Use of Conformationally Restricted Benzamidines as Arginine Surrogates in the Design of Platelet GPIIb-IIIa Receptor Antagonists[1]

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The use of 5,6-bicyclic amidines as arginine surrogates in the design of a novel class of potent platelet glycoprotein IIb-IIIa receptor (GPIIb-IIIa) antagonists is described. The additional conformational restriction offered by the bicyclic nucleus results in 20−400-fold increases in potency compared to the freely flexible, acyclic benzamidine counterpart. The design, synthesis, structure−activity relationships (SAR), and *in vitro* activity of this novel class of GPIIb-IIIa antagonists are presented.

Introduction

The process of platelet aggregation,[2] and its role in the acute thrombotic events, that can result from mechanical or natural rupture of atherosclerotic plaques have been well characterized.[3] Disruption of an arterial atherosclerotic plaque, either spontaneously or following balloon angioplasty, exposes collagen and von Willebrand factor (vWF) at the site of damage and promotes platelet adhesion. As a consequence, the bound platelets become activated and undergo conformational changes that result in the activation of glycoprotein IIb-IIIa (GPIIb-IIIa) receptors on the platelet surface. GPIIb-IIIa binds plasma fibrinogen, which due to its multivalent structure results in the cross-linking of platelets and consequently in platelet aggregation. This process of aggregation at the site of plaque rupture may ultimately lead to arterial occlusion with the clinical sequela of myocardial infarction or stroke. In an attempt to modulate aggressive aggregation processes and thus identify therapies to prevent such vaso-occlusive disorders, antagonists of the GPIIb-IIIa receptor have been proposed as potential therapeutic agents. Early macromolecular approaches, including monoclonal antibodies directed to GPIIb-IIIa[4] as well as peptide-based antagonists of the receptor,[5] have shown great promise as acute parenteral antithrombotic agents. More recently, the pharmaceutical strategy has focused on the design of small molecule, orally active antagonists for the chronic and/or prophylactic treatment of arterial thrombosis.

The binding of fibrinogen to GPIIb-IIIa is mediated in part by receptor recognition of the tripeptide sequence Arg-Gly-Asp (RGD).[6] Accordingly, small molecules that are able to mimic the RGD sequence can act as antagonists of fibrinogen binding, thereby blocking platelet aggregation.[7] A number of potent and selective peptide-based and small molecule RGD mimics have been reported that use benzamidines as an arginine surrogate.[8] These surrogates have generally been appended to a variety of acyclic, monocyclic, and bicyclic nuclear spacers connected to an acidic aspartate isostere (Figure 1). We chose to investigate the potential utility of amidine-substituted 5,6-bicyclic heterocycles as restricted benzamidine analogs. This analysis resulted in a series of antagonists represented by general structure B in which a 5,6-bicyclic arginine isostere is connected via an acyclic or cyclic nuclear linker to an acidic side chain (as the aspartate surrogate). In this report, we describe in detail the design, synthesis, structure−activity relationships (SAR), and pharmacological properties of this novel series of potent GPIIb-IIIa antagonists.

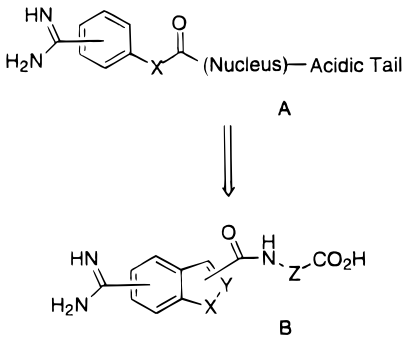

Figure 1. General structure of 5,6-bicyclic amidino acids (B) as platelet GPIIb-IIIa receptor antagonists.

Chemistry

As direct comparators for the 5,6-bicyclic series, the freely flexible, acyclic benzamidino acids **4a**−**c** were prepared according to the conditions outlined in Scheme 1. Alkylation of anilines **la**,**b** or phenol **1c** using *tert*-butyl bromoacetate afforded esters **2a**−**c.** Deprotection (TFA) to the corresponding acids followed directly by condensation with *tert*-butyl 7-aminoheptanoate gave the nitrile amides **3a**−**c**. Coupling reagents, such as DCC and CDI, could be used in the coupling reaction; however, the water soluble carbodiimide 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) was commonly employed due to the ease of workup. Using this reagent, the crude product was isolated in sufficient homogeneity to allow purification by simple recrystallization. Nitrile to amidine conversion en route

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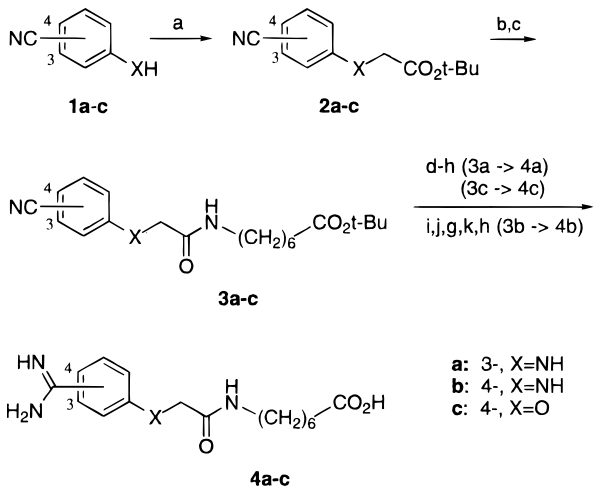
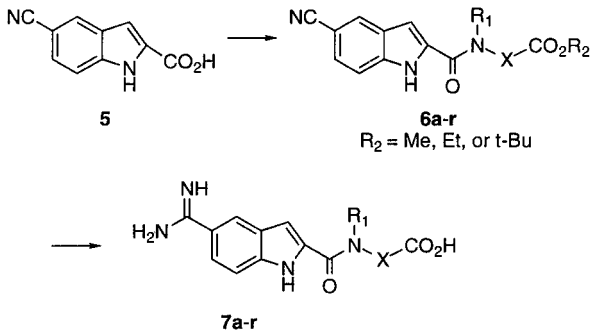
Scheme 1[a]



[a] Reagents: (a) *tert*-butyl bromoacetate, K_2CO_3; (b) TFA, anisole; (c) EDC, DMAP, DIEA, *tert*-butyl 7-aminoheptanoate; (d) H_2S, pyr; (e) MeI; (f) NH_4OAc; (g) Boc_2O, K_2CO_3; (h) TFA, anisole; (i) EtOH, HCl gas; (j) NH_3; (k) NaOH.

Scheme 2

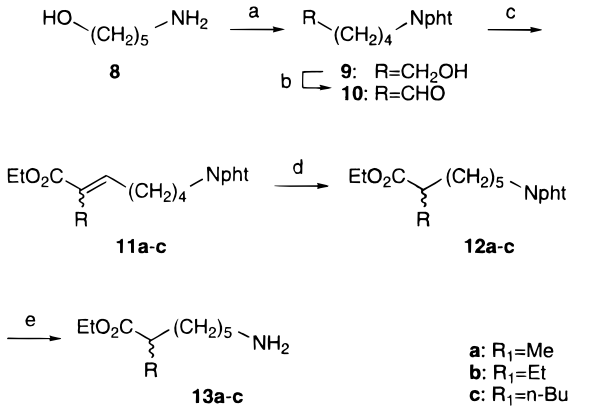


a: R_1=H, X=$(CH_2)_4$
b: R_1=H, X=$(CH_2)_5$
c: R_1=H, X=$(CH_2)_6$
d: R_1=H, X=$(CH_2)_7$
e: R_1=Me,X=$(CH_2)_6$
f: R_1=H, X=$CH_2C(O)NH(CH_2)_3$
g: R_1=H, X=$(CH_2)_2C(O)NH(CH_2)_2$
h: R_1=H, X=$(CH_2)_3C(O)NHCH_2$
i: R_1=H, X=CH_2(1,4-Phenyl)CH_2
j: R_1=H, X=CH_2(1,4-Phenyl)$(CH_2)_2$
k: R_1=H, X=$(CH_2)_5CH(Me)$
l: R_1=H, X=$(CH_2)_5CH(Et)$
m: R_1=H, X=$(CH_2)_5CH$(n-Bu)
n: R_1=H, X=$(CH_2)_4CH(Me)CH_2$
o: R_1=H, X=$(CH_2)_4CH(Et)CH_2$
p: R_1=H, X=$(CH_2)_4CH$(n-Bu)CH_2
q: R_1=H, X=$(CH_2)_4CH$(n-Hex)CH_2
r: R_1=H, X=$(CH_2)_4CH$(Phenyl)CH_2

to products **4a**−**c** was accomplished by one of two methods. In the conversion of **3a,c** to amidino acids **4a**,**c**, respectively, the well-documented three-step procedure, which proceeds via the thioamide/thioimidate intermediates, was employed.[9] Attempts to convert nitrile **3b** to the corresponding thioamide using this methodology were unsuccessful, necessitating the use of Pinner conditions to effect nitrile to amidine conversion.[10] In either route, the intermediate amidino ester products were protected as the N-Boc derivatives to facilitate purification. Deprotection of the Boc-protected amidino esters afforded the desired amidino acids **4a**−**c**.

Preparation of the target molecules used to study the SAR of the acidic side chain portion of structure B is shown in Scheme 2. Indole acid (**5**),[11] used as the precursor to a common amidine-substituted 5,6-bicyclic nucleus, was condensed with a variety of structurally diverse amino ester side chains to afford the nitrile amide derivatives **6a**−**r**. In most cases, the required amino ester side chains were derived from the corresponding acids which were either commercially available or prepared according to previously published methods. During the preparation of nitrile amide **6h** (R_2 = *tert*-butyl), a variety of attempts were made to couple acid **5** with the dipeptide side chain derived from γ-amino-*n*-butyric acid and glycine. Unfortunately, only poor yields of the coupled product (**6h**) were realized, necessitating the more linear approach of condensing acid **5** with ethyl γ-amino-*n*-butyrate, subsequent saponification of the ester, and coupling of the resulting acid with glycine *tert*-butyl ester. Nitrile to amidine conversion en route to products **7a**−**r** again was accomplished using either Pinner conditions[10] or the thioamide/thioimidate route.[9] Attempts to improve the efficiency of the synthetic routes through the large scale preparation of Boc- or Cbz-protected 5-amidinoindole-2-carboxylate met with limited success due to poor yields in the amidine-forming reaction.

Scheme 3[a]

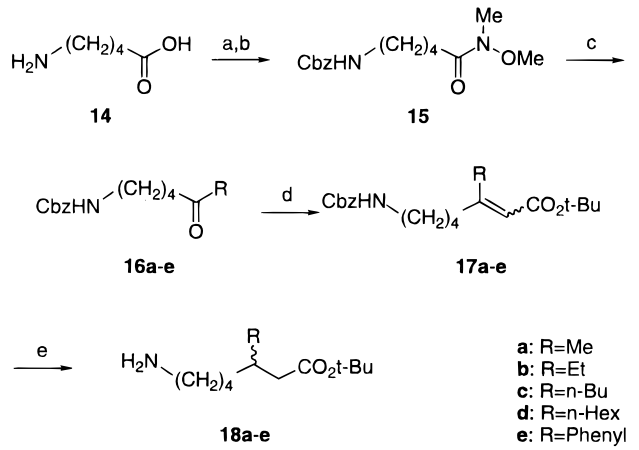


[a] Reagents: (a) phthalic anhydride; (b) $(COCl)_2$, DMSO, TEA; (c) alkyl phosphonate, KO-*t*-Bu or NaH; (d) 10% Pd/C, H_2; (e) NH_2NH_2.

The syntheses of substituted side chains **13a**−**c** and **18a**−**e**, which were required for the preparation of amidino acids **7k**−**m** and **7n**−**r**, respectively, are depicted in Schemes 3 and 4. The α-substituted derivatives **13a**−**c** were derived from 5-amino-1-pentanol (**8**; Scheme 3) which was protected as the corresponding phthalimide **9** and subsequently oxidized under Swern conditions[12] to afford the common aldehyde **10**. Horner−Emmons reaction[13] with the appropriate alkyl phosphonates yielded the α,β-unsaturated esters **11a**−**c** as a mixture of geometrical isomers. The isomers were not generally separated but were taken on directly. Hydrogenation to the saturated esters **12a**−**c** and subsequent deprotection using hydrazine afforded amino esters **13a**−**c** which were condensed directly with acid **5** to give nitrile amides **7k**−**m** (Scheme 2).

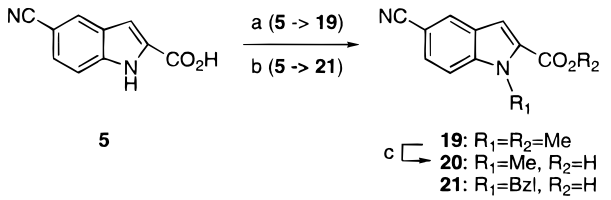
Amino ester side chains containing substituents at the position β to the carboxylate (**18a**−**e**) were prepared according to Scheme 4, beginning with commercially available 5-aminovaleric acid (**14**). Protection of the primary amine using benzyl chloroformate and subsequent derivatization of the carboxylate afforded the Cbz-protected Weinreb amide **15**,[14] which was used as a common intermediate. Treatment with the appropriate commercially available Grignard or alkyllithium reagents afforded ketones **16a**−**e**. In the case where R = hexyl (**16d**), it was necessary to generate the appropriate Grignard reagent from 1-bromohexane. Condensation of ketones **16a**−**e** with *tert*-butyl diethylphospho-

Scheme 4[a]



[a] Reagents: (a) benzyl chloroformate, K_2CO_3; (b) isobutyl chloroformate, NH(OMe)Me·HCl, *N*-methylmorpholine; (c) RLi or RMgBr; (d) *tert*-butyl diethylphosphonoacetate, KO-*t*-Bu; (e) 10% Pd/C, H_2.

Scheme 5[a]



[a] Reagents: (a) KOH, DMSO, MeI; (b) KOH, DMSO, benzyl bromide; (c) LiOH.

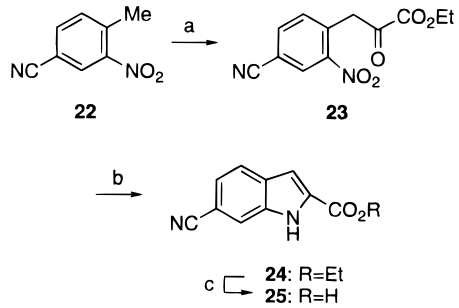
noacetate gave the corresponding α,β-unsaturated esters **17a**−**e** as mixtures of geometrical isomers. Hydrogenation of the carbon−carbon double bond and simultaneous hydrogenolysis of the Cbz protecting group was effected under conditions of catalytic hydrogenation, resulting in the corresponding amino esters **18a**−**e**. Direct condensation with acid **5** gave nitrile amides **7n**−**r** (Scheme 2).

In order to explore the SAR of the bicyclic component and the relative amidine position on general structure B, a variety of cyano-substituted 5,6-bicyclic acids were prepared using either literature methods or the routes depicted in Schemes 5−9. Condensation of the resulting acids with the appropriate amino ester side chains and conversion of the resulting nitrile amides to the desired amidino acids are shown in Scheme 10.

The *N*-methyl- and *N*-benzylindole-2-carboxylic acids were derived from 5-cyanoindole-2-carboxylate (**5**)[11] as depicted in Scheme 5. In the case of the *N*-methyl derivative, simultaneous N-methylation/esterification of acid **5** using potassium dimsylate and excess methyl iodide afforded the *N*-methyl methyl ester **19** which was subsequently hydrolyzed to give the *N*-methyl acid **20**. The *N*-benzyl acid **21** was prepared in a similar fashion with the exception that quenching the dianion of **5** with a single equivalent of benzyl bromide afforded the *N*-benzyl acid as the primary product.

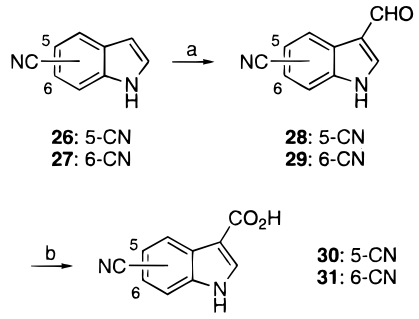
Preparation of the 2,6-disubstituted indole nucleus was accomplished using the Riessert indole synthesis[15] similar to Kermack's original conditions (Scheme 6).[16] Benzylic deprotonation of tolunitrile **22**, which was prepared according to literature methods,[17] and quenching the anion with diethyl oxalate afforded the indole precursor **23**. Reduction of the nitro group followed by

Scheme 6[a]



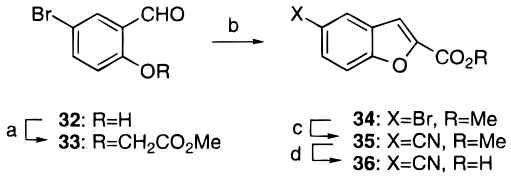
[a] Reagents: (a) NaOEt, diethyl oxalate; (b) Zn, HOAc; (c) NaOH.

Scheme 7[a]



[a] Reagents: (a) $POCl_3$, DMF; (b) $NaClO_2$, NaH_2PO_4.

Scheme 8[a]



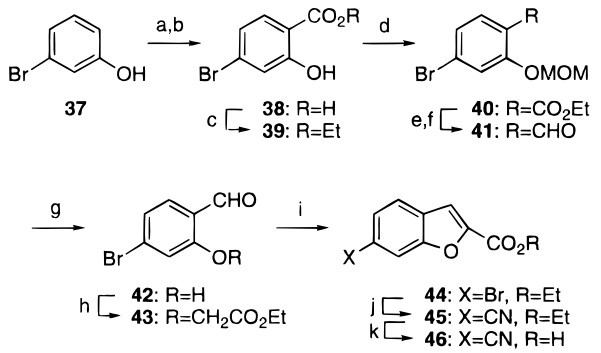
[a] Reagents: (a) methyl α-bromoacetate, K_2CO_3, NaI; (b) NaOMe; (c) CuCN, CuI, 160 °C; (d) LiOH.

in situ cyclization afforded the indole product **24** which was saponified to give the desired 6-cyanoindole-2-carboxylate (**25**).

The 3,5- and 3,6-disubstituted indole nuclei were prepared from 5-cyanoindole (**26**) and 6-cyanoindole (**27**), respectively (Scheme 7). While 5-cyanoindole was commercially available, the 6-cyano derivative was prepared according to the method of Batcho et al.[18] Regioselective formylation at the C-3 position (**28** and **29**) and subsequent oxidation using isobutylene as a chlorine scavenger[19] afforded the requisite 5-cyano- and 6-cyanoindole-3-carboxylic acids (**30** and **31**).

The synthesis of 5-cyanobenzofuran-2-carboxylate was modeled from the literature[20] and is described in Scheme 8. Alkylation of commercially available 5-bromosalicylaldehyde (**32**) with methyl α-bromoacetate afforded aldehyde **33** which was subjected to base-induced ring closure and *in situ* dehydration to give methyl 5-bromobenzofuran-2-carboxylate (**34**). Limited attempts at combining the base-induced alkylation and ring closure reactions into a single step resulted in substantially reduced yields compared to the two-step procedure and were not pursued further. Bromide displacement using copper(I) cyanide and copper(I) iodide[21] at elevated temperatures afforded the requisite methyl 5-cyanobenzofuran-2-carboxylate (**35**). Saponification afforded the corresponding 5-cyanobenzofuran-2-carboxylate (**36**).

Scheme 9[a]



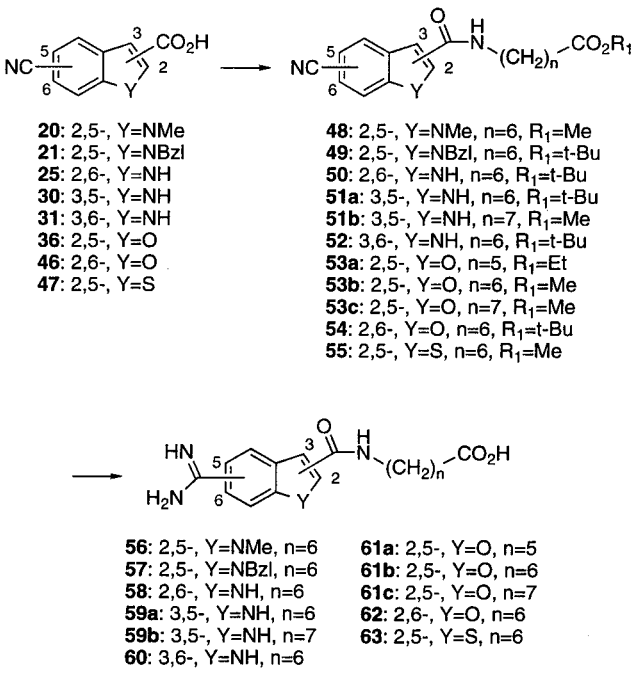
[a] Reagents: (a) NaH; (b) CO_2 (1900 psi), 175 °C; (c) EtOH, H_2SO_4; (d) NaH, chloromethyl methyl ether; (e) $LiAlH_4$; (f) MnO_2; (g) *p*-TosOH, dioxane, H_2O; (h) ethyl α-bromoacetate, K_2CO_3, NaI; (i) DBU; (j) CuCN, CuI, 135 °C; (k) NaOH.

The synthesis of the regioisomeric 2,6-disubstituted benzofuran derivative paralleled that of **36** with the exception that it was first necessary to prepare the requisite 4-bromosalicylaldehyde as shown in Scheme 9. Kolbe−Schmitt[22] carbonylation of sodium 3-bromophenoxide regiospecifically afforded salicylic acid derivative **38** which was subsequently esterified to **39**. Initially, direct conversion of ester **39** to salicylaldehyde **42** was attempted through a two-step reduction/oxidation sequence using $LiAlH_4$ and MnO_2. While reduction to the primary alcohol proceeded smoothly, the desired aldehyde product from the oxidation reaction could not be extracted from the manganese complexes. Accordingly, the phenol was protected as the methoxymethyl (MOM) derivative **40** which was subjected to the same two-step reduction/oxidation sequence to afford benzaldehyde **41**. Acid-catalyzed deprotection of the MOM group afforded the requisite 4-bromosalicylaldehyde (**42**). Alkylation with ethyl α-bromoacetate to afford derivative **43**, cyclization/dehydration to give bromobenzofuran **44**, nitrile formation to give ethyl 5-cyanobenzofuran-2-carboxylate (**45**), and subsequent saponification afforded 6-cyanobenzofuran-2-carboxylate (**46**).

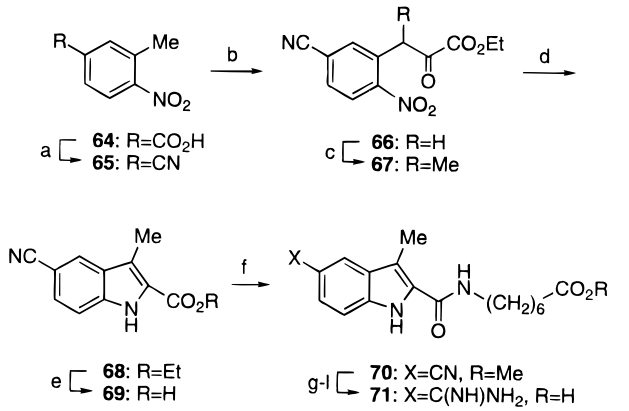
Elaboration of the nitrile-substituted, 5,6-bicyclic acids **20**, **21**, **25**, **30**, **31**, **36**, **46**, and **47**[23] into the desired amidino acid products **56**−**63** parallels the preparation of indole derivatives **7a**−**r** and is depicted in Scheme 10. Condensation of the aromatic acids with the appropriate amino ester gave nitrile amides **48**−**55**. In certain instances, the 5,6-bicyclic acids such as **30** and **36** were coupled to amino ester side chains of varying length (**51a**,**b** and **53a**−**c**, respectively). Conversion to the desired amidino acids **56**−**63** was accomplished by the thioamide/thioimidate route[9] or using Pinner conditions.[10] During the preparation of product **56**, conversion of nitrile **48** to the corresponding thioamide using H_2S proceeded without incident. Upon treatment of the thioamide with methyl iodide in refluxing acetone, however, the only product isolated was starting nitrile **48**, necessitating the use of Pinner conditions.

Preparation of analog **71** began with the synthesis of the 3-methylindole nucleus which was accomplished using the Riessert indole synthesis[15] as shown in Scheme 11. Treatment of commercially available 3-methyl-4-nitrobenzoic acid (**64**) with phosphorous pentachloride and *p*-toluenesulfonamide gave the tolunitrile derivative **65**.[24] Sequential bis alkylation at the benzylic position, first using diethyl oxalate to give derivative

Scheme 10



Scheme 11[a]



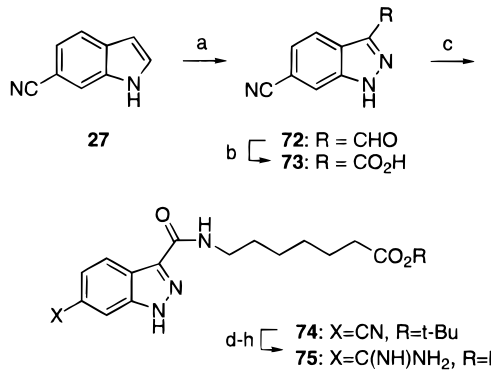
[a] Reagents: (a) PCl_5, *p*-toluenesulfonamide; (b) Na, $(CO_2Et)_2$, EtOH; (c) NaH, MeI; (d) Zn, HOAc; (e) LiOH; (f) EDC, DMAP, DIEA, methyl 7-aminoheptanoate hydrochloride; (g) H_2S, pyridine, TEA; (h) MeI; (i) NH_4OAc; (j) di-*tert*-butyl dicarbonate, K_2CO_3; (k) LiOH; (l) TFA, anisole.

66 and subsequently with MeI, afforded the Riessert substrate **67**. Reductive cyclization afforded the requisite 3-methylindole nucleus (**68**) which was saponified to acid **69**. Elaboration to nitrile amide **70** and subsequently to amidino acid **71** followed from previously described conditions.

Preparation of the amidinoindazole derivative began with nitrosation of 6-cyanoindole (**27**) to afford the 3-formylindazole nucleus (**72**; Scheme 12).[25] Oxidation with sodium chlorite and monobasic sodium phosphate using isobutylene as a chlorine scavenger[19] afforded 6-cyanoindazole-3-carboxylate (**73**), which was elaborated to amidino acid **75** using the methods described above.

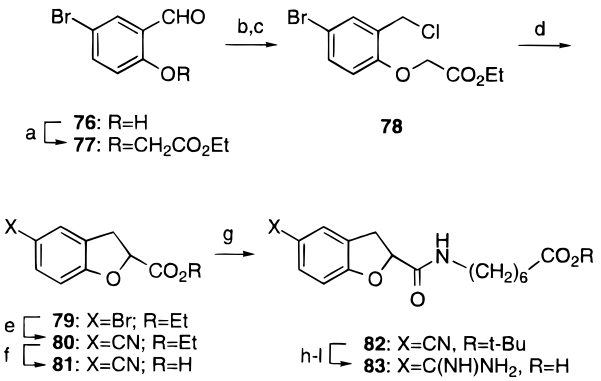
The preparation of the 2,3-dihydrobenzofuran derivative is depicted in Scheme 13, beginning with the preparation of the 5-cyano-2,3-dihydrobenzofuran-2-carboxylate nucleus according to the general methods of Edwards et al.[26] Alkylation of commercially available 5-bromosalicylaldehyde (**76**) with ethyl bromoacetate

Scheme 12[a]



[a] Reagents: (a) $NaNO_2$, HCl; (b) $NaClO_2$, NaH_2PO_4; (c) EDC, *tert*-butyl 7-aminoheptanoate, DMAP, DIEA; (d) H_2S, pyridine, TEA; (e) MeI; (f) NH_4OAc; (g) di-*tert*-butyl dicarbonate, K_2CO_3; (h) TFA, anisole.

Scheme 13[a]



[a] Reagents: (a) ethyl bromoacetate, K_2CO_3, NaI; (b) $NaBH_4$; (c) $SOCl_2$, pyridine; (d) NaH; (e) CuI, CuCN, 160 °C; (f) LiOH; (g) EDC, *tert*-butyl 7-aminoheptanoate, DMAP, DIEA; (h) H_2S, pyridine, TEA; (i) MeI; (j) NH_4OAc; (k) di-*tert*-butyl dicarbonate, K_2CO_3; (l) TFA, anisole.

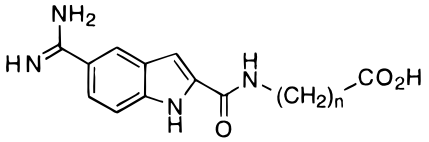
and catalytic NaI afforded phenoxyacetate **77**. Selective reduction of the aldehyde, followed by treatment of the resulting alcohol with thionyl chloride in pyridine, afforded the benzylic chloride **78**. Base-induced, intramolecular displacement of the chloride afforded the cyclized 2,3-dihydrobenzofuran nucleus (**79**). Conversion to nitrile **80** and subsequent saponification gave 5-cyano-2,3-dihydrobenzofuran-2-carboxylate (**81**) which was elaborated to amidino acid **83** following previously described methodology.

Results and Discussion

The ability of the amidino acids **4a**−**c**, **7a**−**r**, **56**−**63**, **71**, **75**, and **83** to block the binding of fibrinogen to the platelet GPIIb-IIIa receptor was measured in two assay systems. Antagonism of fibrinogen binding to a purified receptor preparation was determined using an enzyme-linked immunosorbent assay (ELISA),[27] while functional inhibition was measured by the compounds' ability to attenuate ADP-induced (fibrinogen-mediated) platelet aggregation in human platelet-rich plasma (PRP).[28]

The initial goal in this study was to design a novel class of nonpeptidyl mimics of the RGD sequence with a restricted benzamidine isostere whose structure would be amenable to the rapid exploration of the SAR of the series. In that indole amidines have been previously employed as probes for the specificity pocket of arginine

Table 1. Antagonism of Platelet GPIIb-IIIa by 2,5-Disubstituted Indole Amidines **7a**−**d**

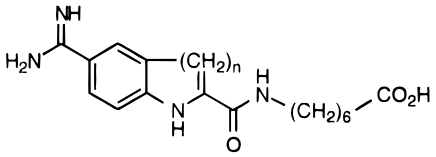


Entry	n	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7a	4	48.0 ± 8.0	> 100
7b	5	30.0 ± 4.0	> 100
7c	6	0.68 ± 0.04	2.8 ± 0.15
7d	7	9.8 ± 1.9	> 100

endopeptidases, initial efforts focused on the use of 5-amidinoindole as the restricted bicyclic unit.[29] In an attempt to mimic the critical distance between the guanidyl- and carboxyl-binding sites in receptor-bound RGD sequences, acidic side chains of varying length were appended via an amide bond to the 2-position of the indole nucleus (**7a**−**d**; Table 1). Amidino acid **7c** was at least 10-fold more potent than the other derivatives in both the purified receptor binding assay (ELISA) and the platelet aggregation assay (PRP), suggesting that the eight-atom tether between the indole nucleus and the acidic carboxylate provides the best approximation of the spatial relationship between guanidyl- and carboxyl-binding sites. The strict spatial requirements governing this series is evidenced by the fact that shortening or lengthening the acidic side chain by a single carbon−carbon bond (1.4 Å) causes at least a 10-fold decrease in potency. The lower activity of derivatives **7a**−**d** in the functional (PRP) versus ELISA assays could be due to multiple factors including plasma protein or lipid binding and/or the high fibrinogen concentrations present in the PRP assay.

It has been documented that conformational definition in the central region of RGD mimics enhances their potency against GPIIb-IIIa.[30] To assess whether the additional conformational restriction offered by the indole nucleus compared to benzamidine enhances the activity of this series, the acyclic derivative **4b** was prepared and its activity compared to the bicyclic counterpart **7c** (Table 2). Amidine **7c** is 34- and 17-fold more potent than its acyclic counterpart **4b** in the ELISA and PRP assays, respectively. A number of plausible explanations might explain the greater activity of the bicyclic series: One, the indole nucleus might provide additional π-stacking within that region of GPIIb-IIIa, or two, the electronic character of the indole nitrogen (**7c**) is sufficiently different from that of the aniline (**4b**) resulting in enhanced interaction within GPIIb-IIIa. Alternatively, the indole nucleus may induce a preferred geometrical relationship between the amidine, hydrogen bond-donating NH, and acidic side chain. Figure 2 shows the molecular overlays of low-energy models of the cyclic indole analog **7c** and the acyclic benzamidine **4b**.[31] There is a significant energy penalty for acyclic derivative **4b** to adopt the conforma-

Table 2. Comparison of Indole Amidine **7c** to Its Benzamidine Analog **4b**: Effects of Conformational Restriction in the Basic Component of RGD Mimics



Entry	n	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7c	1	0.68 ± 0.04	2.80 ± 0.15
4b	0	23.0 ± 2.6	67.0 ± 2.4

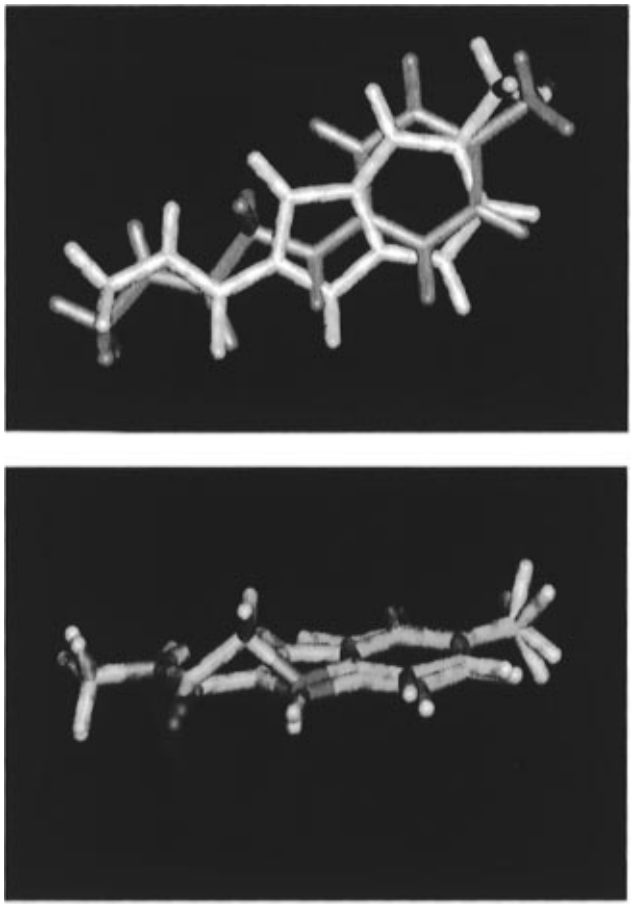
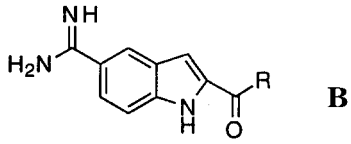
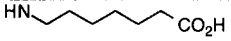
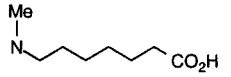
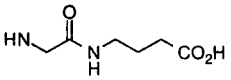
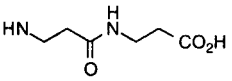
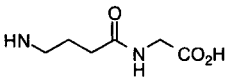
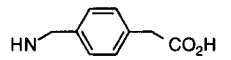
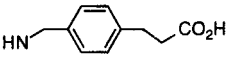


Figure 2. (Top) Structure overlay of a low-energy conformation for a model of the indole **7c** in green and a low-energy conformation of the acyclic benzamidine **4b** in blue. The minimized energy for **7c** was −12.03 kcal/mol; the minimized energy for **4b** was −22.15 kcal/mol. (Bottom) Edge view of the structure overlay of the low-energy conformations depicted in the top panel with the superimposition of the heteroatoms and the methyl group representing the amidine moiety. The acyclic benzamidine undergoes a deformation of the methylene group in order to meet the shorter heteroatom distances of the indole compound. The energy of this conformation of **4b** was −8.82 kcal/mol. The energy difference of 13.33 kcal/mol represents the energy penalty for the acyclic series to assume the proposed preferred geometrical relationships of the heteroatom interactions offered by the indole analog **7c**.

tion of cyclic analog **7c** which may explain the 34-fold difference in activity between the two. Since the pK_a of the amidines in derivatives **7c** and **4b** are 12.17 and 11.02, respectively, it is unlikely that the enhanced potency of analog **7c** is due to differences in basicity.

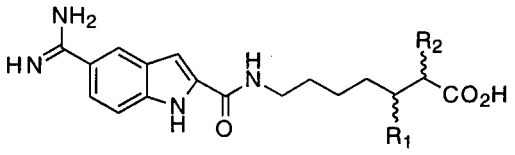
Table 3. Effect of Side Chain Modifications on Antagonism of Platelet GPIIb-IIIa: Indole Amidines **7e**−**j**



Entry	R	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7c		0.68 ± 0.04	2.8 ± 0.15
7e		0.34 ± 0.07	3.0 ± 0.06
7f		9.9 ± 1.10	50.0 ± 4.3
7g		0.76 ± 0.08	3.6 ± 1.1
7h		7.4 ± 0.83	32.0 ± 10.7
7i		14.0 ± 3.1	47.0 ± 8.5
7j		4.0 ± 0.55	39.0 ± 3.5

Having identified a nonpeptidyl RGD mimic (**7c**) with modest activity against GPIIb-IIIa, we turned our attention to exploring the SAR in an effort to enhance the potency of the series. In an attempt to better represent the peptidic nature of the physiological ligands for GPIIb-IIIa, the introduction of hydrogen bond donor/acceptor groups in the acidic side chain was undertaken. Derivative **7e** (Table 3) was explored to determine the role of the amide NH, whereas agents **7f**−**h** were prepared to make the acidic side chain of lead structure **7c** better resemble the peptidyl backbone of the RGD sequence. Removal of the hydrogen bond-donating capacity of the amide NH through *N*-methylation (**7e**) resulted in a 2-fold increase in activity in the ELISA suggesting that a H-bond donor at this site is not critical for good potency in the series. Since molecular modeling studies[32] show that the N-Me has little impact on the conformational biases of the acidic side chain, the increase in activity suggests the occurrence of a lipophilic interaction between the methyl group and the receptor. Incorporation of hydrogen bond donor/acceptor pairs in the form of amide bonds was not tolerated at the N- and C-terminal ends of the acidic side chain (**7f,h**, respectively), resulting in 14- and 11-fold losses in potency in the ELISA. Internal placement of the amide bond (agent **7g**) results in a derivative which contains the identical atom spacing as is present between the Gly-Asp amide bond and the β-carboxyl of

Table 4. Effects of Hydrophobic Substitution Proximal to the Terminal Carboxylate: Indole Amidines **7k−r**



Entry	R_1	R_2	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7c	H	H	0.68 ± 0.04	2.8 ± 0.15
7k	H	Me	6.9 ± 1.1	43.7 ± 13.7
7l	H	Et	27.0 ± 5.0	> 100
7m	H	n-Bu	16.0 ± 2.0	> 100
7n	Me	H	0.31 ± 0.04	2.8 ± 0.21
7o	Et	H	0.44 ± 0.06	5.2 ± 0.38
7p	n-Bu	H	0.79 ± 0.16	25.3 ± 5.7
7q	n-Hex	H	0.59 ± 0.06	59.0 ± 7.7
7r	Phe	H	0.46 ± 0.05	4.9 ± 1.1

Asp in the RGD sequence. While incorporation of the amide group at this position was tolerated, it did not add to the overall activity of the series.

Derivative **7c** possesses a freely flexible acidic side chain, capable of binding in more than a single conformation. To assess the impact of conformational restriction, a phenyl ring was incorporated into the flexible side chain in order to reduce the number of conformational degrees of freedom. In an energy-minimized conformation, the distance from the amide nitrogen to the carboxylate carbon is 8.9 Å in the lead structure **7c**. Both the phenylacetic acid (**7i**) and the phenylpropionic acid (**7j**) derivatives (7.8 and 9.5 Å, respectively) were prepared in order to approximate this distance.[33] Unfortunately, this met with little success as agent **7c** was 20- and 6-fold more potent in the ELISA than analogs **7i,j**, respectively. Phenoxyacetic[34] and phenylpropionic[35] acids have been previously used as Asp surrogates in the design of very potent GPIIb-IIIa receptor antagonists, suggesting that unless agents **7i,j** bind to the receptor in a different orientation, the potency loss is not likely due to steric effects. It is possible that either the amide to carboxylate distances in derivatives **7i,j** do not provide an accurate enough approximation of the six-carbon tether present in analog **7c** or a freely flexible side chain within this particular series of GPIIb-IIIa receptor antagonists is required for tight binding.

The impact of lipophilic substituents proximal to the carboxylate in nonpeptidal GPIIb-IIIa receptor antagonists has been previously studied.[36] To probe for the presence of a lipophilic binding site proximal to the carboxylate in the bound orientation of compound **3c** and to examine the effects of additional lipophilic interactions on the activity of this series, α- and β-substituted carboxylate derivatives (**7k−m** and **7n−r**, respectively) were prepared and evaluated (Table 4).

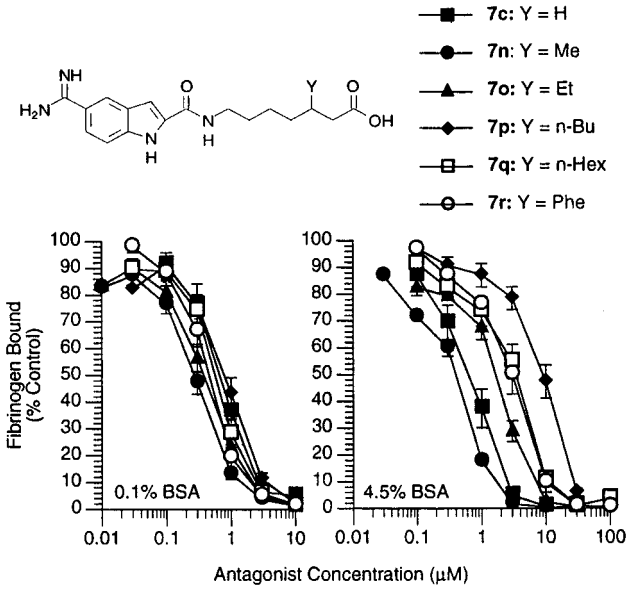
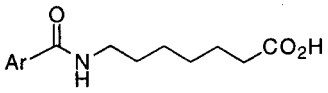
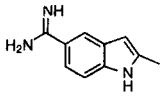
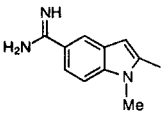
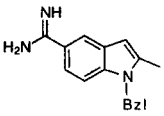
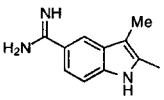
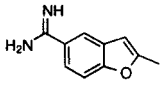
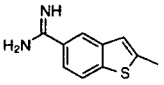
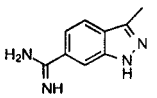
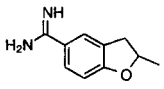


Figure 3. Effect of serum albumin on GPIIb-IIIa antagonism by indole amidines **7c,n−r**.

Since the literature suggests that the preferred absolute stereochemistry at the site of substitution is series dependent,[8a,36a,37] we initially chose to prepare derivatives **7k−r** in racemic form to gauge the impact of substituents adjacent to the carboxylate in this particular series. The incorporation of any alkyl substituents at the position α to the terminal carboxylate decreased activity in both the ELISA and the functional assay (e.g., **7k−m**). In contrast, lipophilic substituents at the β-position, regardless of size, were well tolerated. The fact that both small (methyl, **7n**) and large (phenyl, **7r**) lipophilic groups modestly enhanced the activity of the series in the ELISA assay suggests the presence of an ill-defined binding site in that region of the receptor. While increases in activity were observed for agents **7n−r** in the ELISA, similar increases were not observed in the functional assay (PRP; Table 4), in which the methyl and phenyl substituents had either a neutral or a negative impact on aggregation. The disparity between the ELISA and PRP data may indicate that the introduction of lipophilic substituents enhances the binding of these agents to various plasma constituents in the PRP assay, decreasing the effective concentration of the compound. To investigate this possibility, the effect of elevated levels of a representative plasma constituent on the ability of agents **7n−r** to antagonize the GPIIb-IIIa receptor was measured (Figure 3). In this case, bovine serum albumin (BSA) was used as a surrogate for human serum albumin (HSA). While increased levels of BSA in the ELISA (4.5%, w/v) had little impact on the activity of the unsubstituted derivative **7c**, the dose-response curves for the β-substituted analogs **7n−r** were shifted. For compounds **7n−p** the degree of shift was directly proportional to the size of the substituent, with the butyl, hexyl, and phenyl derivatives all suffering similar losses in potency of approximately 85%. The data would suggest that while lipophilic substituents at the position β to the free carboxylate enhanced the inherent ability of this series to antagonize GPIIb-IIIa (ELISA), the value of such structural manipulations would appear limited due to increased interactions with various protein constituents in physiologically relevant media. Accordingly, the

Table 5. Effects of Nuclear Modifications on Antagonism of Platelet GPIIb-IIIa: Amidines **56**, **57**, **61b**, **63**, **71**, **75**, and **83**

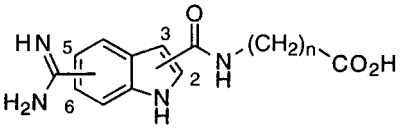


Entry	Ar	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7c		0.68 ± 0.04	2.8 ± 0.15
56		2.9 ± 0.13	7.5 ± 0.29
57		0.90 ± 0.17	21.0 ± 4.5
71		1.7 ± 0.55	4.1 ± 0.93
61b		0.04 ± 0.004	0.27 ± 0.003
63		0.85 ± 0.09	7.3 ± 2.7
75		0.02 ± 0.001	0.14 ± 0.01
83		0.87 ± 0.15	3.4 ± 0.81
SC54701A			0.035 ± 0.003

preparation of enantiomeric pairs to assess stereochemical effects of β-substituents was not pursued.

The inability to enhance the functional activity of the lead structure **7c** through structural manipulation of the acidic side chain prompted us to direct our attention to studying the SAR surrounding the 5,6-bicyclic indole ring. Two immediate sites for exploration were the N-1 and C-3 atoms, resulting in the preparation and evaluation of derivatives **56**, **57**, and **71** (Table 5). Compound **71**, which possesses a lipophilic methyl group at C-3, was only 2.5- and 1.5-fold less active than agent **7c** in the ELISA and PRP assays, respectively. *N*-Methylation (**56**) of the indole N-H reduces activity in the ELISA and PRP assays by 4- and 2.5-fold, respectively. Functionalization as the *N*-benzyl derivative (**57**), however, restores activity in the ELISA, indicating that a hydrogen bond donor in this region is not an absolute requirement for good potency. The ELISA activity of **57** relative to the *N*-methyl derivative **56** indicates that it may in fact be possible to enhance receptor affinity

Table 6. Antagonism of Platelet GPIIb-IIIa by Regioisomeric Indole Amidines **58**–**60**



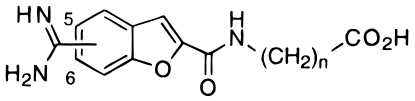
Entry	n	Substitution Pattern	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
7c	6	2,5-	0.68 ± 0.04	2.8 ± 0.15
58	6	2,6-	0.15 ± 0.02	1.3 ± 0.4
59a	6	3,5-	> 100	> 100
59b	7	3,5-	> 100	> 100
60	6	3,6-	0.10 ± 0.01	0.65 ± 0.19

through increased lipophilic interactions surrounding the 5,6-bicyclic nucleus. However, the opposite trends in activity between the ELISA and PRP data suggest that the usefulness of such structural manipulations might again be limited due to enhanced interactions with plasma components.

The critical tether length between the indole nucleus and the terminal carboxylate was well characterized through the study of derivatives **7a**–**d**. Regioisomeric derivatives **58**–**60** (Table 6) were prepared to determine the optimal substitution pattern between the basic amidine and the acidic side chain. While the interatomic distances between indole atom pairs C-2/C-5 (**7c**), C-2/C-6 (**58**), and C-3/C-6 (**60**) are all similar (4.5, 4.5, and 4.2 Å, respectively), the interatomic distance between C-3 and C-5 (**59a**) is only 3.7 Å.[33] The one carbon homolog **59b** was prepared in an attempt to compensate for this 0.8 Å discrepancy. In both assays, the 2,6- and 3,6-disubstituted regioisomers (**58** and **60**, respectively) displayed greater potency than the parent compound **7c**, while neither of the 3,5-disubstituted analogs (**59a**,**b**) displayed detectable activity in either assay. Perhaps the lack of potency for derivatives **59a**,**b** indicates that the 3,5-disubstitution pattern does not allow a suitable approximation of the critical distance between the guanidyl- and carboxyl-binding sites within the GPIIb-IIIa receptor. The distance between the sites of substitution and the geometrical relationship in regioisomers **7c**, **58**, and **60** are nearly identical. However, derivatives **58** and **60** bind with a 5-fold higher affinity than agent **7c**, suggesting the presence of a preferred spatial orientation between the amidine and the indole N-H.

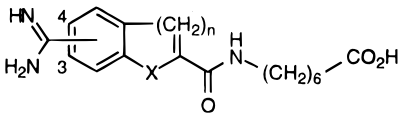
The benzofuran, benzo[*b*]thiophene, and indazole derivatives **61b**, **63**, and **75**, respectively (Table 5), were prepared to study the impact of incorporating hydrogen bond acceptor atoms in the B-ring of the 5,6-bicyclic nucleus. The benzo[*b*]thiophene analog **63** displayed similar activity to the indole **7c**, consistent with the fact that a hydrogen bond donor at this site is not required for receptor binding. On the other hand, the benzofuran (**61b**) and indazole (**75**) derivatives exhibited improvement in their ability both to bind to purified GPIIb-IIIa (ELISA) and to inhibit ADP-induced platelet aggregation (PRP). The 17- and 34-fold increases in potency in

Table 7. Modifications to the Benzofuran Series: Amidines **61a–c** and **62**



Entry	Amidine Substitution	n	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
61a	5-	5	2.30 ± 0.29	16.0 ± 6.7
61b	5-	6	0.04 ± 0.004	0.27 ± 0.003
61c	5-	7	3.3 ± 0.64	29.7 ± 10.6
62	6-	6	1.10 ± 0.08	7.2 ± 1.1

Table 8. Comparison of 5,6-Bicyclic Amidines **58** and **61b** to Their Acyclic Counterparts **4b** and **4c**, Respectively



Entry	Amidine Subst	X	n	ELISA IC_{50} (μM)	PRP IC_{50} (μM)
58	3-	NH	1	0.15 ± 0.02	1.30 ± 0.4
4a	3-	NH	0	64.0 ± 7.5	> 100
61b	4-	O	1	0.04 ± 0.004	0.27 ± 0.003
4c	4-	O	0	1.10 ± 0.06	2.60 ± 0.06

the ELISA observed for the benzofuran and indazole analogs, respectively (**61b** and **75**), suggests that a hydrogen bond acceptor in this region is optimal for tight binding. Since neither the benzofuran oxygen nor the indazole N-2 are geometrically disposed to allow intramolecular hydrogen bonding to the side chain amide NH, the increased activity observed for analogs **61b** and **75** may be due to intermolecular hydrogen bonding with the receptor and not to an altered side chain orientation. Saturation of analog **61b** to the 2,3-dihydrobenzofuran derivative **83** resulted in a 20-fold loss in potency in the ELISA. Changes in the physical chemical properties of the molecule as a result of saturating the benzofuran nucleus could be responsible for the reduced activity of analog **83**, including disruption of the planarity of the five-member ring, modified H-bonding capacity of the benzofuran and 2,3-dihydrobenzofuran oxygen, and differences in the pK_bs of the amidines. Data for the clinical agent from Searle (SC54701A) is included in Table 5 as a comparator.[8b]

It had been shown earlier that strict spatial and geometrical relationships between the amidine, the indole N-H, and the acidic side chain governed the activity of the amidinoindole series of antagonists. To probe whether these same geometrical and spatial constraints applied to the benzofuran series, which now contains a hydrogen bond acceptor in the B-ring of the 5,6-bicyclic system, agents **61a**,**c** and **62** were prepared and evaluated (Table 7). Similar to the indole series, strict spatial requirements govern the activity of the benzofuran class as evidenced by the fact that either increasing or decreasing the length of the tether connecting the terminal carboxylate to the amide nitrogen by only one carbon (**61a**,**c**, respectively) causes 57- and 83-fold losses in potency, respectively. In contrast to the indole series, however, the 2,5-disubstitution pattern (**61b**) is preferred over the 2,6-array (**62**), indicating that the correct geometrical relationship between the amidine, the acidic side chain, and the hydrogen bond-accepting oxygen atom is also critical for tight binding to GPIIb-IIIa.

The 34-fold difference in potency (ELISA) observed between indole amidine **7c** and its acyclic counterpart **4b** suggested that additional conformational restriction in the basic component of RGD mimics leads to enhanced interactions at the receptor. To determine if this trend holds true for other members of the 5,6-bicyclic series, derivatives **4a**,**c** were compared to their restricted partners **58** and **61b**, respectively (Table 8). In both cases, the additional conformational constraints offered by the 5,6-bicyclic nucleus resulted in enhanced potency, confirming that conformationally restricted benzamidines can exhibit advantages over benzamidine itself.

Table 9. Inhibition of Adhesive Protein Binding to Platelet GPIIb-IIIa and the Vitronectin Receptor ($\alpha_v\beta_3$) by Amidino Acids **60**, **61b**, and **75**

Entry	ELISA IC_{50} (μM) GPIIb-IIIa	ELISA IC_{50} (μM) $\alpha_v\beta_3$
60	0.10 ± 0.01	> 100
61b	0.04 ± 0.004	>100
75	0.02 ± 0.001	>100

The RGD motif is also recognized by other integrins such as the vitronectin receptor ($\alpha_v\beta_3$), and therefore, mimics of the RGD sequence can serve as antagonists of receptors other than GPIIb-IIIa. As representatives from this study, amidinoindole **60**, benzofuran **61b**, and indazole **75** were studied and found to bind selectively to the GPIIb-IIIa receptor, failing to compete with vitronectin for binding to its receptor ($\alpha_v\beta_3$) at concentrations as high as 100 μM (Table 9).[27]

The systematic SAR around a novel class of nonpeptidyl RGD mimics containing constrained benzamidine surrogates that act as potent and selective platelet GPIIb-IIIa antagonists has been described. The antagonists were derived from 5,6-bicyclic amidines which permitted the study of specific spatial and geometrical relationships between critical structural elements. The ability to define the orientation between amidine, acidic side chain, and hydrogen bond donor atoms led to increased potency. While a large number of nonpeptidyl GPIIb-IIIa antagonists have utilized benzamidine as an arginine surrogate, this study would suggest that the bicyclic nuclei can offer distinct advantages in terms of *in vitro* potency. The limitation of this series in its current form is the poor oral bioavailability of the free amidino acids, indicating that the use of prodrugs and/or formulations may be necessary to achieve useful plasma levels following oral administration.

Experimental Section

The syntheses of analogs **4a**, **7c**,**k**,**n**, **58**, **61b**, and **75** are described below. The experimental techniques employed to prepare the intermediates leading up to and including final products **4b**,**c**, **7a**,**b**,**d**−**j**,**l**−**m**,**o**−**r**, **56**, **57**, **59a**,**b**, **60**−**63**, **71**, **75**, and **83** pattern those described below and are included in the Supporting Information with the appropriate physical chemical data.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus calibrated with known compounds and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on a General Electric QE-300 spectrometer using either deuterated dimethyl sulfoxide in the absence (DMSO-d_6) or presence (DMSO-d_6/TFA) of trifluoroacetic acid or deuterated chloroform ($CDCl_3$) as the solvent, and chemical shifts are reported in parts per million (ppm) relative to dimethyl sulfoxide (DMSO; 2.49 ppm) or chloroform ($CHCl_3$; 7.25 ppm). Infrared spectra (IR) were run either as solutions in $CHCl_3$ or as pellets in KBr and were recorded on a Nicolet 510P spectrometer. Field desorption mass spectra (FDMS) were obtained on a VG Analytical VG70SE mass spectrometer. Fast atom bombardment high-resolution mass spectra (FAB-HRMS) were obtained on a VG Analytical VGZAB-2SE mass spectrometer. Combustion analyses were performed on a Control Equipment Corp. 440 elemental analyzer and were within 0.4% of the calculated values. Medium pressure liquid chromatography (MPLC) was performed using PrepPak silica gel cartridges on a Waters Prep LC/System 500A. Flash chromatography was performed over silica gel 60 (230−400 mesh ASTM). Preparative centrifugal thin-layer chromatography (PCTLC) was performed on a Harrison Model 7924 chromatotron with Merck silica gel 60 PF_{254} containing $CaSO_4 \cdot 0.5H_2O$ binder. All reactions requiring anhydrous conditions and/or an inert atmosphere were performed under a positive N_2 flow. Reverse phase chromatography was performed on a Ranin Rabbit chromatography system equipped with HDX pumps and using a NovaPak C_{18} (41.4 × 300) column. Ethyl 4-aminobutyrate hydrochloride and 5-cyanoindole were purchased from Aldrich Chemical Co. (Milwaukee, WI).

The ability of the amidino acids prepared in this study to antagonize the GPIIb-IIIa receptor was measured in two different assay systems. Antagonism in a purified receptor binding assay was determined by an ELISA (enzyme-linked immunosorbent assay) using purified human platelet GPIIb-IIIa, biotinylated fibrinogen, alkaline phosphatase-labeled goat antibiotin, and *p*-nitrophenyl phosphate, as previously reported.[27] Functional inhibition of the GPIIb-IIIa receptor was reflected in the compounds' ability to antagonize ADP-induced (fibrinogen-mediated) platelet aggregation in human platelet-rich plasma (PRP).[28] The vitronectin receptor binding assay was run using purified human placenta $\alpha_v\beta_3$ (VnR), biotinylated vitronectin, alkaline phosphatase-labeled goat antibiotin, and *p*-nitrophenol phosphate, as previously reported.[27] Adenosine diphosphate, alkaline phosphatase-labeled goat antibiotin, and bovine serum albumin (BSA) were purchased from Sigma Chemical Co. (St. Louis, MO). *p*-Nitrophenol phosphate was purchased from Bio-Rad (Hercules, CA).

Glycine, *N*-(3-Cyanophenyl)-, 1,1-Dimethylethyl Ester (2a). A solution of 20.0 g (169.2 mmol) of 3-aminobenzonitrile (**1a**) in 400 mL of DMF was treated with 60.0 g (434 mmol) of K_2CO_3 followed by 12.8 mL (86.7 mmol) of *tert*-butyl bromoacetate. The mixture was heated at 80 °C for 16 h, cooled, and filtered. The solvent was removed *in vacuo* and the residue partitioned between EtOAc and H_2O. The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give an oil. Purification by MPLC (SiO_2; 10% EtOAc in hexanes) afforded 19.45 g (83.7 mmol, 49%) of ester **2a** as an oily solid: ^{1}H NMR (DMSO-d_6) δ 7.26−7.18 (m, 1H), 6.94−6.82 (m, 2H), 6.42 (t, J = 6.2 Hz, 2H), 3.80 (d, J = 6.2 Hz, 2H), 1.37 (s, 9H); IR ($CHCl_3$) 3412, 2989, 2231, 1734, 1605, 1370, 1156 cm^{-1}; FDMS *m/e* 232 (M^+). Anal. ($C_{13}H_{16}N_2O_2$) C, H, N.

Nonanoic Acid, 9-[(3-Cyanophenyl)amino]-8-oxo-, 1,1-Dimethylethyl Ester (3a). A solution of 18.0 g (77.5 mmol) of *tert*-butyl ester **2a** in 225 mL of CH_2Cl_2 was treated with 84.0 mL (773 mmol) of anisole, and the mixture was cooled to 0 °C. The solution was treated with 59.0 mL (766 mmol) of TFA in a dropwise manner, the cold bath was removed, and the reaction was allowed to stir at ambient temperature until no starting ester could be detected by TLC (24 h). The reaction was concentrated *in vacuo* and the oil poured into saturated aqueous $NaHCO_3$. The basic mixture was washed twice with EtOAc and acidified to ∼pH 3 with 5 N aqueous HCl, resulting in the precipitation of the desired acid. The acid was filtered and dried to afford 12.41 g of a solid.

A solution of 1.60 g (9.08 mmol) of the preceding acid in 50 mL of CH_2Cl_2 was treated with 1.70 g (9.87 mmol) of 4-(dimethylamino)pyridine, 6.30 mL (36.2 mmol) of *N*,*N*-diisopropylethylamine, and 2.75 g (13.7 mmol) of *tert*-butyl 7-aminoheptanoate. The mixture was treated with 3.50 g (18.3 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, and the reaction stirred at ambient temperature until all of the starting acid had been consumed (∼15 h). The mixture was washed sequentially with 1 N aqueous citric acid (1×), H_2O (1×), 1 N aqueous NaOH (1×), and H_2O (1×). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 4.16 g of a solid. Purification by flash chromatography (SiO_2; 25% hexanes in EtOAc) afforded 2.40 g (6.66 mmol, 52% over two steps) of nitrile amide **3a** as a solid: ^{1}H NMR (DMSO-d_6) δ 7.90 (t, J = 5.5 Hz, 1H), 7.25−7.19 (m, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.84−6.76 (m, 2H), 6.46 (t, J = 5.9 Hz, 1H), 3.63 (d, J = 5.9 Hz, 2H), 3.08−2.99 (m, 2H), 2.11 (t, J = 7.3 Hz, 2H), 1.46−1.29 (m, 13H), 1.23−1.12 (m, 4H); IR ($CHCl_3$) 3409, 2936, 2232, 1719, 1670, 1606, 1152 cm^{-1}; FDMS *m/e* 359 (M^+). Anal. ($C_{20}H_{29}N_3O_3$) C, H, N.

Nonanoic Acid, 9-[[3-(Aminoiminomethyl)phenyl]amino]-8-oxo-, Mono(trifluoroacetate) (4a). A solution of 2.00 g (5.56 mmol) of nitrile amide **3a** in 100 mL of a 10% TEA in pyridine mixture was treated with a stream of $H_2S_{(g)}$ for 5 min. The reaction was stirred at ambient temperature until TLC analysis indicated the absence of starting nitrile (40 h). The mixture was concentrated *in vacuo*, and the oil was subjected to flash chromatography (2.5% MeOH in $CHCl_3$) to afford 1.20 g (3.05 mmol, 55%) of the corresponding thioamide. The thioamide (1.10 g, 2.80 mmol) was dissolved in 30 mL of acetone, and the solution was treated with 4.56 g (32.1 mmol, 11 equiv) of MeI. The reaction was heated to reflux for 1 h and evaporated *in vacuo*. The resulting residue was reconstituted in 5 mL of MeOH, and a solution of 0.43 g (5.60 mmol, 2 equiv) of NH_4OAc in 5 mL of MeOH was added. The mixture was heated to reflux for 2 h and concentrated *in vacuo*, and the resulting oil was taken up in 50 mL of a 1:1 THF:H_2O mixture. The solution was treated with 1.60 g (11.2 mmol, 4 equiv) of K_2CO_3 followed by 2.44 g (11.2 mmol, 4 equiv) of di-*tert*-butyl dicarbonate. The reaction was stirred for 72 h and was diluted with 50 mL of EtOAc and 50 mL of brine. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The resulting oil was subjected to MPLC (25% EtOAc in hexanes) to afford 0.70 g (1.46 mmol, 29% from nitrile amide **3a**) of the corresponding Boc-protected amidino *tert*-butyl ester as an oil: ^{1}H NMR ($CDCl_3$) δ 7.24−7.19 (m, 2H), 7.14−7.08 (m, 1H), 6.76−6.67 (m, 2H), 4.73−4.64 (m, 1H), 3.76 (br s, 2H), 3.26−3.18 (m, 2H), 2.13 (t, J = 7.4 Hz, 2H), 1.57−1.37 (m, 22H), 1.29−1.14 (m, 4H); IR ($CHCl_3$) 2982, 1718, 1666, 1607, 1584, 1524, 1295, 1162 cm^{-1}; FDMS *m/e* 477 (M + 1). Anal. ($C_{25}H_{40}N_4O_5 \cdot 0.5H_2O$) C, H, N.

A mixture of 0.60 g (1.30 mmol) of the Boc-protected amidino *tert*-butyl ester in 5 mL of anisole was treated with 10 mL of TFA. The reaction was stirred at ambient temperature until TLC analysis indicated the complete disappearance of starting material (16 h). The mixture was concentrated *in vacuo* and the resulting oil triturated with Et_2O to afford the trifluoroacetate salt of amidino acid **4a** as a solid in 73% yield (21% overall yield from nitrile amide **3a**): ^{1}H NMR (DMSO-d_6) δ 11.99 (br s, 1H), 9.14 (br s, 2H), 9.10 (br s, 2H), 7.97−7.85 (m, 1H), 7.26 (t, J = 7.6 Hz, 1H), 6.97−6.78 (m, 3H), 6.41−6.28 (m, 1H), 3.68 (s, 2H), 3.10−2.97 (m, 2H), 2.15 (t, J = 7.2 Hz, 2H), 1.54−1.13 (m, 8H); IR (KBr) 3355, 3111, 1728, 1672, 1641,

1206, 1131, 724 cm^{-1}; FDMS *m/e* 321 (M + 1). Anal. ($C_{16}H_{24}N_4O_3 \cdot CF_3CO_2H$) C, H, N.

Heptanoic Acid, 7-[[(5-Cyano-1*H*-indol-2-yl)carbonyl]-amino]-, Ethyl Ester (6c). A solution of 2.75 g (14.8 mmol) of 5-cyanoindole-2-carboxylate[11] in 100 mL of CH_2Cl_2 was treated with 3.50 g (28.6 mmol) of 4-(dimethylamino)pyridine, 4.00 mL (23.0 mmol) of *N*,*N*-diisopropylethylamine, and 4.00 g (19.1 mmol) of ethyl 7-aminoheptanoate hydrochloride.[38] The mixture was treated with 3.70 g (19.3 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, and the reaction stirred at ambient temperature until all of the starting acid had been consumed (~48 h). The mixture was washed sequentially with 1 N aqueous citric acid (50 mL), H_2O (50 mL), 1 N aqueous NaOH (50 mL), and H_2O (50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 4.10 g of a paste. Recrystallization from EtOAc/hexanes afforded 3.25 g (9.52 mmol, 64%) of **6c** as a white solid: ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 8.61 (t, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.58−7.46 (m, 2H), 7.23 (s, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.36−3.20 (m, 2H), 2.30−2.22 (m, 2H), 1.67−1.44 (m, 4H), 1.35−1.24 (m, 4H), 1.13 (t, J = 7.0 Hz, 3H); IR (KBr) 3345, 3225, 2219, 1703, 1637, 1565, 1333, 1275 cm^{-1}; FDMS *m/e* 341 (M^+). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N.

Preparation of Heptanoic Acid, 7-[[5-(Aminoiminomethyl)-1*H*-indol-2-yl]amino]- (7c). Nitrile amide **6c** was converted to the corresponding amidino ester using Pinner conditions.[10] A solution of 1.50 g (4.18 mmol) of nitrile amide **6c** in 250 mL of EtOH was treated with a stream of HCl gas for 30 min. The reaction vessel was sealed, and the solution was stirred until ^{1}H NMR indicated complete conversion to the imino ether (48 h). The reaction was concentrated *in vacuo*, reconstituted in EtOH, and evaporated *in vacuo* again. The residue was taken up in 250 mL of EtOH, and the mixture was treated with a stream of NH_3 gas for 30 min. The vessel was sealed, and the contents were stirred until analysis by ^{1}H NMR revealed the complete consumption of imino ether (24 h). The reaction was concentrated *in vacuo* to afford 820 mg (2.08 mmol, 50%) of the corresponding amidino ester hydrochloride as a white solid.

A 260 mg (0.65 mmol) sample of the amidino ester hydrochloride was taken up in 13 mL of THF and treated with 13.0 mL of 0.10 N aqueous LiOH. The reaction was stirred for 16 h, the THF was removed *in vacuo*, and the aqueous layer was acidified to pH 4 with 1 N aqueous HCl. The resulting solid was filtered, dried, and purified by reverse phase chromatography (0.5% NH_3CO_2H and 30% MeOH in H_2O) to afford 151 mg (0.46 mmol, 32% over two steps) of the formate salt of amidino acid **7c**: ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1H), 9.10 (br s, 2H), 8.55 (br s, 2H), 8.20 (s, 1H), 7.62−7.55 (m, 2H), 7.24 (s, 1H), 3.40 (t, J = 7.0 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 1.70−1.55 (m, 4H), 1.47−1.34 (m, 4H); IR (KBr) 3315, 1642, 1543, 1407, 1334, 744 cm^{-1}; FAB-HRMS *m/e* $C_{17}H_{23}N_4O_3$ calcd 331.1770, found 331.1774. Anal. ($C_{17}H_{22}N_4O_3$) C, H, N.

2*H*-Isoindole-2-pentanol, 1,3-Dihydro-1,3-dioxo- (9). A mixture of 14.4 g (97.2 mmol) of phthalic anhydride and 10 g (96.6 mmol) of 5-amino-1-pentanol (**8**) was heated at 130 °C for 16 h. The reaction was allowed to cool to room temperature and concentrated *in vacuo*. The crude oil was purified by MPLC (2% MeOH in $CHCl_3$) to afford 21.42 g (91.9 mmol, 94%) of phthalimide **9** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.84−7.78 (m, 2H), 7.72−7.65 (m, 2H), 3.67 (t, J = 7.1 Hz, 2H), 3.62 (t, J = 6.5 Hz, 2H), 2.13−2.04 (br s, 1H), 1.75−1.57 (m, 4H), 1.47−1.38 (m, 2H); IR ($CHCl_3$) 3019, 2943, 1772, 1711, 1439, 1398, 1367, 1052 cm^{-1}; FDMS *m/e* 234 (M + 1). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

2*H*-Isoindole-2-pentanal, 1,3-Dihydro-1,3-dioxo- (10). A −78 °C solution of 12.0 mL (17.5 g, 138 mmol) of oxalyl chloride in 200 mL of CH_2Cl_2 was treated with a solution of 16.3 mL (18.0 g, 230 mmol) of DMSO in 100 mL of CH_2Cl_2 in a dropwise manner. After stirring at −78 °C for 5 min, a solution of 21.4 g (92.0 mmol) of alcohol **9** in 100 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at −78 °C for 15 min when 64.0 mL (46.5 g, 460 mmol) of Et_3N was added in one portion. The cold bath was removed, and the reaction was allowed to reach 0 °C before 200 mL of H_2O was added. The organic layer was separated, washed with 1 N aqueous HCl (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 29.0 g of an oil. Purification by MPLC (15% then 25% EtOAc in hexanes) afforded 20.19 g (87.4 mmol, 95%) of aldehyde **10**: ^{1}H NMR ($CDCl_3$) δ 9.74 (s, 1H), 7.85−7.78 (m, 2H), 7.73−7.64 (m, 2H), 3.75−3.63 (m, 2H), 2.55−2.46 (m, 2H), 1.78−1.60 (m, 4H); IR ($CHCl_3$) 3026, 1773, 1713, 1398, 1051 cm^{-1}; FDMS *m/e* 231 (M^+). Anal. ($C_{13}H_{13}NO_3$) C, H, N.

2-Heptanoic Acid, 7-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)-2-methyl-, Ethyl Ester (11a). To a 0 °C mixture of 3.60 g (32.5 mmol, 1.5 equiv) of potassium *tert*-butoxide in 100 mL of THF was added 7.70 g (32.5 mmol) of triethyl 2-phosphonopropionate in a dropwise manner. After stirring at 0 °C for 15 min, a solution of 5.0 g (21.6 mmol, 1 equiv) of aldehyde **10** in 10 mL of THF was added dropwise. The reaction was stirred at ambient temperature until TLC analysis indicated complete consumption of starting aldehyde **10** (1 h). The mixture was quenched by the careful addition of 100 mL of brine. Ethyl acetate (100 mL) was added, the layers were separated, and the aqueous phase was extracted with 50 mL of EtOAc. The combined organic layers were washed with 100 mL of H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 8.35 g of an oil. Purification by MPLC (1% MeOH in $CHCl_3$) afforded 8.85 g (15.4 mmol, 71%) of product **11a** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.89−7.83 (m, 2H), 7.76−7.68 (m, 2H), 5.93−5.86 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.70 (t, J = 7.2 Hz, 2H), 2.57−2.46 (m, 2H), 1.88 (d, J = 1.0 Hz, 3H), 1.77−1.66 (m, 2H), 1.53−1.42 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); IR ($CHCl_3$) 3015, 2934, 1772, 1711, 1398, 1230 cm^{-1}; FDMS *m/e* 315 (M^+). Anal. ($C_{18}H_{21}NO_4$) C, H, N.

2*H*-Isoindole-2-heptanoic Acid, α-Methyl-1,3-dihydro-1,3-dioxo-, Ethyl Ester (12a). A solution of 4.80 g (15.2 mmol) of α,β-unsaturated ester **11a** in 30 mL of glacial HOAc was treated with 0.50 g of 10% Pd/C which had been prewetted with the same solvent. The mixture was hydrogenated at an initial pressure of 50 psi for 7 h. The reaction was filtered through Celite and concentrated *in vacuo* to afford 4.1 g (12.9 mmol, 85%) of product **12a** in analytically pure form as an oil: ^{1}H NMR ($CDCl_3$) δ 7.89−7.82 (m, 2H), 7.74 (m, 2H), 4.11 (q, J = 7.1, 2H), 3.67 (t, J = 7.2 Hz, 2H), 2.44−2.35 (m, 1H), 1.74−1.60 (m, 4H), 1.39−1.28 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H); IR ($CHCl_3$) 2940, 1771, 1711, 1468, 1398, 1372, 1187 cm^{-1}; FDMS *m/e* 317 (M^+). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

Heptanoic Acid, 7-[[(5-Cyano-1*H*-indol-2-yl)carbonyl]-amino]-2-methyl-, Ethyl Ester (6k). A solution of 4.10 g (13.0 mmol) of phthalimido ester **12a** in EtOH (150 mL) was treated with 6.30 mL (6.50 g, 130 mmol) of hydrazine hydrate and the mixture heated to reflux for 1 h. The reaction was allowed to cool and concentrated *in vacuo*. The residue was partitioned between Et_2O and 1 N aqueous NaOH. The organic layer was separated, washed with 1 N aqueous NaOH, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to afford 1.90 g of crude amino ester **13a** which was used in the subsequent reaction without purification.

Amino ester **13a** was coupled to 5-cyanoindole-2-carboxylate[11] according to the conditions used in the preparation of **6c** to afford product **6k** in 40% yield (from **12a**) following recrystallization from EtOAc: mp 144−145 °C; ^{1}H NMR ($CDCl_3$) δ 10.65 (br s, 1H), 8.03 (s, 1H), 7.59−7.48 (m, 2H), 6.95 (d, J = 1.6 Hz, 1H), 6.51−6.43 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.55−3.46 (m, 2H), 2.49−2.38 (m, 1H), 1.76−1.62 (m, 3H), 1.52−1.31 (m, 5H), 1.25 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H); IR ($CHCl_3$) 3446, 2939, 2224, 1723, 1653, 1553, 1328, 1216 cm^{-1}; FDMS *m/e* 355 (M^+). Anal. ($C_{20}H_{25}N_3O_3$) C, H, N.

Heptanoic Acid, 7-[[[5-(Aminoiminomethyl)-1*H*-indol-2-yl]carbonyl]amino]-2-methyl-, Mono(trifluoroacetate) (7k). Nitrile amide **6k** was processed according to conditions used in the conversion of **3a** to **4a** to afford amidino indole **7k** in 24% yield following reverse phase chromatography (20% CH_3CN in H_2O): mp 266−268 °C; ^{1}H NMR (DMSO-d_6/TFA) δ 12.07 (br s, 1H), 9.12 (br s, 2H), 8.75 (br s, 2H), 8.58 (t, J = 5.6 Hz, 1H), 8.19 (s, 1H), 7.62−7.53 (m, 2H), 7.27 (s, 1H), 3.31−3.22 (m, 2H), 2.34−2.22 (m, 1H), 1.58−1.47 (m, 4H), 1.39−1.22 (m, 4H), 1.00 (d, J = 7.0 Hz, 3H), no carboxyl OH

observed; IR (KBr) 3239, 2937, 1713, 1657, 1529, 1193, 1114, 804, 723 cm^{-1}; FDMS *m/e* 345 (M + 1); FAB-HRMS *m/e* $C_{18}H_{25}N_4O_3$ calcd 345.1972, found 345.1896. Anal. ($C_{18}H_{24}N_4O_3 \cdot CF_3CO_2H$) C, H, N.

Carbamic Acid, [5-(Methoxymethylamino)-5-oxopentyl]-, Phenylmethyl Ester (15). A −15 °C solution of 55.0 g (0.22 mol) of 5-(carbobenzyloxyamino)valeric acid (**14**) and 55.4 g (0.26 mol) of 4-methylmorpholine in 500 mL of CH_2Cl_2 was treated with 35.9 g (0.26 mol) of isobutyl chloroformate in a dropwise manner. After stirring for 45 min, 53.4 g (0.55 mol) of *N*,*O*-dimethylhydroxylamine hydrochloride was added in one portion. The reaction was stirred at −15 °C for an additional 3 h at which time it was quenched by the dropwise addition of 500 mL of saturated aqueous $NaHCO_3$. The two layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Purification by MPLC (40% EtOAc in hexanes) afforded 30.5 g (0.10 mol, 40%) of amide **15** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.38−7.29 (m, 5H), 5.09 (s, 2H), 5.05−4.94 (m, 1H), 3.67 (s, 3H), 3.28−3.14 (m, 5H), 2.44 (t, J = 6.8 Hz, 2H), 1.74−1.52 (m, 4H); IR ($CHCl_3$) 3453, 3012, 2941, 1717, 1649, 1516, 1237, 1000 cm^{-1}; FDMS *m/e* 295 (M + 1). Anal. ($C_{15}H_{22}N_2O_4$) C, H, N.

Carbamic Acid, (5-Oxohexyl)-, Phenylmethyl Ester (16a). A −78 °C solution of 8.00 g (272. mmol) of Weinreb amide **15** in THF (200 mL) was treated with 80.0 mL of MeLi (1.4 M in Et_2O, 112 mmol) in a dropwise manner. After complete addition, the mixture was stirred at −78 °C for 0.5 h and then at 0 °C for 0.5 h. The reaction was cooled to −78 °C and quenched by the dropwise addition of saturated aqueous NH_4Cl (50 mL). The two layers were separated, and the organic phase was dried over Na_2SO_4 and filtered. Evaporation of the solvent *in vacuo* afforded 6.10 g of an oil. Purification by flash chromatography (15% EtOAc in hexanes) afforded 4.25 g (17.0 mmol, 63%) of ketone **16a**: ^{1}H NMR (DMSO-d_6) δ 7.38−7.21 (m, 6H), 4.98 (s, 2H), 2.95 (q, J = 6.2 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.04 (s, 3H), 1.48−1.32 (m, 4H); IR ($CHCl_3$) 3454, 2945, 1715, 1516, 1235 cm^{-1}; FDMS *m/e* 249 (M^+). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

2-Heptenoic Acid, 3-Methyl-7-[[(phenylmethoxy)carbonyl]amino]-, 1,1-Dimethylethyl ester (17a). A −10 °C slurry of 7.40 g (193 mmol) of NaH (60% dispersion in oil) in 400 mL of THF was treated with 47.0 g (185 mmol) of *tert*-butyl diethylphosphonoacetate. The temperature of the mixture was allowed to rise to 0 °C, and the mixture was stirred for 2 h before a solution of 22.0 g (88.0 mmol) of ketone **16a** in 75 mL of THF was added dropwise. The reaction was stirred at ambient temperature for 2 h and was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The mixture was diluted with H_2O and EtOAc, and the layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford an oil. Purification by flash chromatography (15% EtOAc in hexanes) afforded 25.81 g (74.3 mmol, 84%) of α,β-unsaturated ester **17a** as an oil: IR ($CHCl_3$) 3453, 2979, 1710, 1646, 1516, 1455, 1369, 1144 cm^{-1}; FDMS *m/e* 348 (M + 1). Anal. ($C_{20}H_{29}NO_4$) C, H, N.

Heptanoic Acid, 3-Methyl-7-[[(5-cyano-1*H*-indol-2-yl)carbonyl]amino]-, 1,1-Dimethylethyl Ester (6n). A solution of 7.30 g (21.0 mmol) of α,βunsaturated ester **17a** in EtOAc (25 mL) was added to a slurry of 10% Pd/C (3.00 g) in 10 mL of EtOAc. The mixture was hydrogenated at atmospheric pressure until TLC indicated the complete consumption of starting material (18 h). The reaction was filtered and concentrated *in vacuo* to afford the crude amino ester **18a** which was taken onto the next step without purification.

Amino ester **18a** was directly coupled to indole acid **5** according to the conditions used in the preparation of **3a** to afford nitrile ester **6n** as a white solid in 38% yield following flash chromatography (40% EtOAc in hexanes): ^{1}H NMR ($CDCl_3$) δ 10.60 (s, 1H), 8.03 (s, 1H), 7.58−7.47 (m, 2H), 6.98 (d, J = 1.6 Hz, 1H), 6.61 (t, J = 5.7 Hz, 1H), 3.61−3.52 (m, 2H), 2.27−2.05 (m, 2H), 2.03−1.91 (m, 1H), 1.75−1.63 (m, 2H), 1.57−1.26 (m, 13H), 0.96 (d, J = 6.6 Hz, 3H); IR ($CHCl_3$) 3446, 3012, 2936, 2224, 1716, 1653, 1554, 1369, 1327, 1156 cm^{-1}; FDMS *m/e* 383 (M^+). Anal. ($C_{22}H_{29}N_3O_3$) C, H, N.

Heptanoic Acid, 3-Methyl-7-[[[5-(aminoiminomethyl)-1*H*-indol-2-yl]carbonyl]amino]-, Mono(trifluoroacetate) (7n). Nitrile amide **6n** was processed according to the conditions used in the conversion of **3a** to **4a** to afford amidinoindole **7n** in 92% yield following trituration of the crude product with hot EtOAc: ^{1}H NMR (DMSO-d_6) δ 12.11 (s, 1H), 11.98 (br s, 1H), 9.15 (s, 2H), 8.89 (s, 2H), 8.65 (t, J = 5.6 Hz, 1H), 8.22 (s, 1H), 7.64−7.52 (m, 2H), 7.29 (d, J = 1.8 Hz, 1H), 3.35−3.23 (m, 2H), 2.26−2.15 (m, 1H), 2.06−1.93 (m, 1H), 1.88−1.76 (m, 1H), 1.57−1.44 (m, 2H), 1.40−1.13 (m, 4H), 0.87 (d, J = 6.5 Hz, 3H); IR ($CHCl_3$) 3330, 3220, 3068, 2942, 1706, 1651, 1569, 1534, 1332, 1190, 1150, 808, 722 cm^{-1}; FDMS *m/e* 345 (M + 1). Anal. ($C_{18}H_{24}N_4O_3 \cdot CF_3CO_2H$) C, H, N.

Benzenepropanoic Acid, 4-Cyano-2-nitro-α-oxo-, Ethyl Ester (23). A solution of 30.60 g (188.0 mmol) of tolunitrile **22**[17] and 20.0 g (1.37 mol) of diethyl oxalate in 300 mL of EtOH was treated with a solution of NaOEt (generated by dissolving 11.30 g (283.0 mmol) of sodium metal in 300 mL of EtOH), and the mixture was stirred at ambient temperature for 16 h. The reaction was neutralized with 56.6 mL of 5 N aqueous HCl. The EtOH was removed *in vacuo*, and the resulting aqueous layer was extracted with CH_2Cl_2 (500 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The oil was placed under high vacuum to remove excess diethyl oxalate resulting in a solid. Purification by MPLC ($CHCl_3$) afforded 43.45 g (165.3 mmol, 88%) of product **23** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.45 (d, J = 8.3 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.85 (dd, J = 8.3, 1.5 Hz, 1H), 7.03 (d, J = 1.1 Hz, 1H), 6.93 (s, 1H), 4.44 (q, J = 7.0 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H); IR ($CHCl_3$) 3438, 3027, 2238, 1708, 1535, 1258 cm^{-1}; FDMS *m/e* 262 (M^+). Anal. ($C_{12}H_{10}N_2O_5$) C, H, N.

1*H*-Indole-2-carboxylic Acid, 6-Cyano-, Ethyl Ester (24). Water (180 mL) was added to a solution of 12.1 g (46.2 mmol) of **23** in 180 mL of glacial AcOH, and the mixture was heated to 75 °C. Zinc dust (230.5 g, 462 mmol) was carefully added in portions to the hot mixture, and after complete addition the reaction was stirred at 75 °C for 1 h. The mixture was cooled, filtered, and concentrated *in vacuo*. The residue was partitioned between H_2O and EtOAc. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a solid. Purification by MPLC (10% EtOAc in hexanes) afforded 3.60 g (16.8 mmol, 36%) of indole **24** as a white solid: ^{1}H NMR (DMSO-d_6) δ 12.25 (s, 1H), 8.10 (s, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.19 (d, J = 1.9 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); IR ($CHCl_3$) 3451, 3025, 2225, 1710, 1322, 1247 cm^{-1}; FDMS *m/e* 214 (M^+). Anal. ($C_{12}H_{10}N_2O_2$) C, H, N.

1*H*-Indole-2-carboxylic Acid, 6-Cyano- (25). A solution of 7.90 g (37.0 mmol) of ester **24** in 200 mL of EtOH was treated with 22 mL of 5 N aqueous NaOH (111 mmol). The reaction was heated to reflux for 3 h. The mixture was cooled and neutralized with 22 mL of 5 N aqueous HCl (111 mmol). The mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and H_2O. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to a solid. Recrystallization from toluene/MeOH afforded 3.10 g (16.6 mmol, 45%) of acid **25** as a white solid: ^{1}H NMR (DMSO-d_6) δ 13.21 (br, 1H), 12.31 (s, 1H), 7.89−7.80 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.18 (s, 1H); IR (KBr) 3293, 2234, 1707, 1530, 1247, 1205 cm^{-1}; FDMS *m/e* 186 (M^+). Anal. ($C_{10}H_6N_2O_2$) C, H, N.

Heptanoic Acid, 7-[[(6-Cyano-1*H*-indol-2-yl)carbonyl]amino]-, 1,1-Dimethylethyl Ester (50). Employing the conditions used in the preparation of **3a**, acid **25** and *tert*-butyl 7-aminoheptanoate were coupled to afford nitrile amide **50** in 59% yield following recrystallization from EtOAc/hexanes: ^{1}H NMR ($CDCl_3$) δ 12.27 (s, 1H), 7.85 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 8.1, 1.1 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 6.55 (t, J = 5.4 Hz, 1H), 3.62−3.53 (m, 2H), 2.24 (t, J = 7.3 Hz, 2H), 1.78−1.59 (m, 4H), 1.51−1.38 (m, 13H); IR ($CHCl_3$) 3451, 2938, 2224, 1719, 1653, 1546, 1321, 1152 cm^{-1}; FDMS *m/e* 369 (M^+). Anal. ($C_{21}H_{27}N_3O_3$) C, H, N.

Heptanoic Acid, 7-[[[6-(Aminoiminomethyl)-1*H*-indol-2-yl]carbonyl]amino]-, Mono(trifluoroacetate) (58). Nitrile amide **50** was processed by the conditions used in the conversion of **3a** to **4a** to afford amidino acid **58** as the

trifluoroacetate salt in 35% overall yield following trituration with hot EtOAc: ^{1}H NMR (DMSO-d_6) δ 12.21 (s, 1H), 11.97 (br s, 1H), 9.22 (br s, 2H), 8.90 (br s, 2H), 8.65 (t, J = 5.5 Hz, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.4, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.21 (s, 1H), 3.34−3.23 (m, 2H), 2.18 (t, J = 7.3 Hz, 2H), 1.59−1.41 (m, 4H), 1.37−1.24 (m, 4H); IR (KBr) 3467, 3354, 3098, 1717, 1667, 1567, 1532, 1195, 1132, 839 cm^{-1}; FDMS *m/e* 331 (M + 1). Anal. ($C_{17}H_{22}N_4O_3$·CF_3CO_2H) C, H, N.

Acetic Acid, (4-Bromo-2-formylphenoxy)-, Ethyl Ester (33). A slurry of 2.01 g (10.0 mmol) of 4-bromosalicylaldehyde (**32**), 1.52 g (11.0 mmol) of K_2CO_3, and 0.30 g (2.00 mmol) of NaI in 3 mL of DMF was treated with 1.25 mL (1.84 g, 11.0 mmol) of ethyl bromoacetate in a dropwise manner. The reaction was stirred at ambient temperature for 15 h, filtered, and concentrated *in vacuo*. The residue was taken up in 50 mL of EtOAc, and the mixture was washed with H_2O (3 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 3.25 g of an oil. Purification by flash chromatography (10% EtOAc in hexanes) afforded 2.90 g (10.0 mmol, quantitative) of **33** as an oil: ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H), 7.83−7.72 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 4.99 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H); IR ($CHCl_3$) 3029, 1757, 1690, 1593, 1481, 1393, 1182, 1128 cm^{-1}; FDMS *m/e* 286, 288 (M^+). Anal. ($C_{11}H_{11}BrO_4$) C, H.

2-Benzofurancarboxylic Acid, 5-Bromo-, Methyl Ester (34). A 0 °C solution of 300 mg (1.04 mmol) of aldehyde **33** in 8 mL of MeOH was treated with 75 mg (1.4 mmol) of NaOMe and the resulting mixture heated to reflux for 15 min. The reaction was cooled and treated with 5 mL of 1 N aqueous citric acid. The MeOH was evaporated *in vacuo*, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 285 mg of a white solid. The solid was taken up in MeOH and the solution treated with a stream of HCl gas. After stirring for 2 h at ambient temperature, the mixture was evaporated *in vacuo*. The solid was recrystallized from hexanes/EtOAc to afford 195 mg (0.76 mmol, 74%) of benzofuran **34** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 1.4 Hz, 1H), 6.74−6.60 (m, 2H), 3.87 (s, 3H), no carboxyl OH observed; IR ($CHCl_3$) 1726, 1572, 1430, 1297, 1219, 1088, 975, 809 cm^{-1}; FDMS *m/e* 254, 256 (M^+). Anal. ($C_{10}H_7BrO_3$) C, H.

2-Benzofurancarboxylic Acid, 5-Cyano-, Methyl Ester (35). A mixture of 700 mg (2.74 mmol) of bromide **34**, 525 mg (2.76 mmol) of CuI, and 500 mg (5.60 mmol) of CuCN in 10 mL of DMF was heated to 155 °C for 16 h. The mixture was cooled, filtered over Celite, and concentrated *in vacuo*. The residue was partitioned between 50 mL of EtOAc and 50 mL of H_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give 755 mg of a yellow solid. Recrystallization from hexanes/EtOAc afforded 495 mg (2.46 mmol, 90%) of nitrile **35** as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 7.99−7.92 (m, 2H), 7.83 (s, 1H), 3.90 (s, 3H); IR ($CHCl_3$) 2229, 1717, 1584, 1302, 1238, 1123, 913, 824, 764 cm^{-1}; FDMS *m/e* 201 (M^+). Anal. ($C_{11}H_7NO_3$) C, H, N.

2-Benzofurancarboxylic Acid, 5-Cyano- (36). The title compound was prepared in 53% yield from methyl ester **35** by following the procedure described for the preparation of acid **25**: ^{1}H NMR (DMSO-d_6) δ 13.90 (br s, 1H), 8.32 (s, 1H), 7.02−7.84 (m, 2H), 7.71 (s, 1H); IR (KBr) 3418, 2235, 1692, 1578, 1425, 1207, 829 cm^{-1}; FDMS *m/e* 187 (M^+). Anal. ($C_{10}H_5NO_3$) C, H, N.

Heptanoic Acid, 7-[[(5-Cyano-2-benzofuranyl)carbonyl]amino]-, Methyl Ester (53b). Employing the conditions used in the preparation of **3a**, nitrile amide **53b** was prepared from acid **36** and methyl 7-heptanoate as a white solid in 48% yield following flash chromatography (0% then 10% THF in CH_2Cl_2): ^{1}H NMR (DMSO-d_6) δ 8.81 (t, J = 5.7 Hz, 1H), 8.32 (s, 1H), 7.87−7.81 (m, 2H), 7.57 (s, 1H), 3.52 (s, 3H), 3.28−3.16 (m, 2H), 2.24 (t, J = 7.4 Hz, 2H), 1.54−1.43 (m, 4H), 1.29−1.20 (m, 4H); IR (KBr) 3369, 2932, 2853, 2226, 1717, 1675, 1599, 1532, 1462, 1435, 1278, 1201, 1124, 822 cm^{-1}; FDMS *m/e* 328 (M^+). Anal. ($C_{18}H_{20}N_2O_4$), C, H, N.

Heptanoic Acid, 7-[[[5-(Aminoiminomethyl)-2-benzofuranyl]carbonyl]Amino]-, Mono(trifluoroacetate) (61b). Nitrile amide **53b** was processed under the conditions used in the conversion of **3a** to **4a** to afford amidino acid **61b** in 41% overall yield following trituration with EtOAc: ^{1}H NMR (DMSO-d_6) δ 11.97 (s, 1H), 9.35 (s, 2H), 9.15 (s, 2H), 8.84 (t, J = 5.1 Hz, 1H), 8.26 (s, 1H), 7.94−7.79 (m, 2H), 7.67 (s, 1H), 3.35−3.19 (m, 2H), 2.17 (t, J = 7.3 Hz, 2H), 1.60−1.41 (m, 4H), 1.38−1.17 (m, 4H); IR (KBr) 3321, 3109, 2938, 1672, 1647, 1538, 1456, 1206, 1190, 1132 cm^{-1}; FDMS *m/e* 332 (M + 1). Anal. ($C_{17}H_{21}N_3O_4$·CF_3CO_2H) C, H, N.

1*H*-Indazole-3-carboxylic acid, 6-Cyano- (73). To a slurry of 3.00 g (21.1 mmol) of 6-cyanoindole (**27**)[18] in a solution of 14.6 g (211 mmol) of $NaNO_2$ in 200 mL of H_2O was slowly added 32 mL of 6 N aqueous HCl until pH < 2. After stirring for 3 h, the solution was extracted with EtOAc (5 × 300 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford 3.40 g of crude 3-formyl-6-cyanoindazole (**72**). The aldehyde was not purified but was directly oxidized according to the methods used in the synthesis of **30** to afford 2.58 g (13.8 mmol, 65% overall yield from **27**) of **73**: ^{1}H NMR (DMSO-d_6) δ 14.34 (br s, 1H), 13.26 (br s, 1H), 8.28 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H); IR (KBr) 3167, 3129, 2221, 1737, 1695, 1491, 1233, 1167, 824 cm^{-1}; FDMS *m/e* 187 (M^+). Anal. ($C_9H_5N_3O_2$) C, H, N.

Heptanoic Acid, 7-[[(6-Cyano-1*H*-indazol-3-yl)carbonyl]amino]-, 1,1-Dimethylethyl Ester (74). Employing the conditions used in the preparation of **3a**, nitrile amide **74** was prepared from acid **73** and *tert*-butyl 7-aminoheptanoate in 27% yield following PCTLC (gradient of 10−40% EtOAc in hexanes): ^{1}H NMR (DMSO-d_6) δ 14.11 (s, 1H), 8.54 (t, J = 5.4 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 3.30−3.19 (m, 2H), 2.14 (t, J = 7.2 Hz, 2H), 1.56−1.20 (m, 17H); IR (KBr) 3367, 3155, 2227, 1730, 1641, 1553, 1366, 1153 cm^{-1}; FDMS *m/e* 371 (M + 1). Anal. ($C_{20}H_{26}N_4O_3$) C, H, N.

Heptanoic Acid, 7-[[[6-(Aminoiminomethyl)-1*H*-indazol-3-yl]carbonyl]amino]-, Mono(trifluoroacetate) (75). Nitrile amide **74** was processed under the conditions used in the conversion of **3a** to **4a** to afford amidino acid **75** in 21% overall yield following trituration with hot EtOAc: ^{1}H NMR (DMSO-d_6) δ 14.23 (s, 1H), 12.02 (br, 1H), 9.50 (br s, 2H), 9.11 (br s, 2H), 8.54 (t, J = 5.6 Hz, 1H), 8.42 (d, J = 8.2 Hz, 1H), 8.18 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 3.29−3.49 (m, 2H), 2.28 (t, J = 4.8 Hz, 2H), 1.62−1.49 (m, 4H), 1.46−1.32 (m, 4H); IR (KBr) 3361, 3122, 1704, 1667, 1537, 1210, 1194, 1150, 723 cm^{-1}; FAB-HRMS *m/e* $C_{16}H_{22}N_5O_3$ calcd 332.1723, found 332.1716 (M + 1). Anal. ($C_{16}H_{21}N_5O_3$·CF_3CO_2H) C, H, N.

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Supporting Information Available: Experimental procedures, physical chemical data, and analytical data for all synthetic intermediates and final products of this study (41 pages). Ordering information is given on any current masthead page.

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