MS $(M + H)^+$ 366; ^{1}H NMR (DMSO-d_6) 1.85 (m, 2H), 2.3 (m, 2H), 2.65 (dd, 1H), 2.9 (dd, 1H), 3.05 (m, 1H), 3.5 (s, 3H), 6.95 (s, 4H), 7.6 (m, 9H), 8.9 (s (broad), 2H), 9.25 (s (broad), 2H), 10.1 (s, 1H). Anal. ($C_{25}H_{27}N_3O_4S(CF_3CO_2H)_{1.1}$) C, H, N.

Preparation of (±)-Methyl 4-(Aminocarbonyl)-*β*-[3-(aminoiminomethyl)phenyl]benzenepentanoate Mono-(trifluoroacetate) (19). Part A: 2,4-Dimethoxybenzylamine hydrochloride (6.78 g, 33.3 mmol) was dissolved in dry DMF under N_2. 4-Carboxybenzaldehyde (5 g, 33.3 mmol) was added followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (7 g, 36.6 mmol) and 4-(dimethylamino)pyridine (4 g, 33.3 mmol). The resulting solution was stirred at room temperature for 24 h and quenched in 1 N HCl. After extraction with ethyl acetate, the organic layer was washed with water (3×) and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with ethyl acetate/toluene (20:80, v:v) to give 4-(*N*-2,4-dimethoxybenzenecarboxamido)benzaldehyde as an oil (4.3 g, 43%): MS $(M + H)^+$ 300; ^{1}H NMR ($CDCl_3$) 3.80 (s, 3H), 3.85 (s, 3H), 4.6 (d, 2H), 6.45 (m, 2H), 7.2 (m, 1H), 7.90 (s, 4H), 10.0 (s, 1H).

Part B: Employing methods similar to example **1**, part A, but using 3-acetylbenzonitrile (0.200 g, 1.52 mmol) and 4-(*N*-2,4-dimethoxybenzenecarboxamido)benzaldehyde (0.908 g, 3.04 mmol), 3-[3-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]-1-oxo-2-propenyl]benzonitrile was isolated as a white solid (0.338 g, 52%): MS $(M + H)^+$ 427; ^{1}H NMR ($CDCl_3$) 3.80 (s, 3H), 3.85 (s, 3H), 4.60 (d, 2H), 6.45 (m, 2H), 6.65 (t, 1H), 7.25 (d, 1H), 7.7 (m, 6H), 8.25 (d, 1H), 8.30 (s, 1H).

Part C: Employing methods similar to example **1**, part B, but using 3-[3-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]-1-oxo-2-propenyl]benzonitrile (0.318 g, 0.746 mmol), the residue was chromatographed on silica gel eluting with ethyl acetate/toluene (v:v, 20:80) to afford a mixture of *E* and *Z* isomers of methyl 3-(3-cyanophenyl)-5-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]-2,4-pentadienoate as an oil (0.210 g, 58%): MS $(M + H)^+$ 483; ^{1}H NMR ($CDCl_3$) 375−3.9 (m, 9H), 4.58 (m, 2H), 6.2−6.6 (m, 3H), 7.05−7.8 (m, 12H).

Part D: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-5-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]-2,4-pentadienoate (0.165 g, 0.342 mmol), methyl 3-(3-cyanophenyl)-5-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]pentanoate was isolated as an oil (0.140 g, 84%): MS

$(M + H)^+$ 487; ^1H NMR ($CDCl_3$) 1.95 (m, 2H), 2.45 (t, 2H), 2.6 (m, 2H), 3.15 (m, 1H), 3.59 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H), 4.55 (d, 2H), 6.45 (d, 2H), 6.55 (t, 1H), 7.10 (d, 2H), 7.25 (d, 1H), 7.55 (m, 6H).

Part E: A solution of methyl 3-(3-cyanophenyl)-5-[4-[*N*-(2,4-dimethoxybenzyl)benzamido]]pentanoate (0.140 g, 0.288 mmol) in acetonitrile was added to a solution of ceric ammonium sulfate (0.686 g, 1.152 mmol) in water. The resulting solution was heated at 60 °C for 4 h, cooled to room temperature, and poured into water. The water was extracted with ethyl acetate (2×) and the organic layer washed with water and brine and dried over magnesium sulfate. After the solvent was removed, the residue was chromatographed on silica gel, ethyl acetate/toluene (90:10, v:v), to give methyl 3-(3-cyanophenyl)-5-(4-benzamido)pentanoate as an oil (0.053 g, 55%): MS $(M + NH_4)^+$ 354; ^1H NMR (DMSO-d_6) 1.95 (m, 2H), 2.4 (m, 2H), 2.65 (dd, 1H), 2.8 (dd, 1H), 3.05 (m, 1H), 3.45 (s, 3H), 7.19 (d, 2H), 7.25 (s (broad), 1H), 7.56 (m, 6H), 7.90 (s (broad), 1H).

Part F: Employing the method of example **1**, part D but using methyl 3-(3-cyanophenyl)-5-(4-benzamido)pentanoate (0.050 g, 0.148 mmol), the title compound **19** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 16 min), as a solid (0.030 g, 57%): mp >200 °C; MS $(M + H)^+$ 354; ^1H NMR (DMSO-d_6) 1.95 (m, 2H), 2.45 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 7.20 (d, 2H), 7.25 (s, 1H), 7.6 (m, 8H), 7.85 (s, 1H), 8.95 (s (broad), 2H), 9.30 (s (broad), 2H). Anal. ($C_{20}H_{23}N_3O_3(CF_3CO_2H)_{1.0}$) C, H, N.

Preparation of (±)-Methyl 4-Amino-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Mono(trifluoroacetate) (20). Part A: Employing methods similar to example **1**, part A, but using 3-acetylbenzonitrile (987 g, 6.8 mmol) and 4-nitrobenzaldehyde (1.0 g, 6.8 mmol), 3-[3-(4-nitrophenyl)-1-oxo-2-propenyl]benzonitrile was isolated as a white solid (1.7 g, 97%): MS 279 $(M + H)^+$; ^1H NMR ($CDCl_3$) 7.60 (d, 1H), 7.70 (t, 1H), 7.85 (m, 4H), 8.25 (m, 4H).

Part B: Employing methods similar to example **1**, part B, but using 3-[3-(4-nitrophenyl)-1-oxo-2-propenyl]benzonitrile (0.500 g, 1.79 mmol), the residue was chromatographed on silica gel, ethyl acetate/toluene (20:80, v:v), to afford methyl 3-(3-cyanophenyl)-5-(4-nitrophenyl)-2,4-pentadienoate (0.441 g, 74%) as a mixture of the *E*/*Z* isomers: MS 335 $(M + H)^+$; ^1H NMR ($CDCl_3$) 3.6 (s, 3H), 3.8 (s, 3H), 5.9 (s, 1H), 6.25 (m, 2H), 6.6 (d, 1H), 7.15 (m, 2H), 7.6 (m, 11H), 8.2 (d, 4H), 8.65 (d, 1H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-5-(4-nitrophenyl)-2,4-pentadienoate (0.441 g, 1.32 mmol), the residue was chromatographed on silica gel eluting with ethyl acetate/methylene chloride (10:90, v:v) to yield methyl 3-(3-cyanophenyl)-5-(4-aminophenyl)pentanoate (0.220 g, 54%): MS 309 $(M + H)^+$; ^1H NMR ($CDCl_3$) 1.9 (m, 2H), 2.35 (t, 2H), 2.6 (m, 2H), 3.15 (m, 1H), 3.55 (s, 3H), 6.60 (d, 2H), 6.85 (d, 2H), 7.5 (m, 4H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)-5-(4-aminophenyl)pentanoate (0.220 g, 0.71 mmol), the title compound **20** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 13 min), as a white solid (0.105 g, 45%): mp >200 °C; MS 326 $(M + H)^+$; ^1H NMR (DMSO-d_6) 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 7.1 (q, 4H), 7.55 (m, 2H), 7.7 (m, 2H), 9.3 (d (broad), 4H). Anal. ($C_{19}H_{23}N_3O_2(CF_3CO_2H)_{1.2}$) C, H, N.

Preparation of (±)-Methyl 4-[(Aminoiminomethyl)amino]-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (21). Methyl 3-(3-cyanophenyl)-5-(4-aminophenyl)pentanoate (0.10 g, 0.325 mmol) was dissolved in 5 mL of pyridine, and 3,5-dimethylpyrazole-1-carboxamidine nitrate (0.098 g, 0.048 mmol) was added. The solution was heated at 80 °C overnight, cooled, and partitioned between ethyl acetate and water. The organic layer was washed with a small amount of water and dried over $MgSO_4$. After removing the solvent, the residue (0.150 g, 0.428 mmol) was converted to the amidine employing methods similar to example **1**, part D. The title compound was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 16 min), as a solid (0.080 g, 51%): MS $(M + H)^+$ 368; ^1H NMR (DMSO-d_6) 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 7.15 (q, 4H), 7.35 (s (broad), 4H), 7.65 (m, 4H), 9.05 (s (broad), 2H), 9.25 (s (broad), 2H), 9.65 (s, 1H). Anal. ($C_{20}H_{25}N_5O_2(CF_3CO_2H)_{2.1}$) C, H, N.

Preparation of (±)-Methyl 4-[(Aminoiminomethyl)amino]-β-[3-(aminoiminomethyl)phenyl]benzeneheptanoate Bis(trifluoroacetate) (23). Part A: Employing a method similar to example **1**, part A, but using 3-acetylbenzonitrile (3.7 g, 28.2 mmol) and 4-nitrocinnamaldehyde (5 g, 28.2 mmol), 3-[5-(4-nitrophenyl)-1-oxo-2,4-pentadienyl]-benzonitrile was prepared as a solid (6.5 g, 73%): MS $(M + H)^+$ 319; ^1H NMR ($CDCl_3$) 7.15 (m, 3H), 7.65 (m, 4H), 7.85 (d, 1H), 8.25 (m, 4H).

Part B: Employing methods similar to example **1**, part B, but using 3-[5-(4-nitrophenyl)-1-oxo-2,4-pentadienyl]benzonitrile (2 g, 6.28 mmol), the methyl 3-(3-cyanophenyl)-7-(4-nitrophenyl)-2,4,6-heptatrienoate was prepared as an oil (0.550 g, 25%): MS $(M + NH_4)^+$ 378; ^1H NMR ($CDCl_3$) 3.8 (s, 3H), 5.8 (s, 1H), 6.3 (dd, 1H), 6.65 (d, 1H), 7.15 (dd, 1H), 7.6 (m, 6H), 8.1 (d, 1H), 8.2 (d, 2H).

Part C: Employing methods similar to example **1**, part C, but using methyl 3-(3-cyanophenyl)-7-(4-nitrophenyl)-2,4,6-heptatrienoate (0.363 g, 1 mmol), methyl 3-(3-cyanophenyl)-7-(4-aminophenyl)heptanoate was prepared as an oil (0.296 g, 87%): MS $(M + H)^+$ 337; ^1H NMR ($CDCl_3$) 1.15 (m, 1H), 1.65 (m, 4H), 2.55 (m, 4H), 3.1 (m, 1H), 3.6 (s, 3H), 6.6 (d, 2H), 6.9 (d, 2H), 7.45 (m, 4H).

Part D: Employing methods similar to example **1**, part D, but using methyl 3-(3-cyanophenyl)-7-(4-aminophenyl)heptanoate (0.200 g, 0.595 mmol), the title compound **23** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 20 min), as a white solid (0.110 g, 46%): MS $(M + H)^+$ 396; ^1H NMR (DMSO-d_6) 1.2 (m, 1H), 2.55 (m, 2H), 2.65 (m, 2H), 2.5 (m, 2H), 2.65 (dd, 1H), 2.75 (dd, 1H), 3.1 (m, 1H), 3.5 (s, 3H), 7.1 (d, 2H), 7.2 (d, 2H), 7.4 (s (broad), 4H), 7.55 (t, 1H), 7.6 (d, 1H), 7.65 (m, 2H), 9.05 (s (broad), 2H), 9.25 (s (broad), 2H), 9.65 (s, 1H). Anal. ($C_{22}H_{29}N_5O_2(CF_3CO_2H)_{2.1}$) C, H, N.

Preparation of 4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoic Acid Dihydrochloride (24). Methyl 4-(aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate bis(trifluoroacetate) (**1**) (0.030 g, 0.08 mmol) was dissolved in 0.5 mL of 6 N HCl under N_2 and stirred at room temperature for 48 h. The solution was concentrated to give the title compound **24** as a white solid (0.018 g, 66%): mp >200 °C dec; MS $(M + H)^+$ 339; ^1H NMR (DMSO-d_6) 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 7.40 (d, 2H), 7.55 (m, 2H), 7.75 (m, 4H), 9.1 (d, 4H), 9.25 (d, 4H). Anal. ($C_{19}H_{22}N_4O_2(HCl)_{2.1}$) C, H, N.

Preparation of (±)-Ethyl 4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (25). Employing a method similar to example **26**, part B, using ethanol instead of 2-propanol, the title compound **25** was prepared as a white solid (0.015 g, 7%) after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 17 min): mp >200 °C; MS $(M + H)^+$ 367; ^1H NMR (DMSO-d_6) 1.05 (t, 3H), 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 3.50 (s, 3H), 3.95 (m, 2H), 7.40 (d, 2H), 7.55 (m, 2H), 7.75 (m, 4H), 9.1 (d, 4H), 9.25 (d, 4H). Anal. ($C_{21}H_{26}N_4O_2(CF_3CO_2H)_{2.2}$) C, H, N.

Preparation of (±)-1-Methylethyl 4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]benzenepentanoate Bis(trifluoroacetate) (26). Part A: Methyl 4-cyano-β-(3-cyanophenyl)benzenepentanoate (**7**) (0.250 g, 0.786

mmol) was dissolved in methanol, and LiOH (0.056 g, 2.3 mmol) in 1 mL of water was added. The solution was stirred at room temperature for 2 h and extracted with ethyl acetate. The resultant aqueous layer was made acidic with 1 N HCl and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated to give 4-cyano-β-(3-cyanophenyl)benzenepentanoic acid as an oil (0.138 g, 58%): ^{1}H NMR (DMSO-d_6) 1.95 (m, 2H), 2.3 (m, 3H), 2.70 (dd, 1H), 3.05 (m, 1H), 7.3 (d, 2H), 7.5 (t, 1H), 7.60 (d, 1H), 7.7 (m, 3H), 12.10 (s, 1H).

Part B: 4-Cyano-β-(3-cyanophenyl)benzenepentanoic acid (0.111 g, 0.37 mmol) was dissolved in 2-propanol and treated with anhydrous HCl for 2 min. The resulting solution was stirred at room temperature overnight and then concentrated. The residue was dissolved in fresh 2-propanol, and ammonium carbonate (0.284 g, 2.9 mmol) was added. The solution was stirred at room temperature for 24 h and concentrated, and the title compound **26** was isolated after HPLC purification on a Vydac C-18 column, solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2), using a gradient (R_f = 18 min), as a white powder (0.015 g, 11%): mp >200 °C dec; MS $(M + H)^+$ 381; ^{1}H NMR (DMSO-d_6) 1.15 (dd, 6H), 2.0 (m, 2H), 2.5 (m, 2H), 2.7 (dd, 1H), 2.85 (dd, 1H), 3.15 (m, 1H), 4.80 (m, 1H), 7.40 (d, 2H), 7.55 (m, 2H), 7.75 (m, 4H), 9.1 (d, 4H), 9.25 (d, 4H). Anal. ($C_{22}H_{28}N_4O_2(CF_3CO_2H)_{1.0}$) C, H, N.

Preparation of (±)-4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]-*N*-methylbenzenepentanamide Bis(trifluoroacetate) (27). Part A: Oxalyl chloride was added to a solution of 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoic acid (0.25 g, 0.82 mmol) in 10 mL of methylene chloride under a nitrogen atmosphere at ambient temperature. The reaction mixture was stirred for 2 h and concentrated in vacuo to give a semisolid residue. The residue was taken up in 5 mL of methylene chloride, and 40% methylamine in water (5 mL) was added. The reaction mixture was stirred vigorously for 2 h and then was partioned between 1 N HCl and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated to give the crude product as a semisolid. The residue was purified by flash chromatography on silica gel (100 mL) eluting with methylene chloride/ethyl acetate (v:v, 80:20) to give 4-cyano-β-(3-cyanophenyl)-*N*-methylbenzenepentanamide as a semisolid (0.120 g, 46%): MS 335 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) 7.6−7.4 (m, 6H), 7.17 (d, 2H), 5.3 (m, 1H), 3.27 (m, 1H), 2.67 (d, 2H), 2.55−2.35 (m, 4H), 2.07 (m, 1H), 1.95 (m, 1H).

Part B: Employing methods similar to example **1**, part D, but using 4-cyano-β-(3-cyanophenyl)-*N*-methylbenzenepentanamide (0.1 g, 0.32 mmol), the title compound **27** was isolated after HPLC purification on a Vydac column eluting with solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2) using a gradient (R_f = 15.3 min) as a white solid (0.045 g, 40%): MS 176.7 $(M + 2H)^{2+}$; HRMS calcd 352.2137, found 352.2138; ^{1}H NMR (DMSO-d_6) 9.31 (s, 2H), 9.23 (s, 2H), 9.21 (s, 2H), 9.11 (s, 2H), 7.75−7.65 (m, 5H), 7.55 (d, 2H), 7.37 (d, 2H), 3.15 (m, 1H), 2.55−2.35 (m, 4H), 1.95 (m, 2H). Anal. ($C_{20}H_{25}N_5O(CF_3CO_2H)_{2.4}$) C, H, N.

Preparation of (±)-1-[3-[3-(Aminoiminomethyl)phenyl]-5-[4-(aminoiminomethyl)phenyl]-1-oxopentyl]pyrrolidine Bis(trifluoroacetate) (28). Employing methods similar to example **27**, part A, but using 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoic acid (0.2 g, 0.66 mmol) and pyyrolidine (0.047 g, 0.66 mmol), 1-[3-(3-cyanophenyl)-5-(4-cyanophenyl)-1-oxopentyl]pyrrolidine was isolated after flash chromatography on silica gel eluting with methylene chloride/ethyl acetate (v:v, 60:40) as a viscous oil (0.14 g, 45%): MS 358 $(M + H)^+$, 375 $(M + NH_4)^+$; ^{1}H NMR ($CDCl_3$) 7.55−7.39 (m, 6H), 7.2 (d, 2H), 3.45−3.3 (m, 4H), 3.2 (m, 1H), 2.6−2.4 (m, 4H), 2.17 (m, 1H), 1.95−1.75 (m, 5H).

Part B: Employing methods similar to example **1**, part D, but using 1-[3-(3-cyanophenyl)-5-(4-cyanophenyl)-1-oxopentyl]-pyrrolidine (0.13 g, 0.36 mmol), the title compound **28** was isolated after HPLC purification using a Vydac C-18 column eluting with solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2) using a gradient (R_f = 14.2 min) as a white powder (0.085 g, 60%): MS 392 $(M + H)^+$, 196.7 $(M + 2H)^{2+}$; ^{1}H NMR (DMSO-d_6) 9.31 (s, 2H), 9.23 (s, 2H), 9.20 (s, 2H), 9.12 (s, 2H), 7.75−7.5 (m, 6H), 7.37 (d, 2H), 3.4−3.1 (m, 7H), 2.75−2.45 (m, 2H), 2.0 (m, 2H), 1.85−1.65 (m, 4H). Anal. ($C_{23}H_{29}N_5O_2(CF_3CO_2H)_{2.0}$) C, H, N.

Preparation of (±)-Methyl *N*-[3-[3-(Aminoiminomethyl)phenyl]-5-[4-(aminoiminomethyl)phenyl]-1-oxopentyl]-glycine Bis(trifluoroacetate) (29). Part A: Employing methods similar to example **27**, part A, but using 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoic acid (0.15 g, 0.49 mmol) and methyl glycine ester (0.068 g, 0.54 mmol), methyl *N*-[3-(3-cyanophenyl)-5-(4-cyanophenyl)-1-oxopentyl]glycine was isolated after flash chromatography purification on silica gel (75 mL) eluting with methylene chloride/ethyl acetate (v:v, 75:25) as a colorless viscous oil (0.13 g, 71%): MS 393 $(M + NH_4)$; ^{1}H NMR ($CDCl_3$) 7.57−7.42 (m, 6H), 7.17 (d, 2H), 5.85 (m, 1H), 4.0 (dd, 1H), 3.92 (dd, 1H), 3.25 (m, 1H), 2.65−2.45 (m, 4H), 2.1 (m, 1H), 1.93 (m, 1H).

Part B: Employing methods similar to example **1**, part D, but using methyl *N*-[3-(3-cyanophenyl)-5-(4-cyanophenyl)-1-oxopentyl]glycine (0.11 g, 0.29 mmol), the title compound **29** was isolated after HPLC purification on a Vydac C-18 column eluting with solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2) using a gradient (R_f = 13 min) as a semisolid residue (0.012 g, 10%): MS 205.8 $(M + 2H)^{2+}$; ^{1}H NMR (DMSO-d_6) 9.25 (s, 2H), 9.20 (s, 2H), 9.0 (s, 2H), 8.9 (s, 2H), 8.27 (t, 1H), 7.73−7.52 (m, 6H), 7.37 (d, 2H), 3.8 (dd, 1H), 3.72 (dd, 1H), 3.17 (m, 3H), 2.57−2.42 (m, 2H), 2.0 (m, 2H). Anal. ($C_{22}H_{27}N_5O_3(CF_3CO_2H)_{3.0}$) C, H, N.

Preparation of (±)-4-(Aminoiminomethyl)-β-[3-(aminoiminomethyl)phenyl]-*N*-methoxybenzenepentanamide Bis(trifluoroacetate) (30). Part A: A solution of 3-(3-cyanophenyl)-5-(4-cyanophenyl)pentanoic acid (0.15 g, 0.49 mmol), methoxylamine hydrochloride (0.041 g, 0.54 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.14 g, 0.73 mmol), and 4-(dimethylamino)pyridine (0.15 g, 1.22 mmol) in 5 mL of DMF under a nitrogen atmosphere was stirred for 18 h. The reaction solution was poured into water and extracted with ethyl acetate. The combined organic layer was washed with 1 N HCl (2×), water, brine, and dried over magnesium sulfate, and concentrated to give the crude product as a colorless viscous oil. The product was purified by flash chromatography on silica gel (50 mL) eluting with methylene chloride/ethyl acetate (v:v, 60:40) to give 4-cyano-β-(3-cyanophenyl)-*N*-methoxybenzenepentanamide as a colorless viscous oil (0.15 g, 91%): ^{1}H NMR ($CDCl_3$) 8.03 (bs, 1H), 7.56−7.42 (m, 6H), 7.15 (d, 2H), 3.58 (s, 3H), 3.28 (m, 1H), 2.8−1.85 (m, 6H).

Part B: Employing methods similar to example **1**, part D, but using 4-cyano-β-(3-cyanophenyl)-*N*-methoxybenzenepentanamide (0.12 g, 0.36 mmol), the title compound **30** was isolated after HPLC purification on a Vydac C-18 column eluting with solvent A (acetonitrile/water/TFA, 80:20:0.2) and solvent B (water/TFA, 99.8:0.2) using a gradient (R_f = 14 min) as a white powder (0.058 g, 44%): MS 184.7 $(M + 2H)^{2+}$; HRMS calcd 368.2086, found 368.2083; ^{1}H NMR (DMSO-d_6) 10.9 (s, 1H), 9.28 (s, 2H), 9.21 (s, 2H), 9.08 (s, 2H), 8.98 (s, 2H), 7.73 (d, 2H), 7.67 (m, 2H), 7.56 (m, 2H), 7.38 (d, 2H), 3.35 (s, 3H), 3.12 (m, 1H), 2.55−1.95 (m, 6H). Anal. ($C_{20}H_{25}N_5O_2(CF_3CO_2H)_{2.1}$) C, H, N.

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