Preparation and Pharmacological Evaluation of Novel Glycoprotein (Gp) IIb/IIIa Antagonists. 1. The Selection of Naphthalene Derivatives

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The synthesis and design using molecular modeling techniques for non-peptide, low molecular weight novel fibrinogen receptor (glycoprotein IIb/IIIa: Gp IIb/IIIa) antagonists, is reported. We used a highly potent serine protease inhibitor, Nafamostat, having an amidinonaphthyl unit as the starting compound. The compounds 4-(6-amidino-2-naphthylaminocarbonyl)phenoxyacetic acid (5a) and 4-(6-amidino-2-naphthalenecarboxamido)phenoxyacetic acid (5b) inhibited adenosin-5′-diphospate (ADP)-induced aggregation of human platelet-rich plasma (PRP) with IC_{50} values of 0.05 and 0.07 μM, respectively, and had lost their ability to inhibit a variety of serine proteases, including thrombin, factor Xa, plasmin and trypsin.

Key words glycoprotein IIb/IIIa; amidinonaphthyl compound; structure–activity relationship

The platelet membrane glycoprotein IIb/IIIa[1] (hereinafter abbreviated as Gp IIb/IIIa), or IIb3, belongs to the integrin family, which is one of the receptor groups mediating between cells or between cell substrates, and forms a heterodimer on the platelet surface in the presence of Ca^{++}. Following adhesion of platelets to the injured site of a blood vessel, and on stimulation by adenosine 5′-diphosphate (ADP) or thrombin, Gp IIb/IIIa undergoes stereostructural changes and binds to a ligand having an RGD (arginine–glycine–aspartic acid) sequence,[2—5] such as fibrinogen (Fbs) or von Willebrand's factor (vWF) (Gp IIb/IIIa does not bind to these ligands when it is not stimulated); as a result of this the final stage of the transmission of stimulation,[6—10] namely platelet aggregation, is induced. Therefore, a compound (Gp IIb/IIIa antagonist) which inhibits the binding of Gp IIb/IIIa to these ligands will therefore be a superior antiplatelet agent.

Compounds already known in this area are Ro43-5054,[11] SC-54701A,[12] GR144053,[13] BIBU-52[14] and many other RGD mimetics;[15—19] a number of these compounds are currently undergoing clinical trials.

In this paper, we report our investigation of novel Gp IIb/IIIa antagonists having the RGD-type, three point interaction, and the synthesis of amidinonaphthol derivatives using Nafamostat as a starting compound (Fig. 1).

Chemistry RGD peptide mimics consist of a basic (amidinoaryl moiety) and an acidic (carboxylic acid moiety) part (Fig. 1). Modification of the basic part, the amidinonaphthalene ring was carried out. The geometrical parameters (length and angle) of these compounds were derived by *ab initio* molecular orbital calculations using Gaussian 94 and Spartan.[20]

Preparation of the target compounds in Table 3 is illustrated in Charts 1—4. For the conversion of a cyano group to an amidino group *via* a thioimidate intermediate, the established three-step sequence route was used as follows: the thioimidate was formed by treating the cyano group with hydrogen sulfide followed by alkylation with methyl iodide, then treatment of the methylthioimidate with ammonium acetate afforded the amidine group as the hydriodide salt.[21] Deprotection of the *tert*-butyl esters with trifluoroacetic acid (TFA) or saponification of alkyl esters afforded the target acids in pure form.

The preparation of the carboxylic acid **5a** is shown in Chart 1. Activation of benzoic acid analogs with 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) followed by coupling with **1**, yielded **2**. The bromo derivative **2** was converted to the corresponding cyano **3a** by CuCN.[22] Transformation of the cyano group to the amidino group shown above was carried out to give, after deprotection, the desired acid **5a**.

The preparation of **5b** with the reversed-amide orientation is shown in Chart 2. Condensation of the 2-naphthylcarboxylic acid **9** with the amine **10** afforded the intermediate **3b**. Similarly, **3b** was transformed into the desired compound **5b**.

The amide moieties of **5a** and **5b** were, therefore, replaced with the *trans*-olefin of **5c**, or with the ethylene moiety of **5d**. The cyano **3c** derived from the aldehyde **12** was converted into (*E*)-olefin **5c** and its hydrogenated form **5d**. The preparation of the carboxylic acids **5c** and **5d** is shown in Charts 3 and 4. Wittig reaction[23] of the aldehyde **12** with *p*-methoxybenzyltriphenylphosphonium bromide afforded the *E* isomer **13a** and the *Z* isomer, **13b**. Demethylation[24] of the *E* isomer **13a**, which was separated by recrystallization, gave the hydroxy compound **14**. Alkylation of **14** with *tert*-butyl bromoacetate afforded the ether **3c**. The desired carboxylic acid **5c** was obtained by converting the cyano group to the amidino derivative, as shown above, followed by deprotection of the ester with TFA. Hydrogenation of the olefin **3c** yielded the ethylene compound **3d** (Chart 4). **5d** was prepared as described above.

Results and Discussion

Drug Design The known Gp IIb/IIIa antagonists possess an amidinophenyl unit as a basic constituent. Zablocki reported that the benzamidine–carboxylate complex is a stable

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complex.[12] These results support our use of the amidinophenyl unit for the antagonists. We selected an amidinonaphthalene unit instead of an amidinophenyl unit since Hodohara and co-workers previously reported that amidinonaphthol derivatives developed as synthetic serine protease inhibitors also inhibit the binding of adhesion proteins to platelets by blocking RGD peptide binding sites on Gp IIb/IIIa (IC_{50}=7.0 μM (ADP 10 μM)).[25] *p*-Guanidinobenzoate derivative (Fig. 1) , which does not have an amidinonaphthyl unit in its structure, suppressed fibrinogen binding by 11%, but Nafamostat, which has an amidinonaphthyl unit in its structure, dose-dependently suppressed the fibrinogen binding of derivatives. We hypothesized that the amidinonaphthyl unit was involved in the binding interaction with fibrinogen receptors, since a naphthyl group (for example Nafamostat) would provide an additional CH–π interaction[26—28] within the receptor and a hydrophobicity corresponding to the arginine alkyl chain of the RGD peptide. It is possible that a naphthalene nucleus provides additional π-stacking within

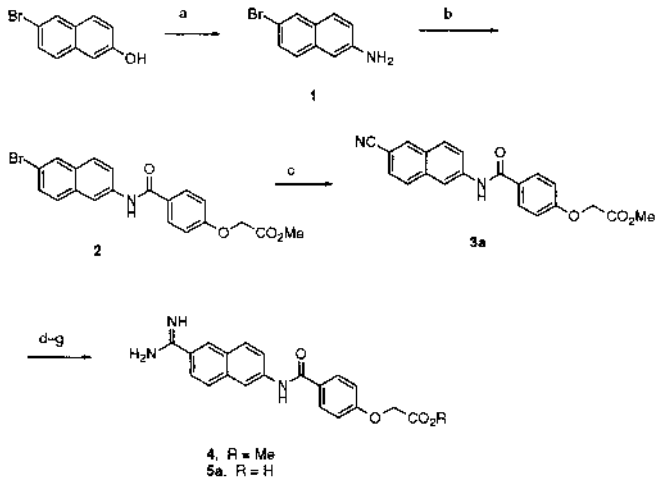


Chart 1. Preparation of **5a**

(a) SO_2, 28% NH_3; (b) $HO_2CC_6H_4OCH_2CO_2CH_3$, CDMT, NMM, CH_2Cl_2; (c) CuCN, DMEU; (d) H_2S, pyridine–triethylamine; (e) MeI, acetone; (f) NH_4OAc; (g) NaOH.

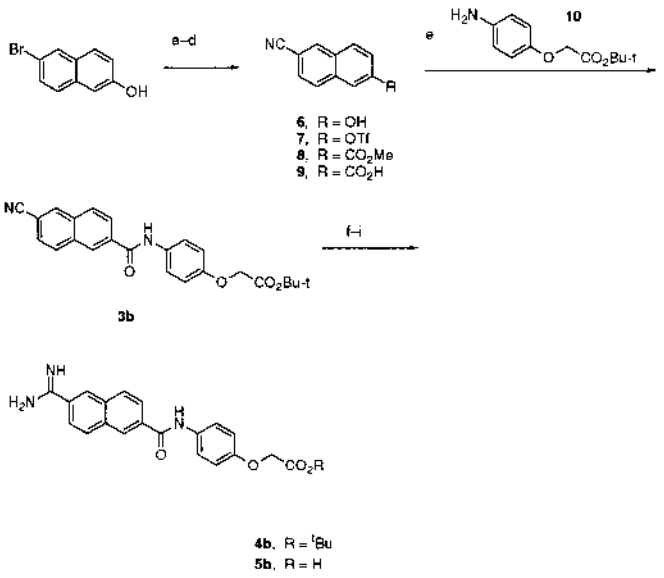


Chart 2. Preparation of **5b**

(a) CuCN, DMF; (b) Tf_2O, pyr.; (c) $Pd(OAc)_2$, PPh_3, CO, MeOH, Et_3N, DMF; (d) LiI, NaCN, DMF; (e) CDMT, NMM, **10**, CH_2Cl_2; (f) H_2S, pyr., Et_3N; (g) MeI, acetone; (h) NH_4OAc, MeOH; (i) TFA, CH_2Cl_2.

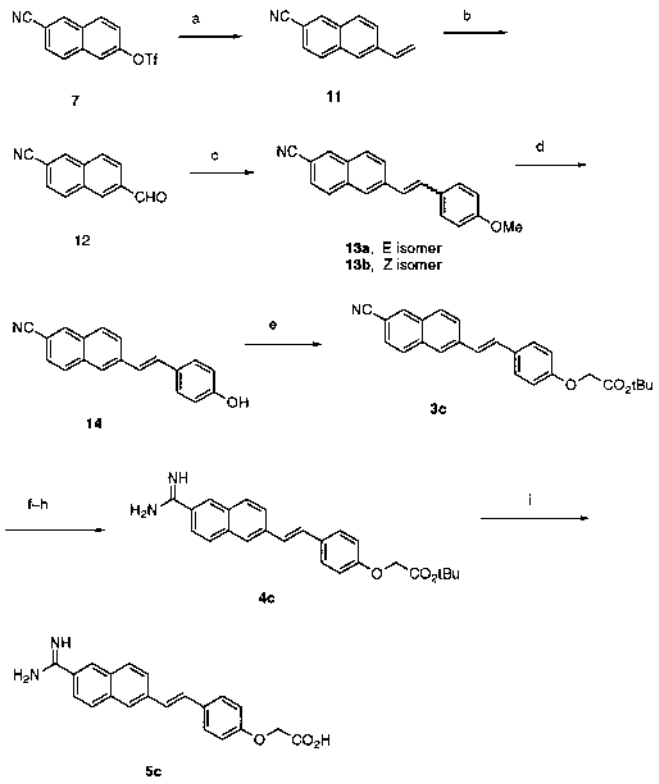


Chart 3. Preparation of **5c**

(a) $Pd(PPh_3)_2Cl_2$, vinyltributyltin, LiCl, DMF; (b) OsO_4, $NaIO_4$, dioxane, H_2O; (c) $Ph_3PCHPhOMe$-*p*; (d) $AlCl_3$, NaI, CH_3CN, CH_2Cl_2; (e) $BrCH_2CO_2$ *tert*-Bu, K_2CO_3, DMF; (f) H_2S, pyr., Et_3N; (g) MeI, acetone; (h) NH_4OAc, MeOH; (i) TFA, CH_2Cl_2.

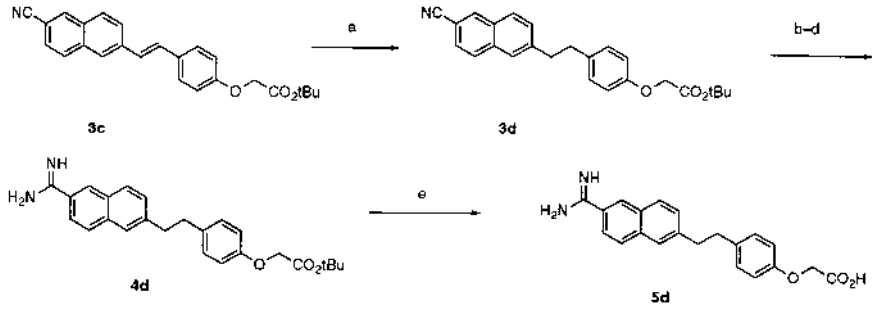


Chart 4. Preparation of **5d**

(a) H_2, 10% Pd–C, dioxane; (b) H_2S, pyr., Et_3N; (c) MeI, acetone; (d) NH_4OAc, MeOH; (e) TFA, CH_2Cl_2.

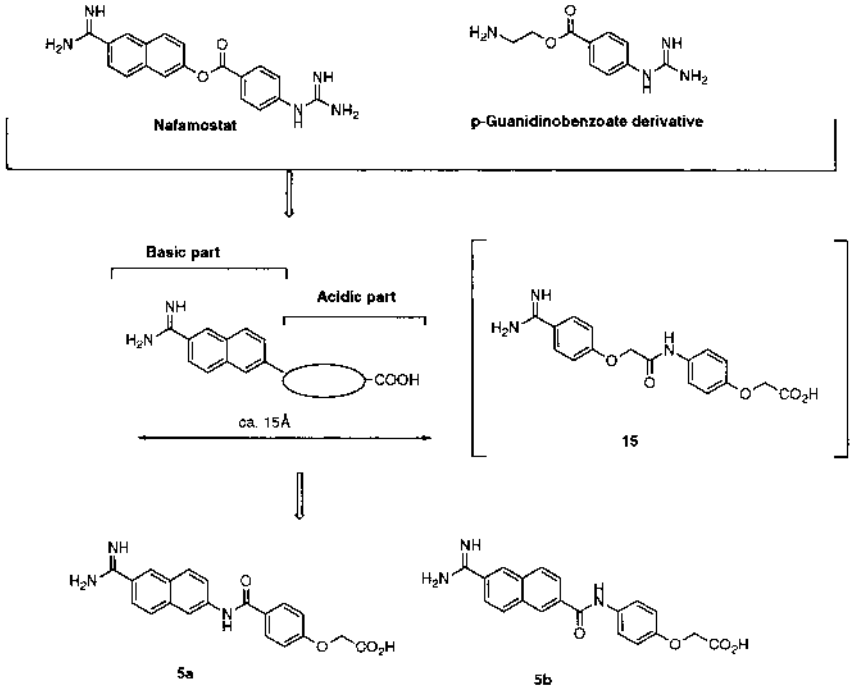


Fig. 1. Design of Active Compounds **5a** and **5b** Starting from Nafamostat

that region of the receptor. In factor Xa inhibitor studies, cation–π interactions seem to provide a novel mechanism for molecular recognition, and compounds having a naphthalene moiety are potent inhibitors.[26—28] High activity in a compound is due to the ability to present the relevant atoms to the receptor in the most appropriate spatial arrangement. The arrangement of amide bonds observed in such compounds is presumably that spatially most relevant to the receptor interaction while the naphthyl group offers an additional conformational restriction to the reported non-peptide antagonists. Also, the a conformation of compound **5a** suggests overlay of the latter's amidine and carboxylate groups with the guanidine and carboxylate groups of SK&F 107260. The cyclic peptide SK&F 107260,[29] which contains a turn–extended–turn conformation, is a potent Gp IIb/IIIa antagonist whose conformation in solution and X-ray structure have been reported. Since a linear peptide is quite flexible, RGD linear peptides, such as Ac–Arg–Gly–Asp–Ser–NH_2, cause some disruption of the binding interaction. Therefore, cyclic RGD-containing compounds such as SK&F 107260 could be good template for the receptor-bound form, since the conformations are limited. At the beginning of this research, we used molecular modeling techniques to examine the conformational profile of other non-peptide antagonists using SK&F 107260 as a template. Compounds already known in this area are Ro43-5054,[11] SC-54701A,[12] GR144053,[13] BIBU-52[14] and many other RGD mimetics.[15—18] Each distance is summarized in Table 1 (Fig. 2). The distance between the carbon (C_1) of the amidino or guanidino group and the carbon (C_2) of the carbonyl group was C_1–C_2. The distance between the carbon (C_1) of the amidino or guanidino group and the hetero atom, which can interact with the receptor, was C_1–(hetero atom). The distance between the carbon (C_2) of the carbonyl group and the hetero atom, which can interact with the receptor, was (hetero atom)–C_2. The C_1–(hetero atom) of SK&F

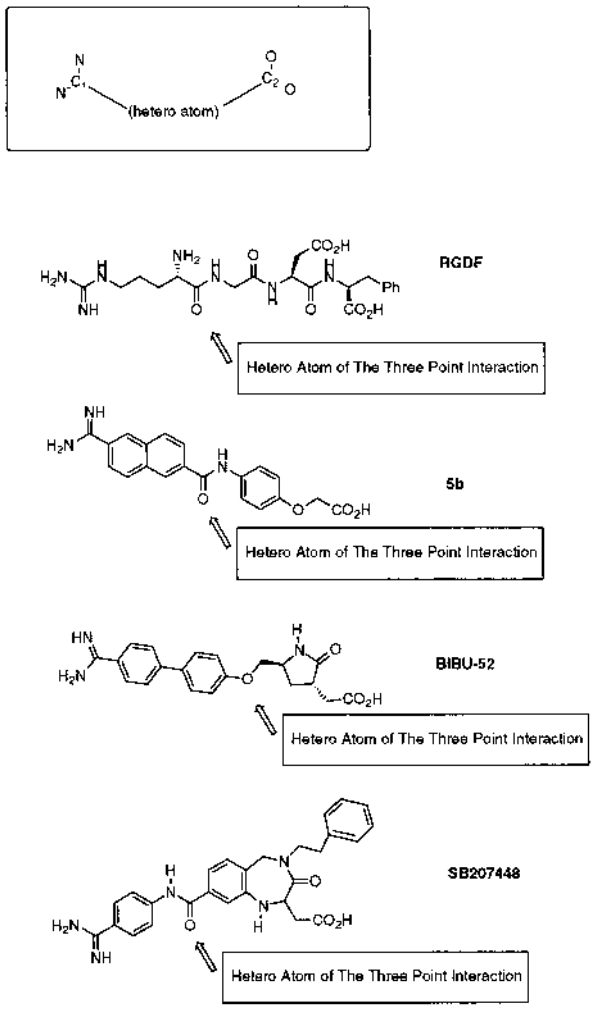
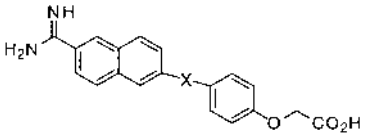


Fig. 2. Three Point Interaction Type of RGDF, BIBU-52, SB207448 and **5b**

Table 1. Pharmacophore Distance of the Three Point Interaction

Compd. No.	Distance (Å)		
	C_1–(Hetero atom)	(Hetero atom)–C_2	C_1–C_2
RGDF	7.7	6.4	14.0
SK&F107260	7.7	6.9	14.4
5b	8.5	7.4	14.0
BIBU-52	10.0	4.6	13.8
SB207448	6.2	8.8	14.9

Table 2. Naphthalene Derivatives: *In Vitro* Inhibition of Platelet Aggregation



Compd. No.	Spacer X	Platelet aggregation PRP IC_{50} (μM)[a]
5a	NHCO	0.05±0.02
5b	CONH	0.07±0.02
5c	CH=CH	1.25±0.25
5d	CH_2CH_2	2.05±0.05
15	—	0.08±0.02
BIBU-52[14]	—	0.07±0.006
Ro 43-8857[11]	—	0.085±0.013

a) Concentration required to inhibit by 50%. Values are means±S.E.M. of three experiments.

107260 and RGD was 7.7 Å. However, the C_1–(hetero atom) of 6-amidinonaphth-2-ylcarbonyl compound **5b** was 8.5 Å. As a starting point, we assumed that this difference between 7.7 Å and 8.5 Å was acceptable for a lead compound. Overlay of these compounds showed that the carbonyl group of the 4-amidinophenylcarbonyl unit, present in most antagonists, does not overlap with the arginine carbonyl group of cyclic peptide SK&F 107260. The distance between the Arg-guanidino group and the Asp-carboxylic group was about 14 Å according to the superimposed stable conformations of SK&F 107260 and other non-peptide antagonists. The carbonyl oxygen of the 6-amidinonaphth-2-ylcarbonyl unit is not capable of accessing the same space as the 4-amidinobiphenylcarbonyl unit in BIBU-52[14] (Fig. 3) or the 4-amidinophenylaminocarbonyl unit in SB207448[30] (Fig. 4), for example, but is capable of accessing the same space as the arginine carbonyl oxygen and amide hydrogen of SK&F 107260 and RGD peptide, as shown in Figs. 5 and 6.

A common corollary of ligand–receptor binding interactions, which states that a three point interaction is all that is required for high specificity and high affinity binding, holds true for many fibrinogen receptor antagonists, as suggested by Zablocki.[18] In RGD peptide, arginine and glycine carbonyls may allow a strong hydrogen bonding with the fibrinogen receptor.

***In Vitro* Pharmacology** In a platelet aggregation assay[31] (Table 2), **5a** exhibed potent inhibit (IC_{50}=0.05 μM, human PRP, ADP). **5b** (IC_{50}=0.07 μM), with a reversed-amide orientation, is also an extremely potent inhibitor of platelet aggregation. The potency of **5a** and **5b**, was comparable with that of BIBU-52 and Ro 43-8857.

Table 3. Energy Differences (in kcal/mol) *in Vacuo* between Conformations **5a** and **5b** Computed from B3LYP/6-31G*, B3LYP/6-31G and RHF/4-31G[a]

	B3LYP/6-31G*	B3LYP/6-31G	RHF/4-31G
16A	+0.2465	+0.2887	+0.1638
16B	0	0	0
17A	+0.0467	+0.0791	+0.6903
17B	0	0	0

a) In every calculation, the amidinonaphthyl unit and phenyl ring in the middle were fixed.

Table 4. Comparison of Apparent Inhibition Constant (Ki_{app})[a] against Various Proteases

Compd.	Ki_{app} (M) against protease			
	Thrombin	F-Xa	Plasmin	Trypsin
Nafamostat	2.85×10^{-7}	4.75×10^{-6}	1.40×10^{-8}	1.38×10^{-8}
5a	2.97×10^{-4}	9.70×10^{-5}	1.29×10^{-4}	1.06×10^{-4}
5b	—	8.88×10^{-5}	7.30×10^{-5}	6.83×10^{-6}
BIBU-52	—	1.64×10^{-4}	2.39×10^{-4}	5.54×10^{-5}
Ro 43-5587	—	3.44×10^{-4}	2.39×10^{-4}	2.92×10^{-4}

a) Values are expressed as the average of at least two experiments. The average error for the assay was ±18%.

Two stable conformations around the amide bond, conformer **16**A or **16**B for **5b**, and **17**A or **17**B for **5a**, are shown in Fig. 7. In these cases, because the *cis*-amide forms are 15—20 kcal/mol[32] unstable compared with the *trans*-amide forms, we excluded them. Our calculation (RHF/6-31G*) indicates that conformer **16**B is more stable than **16**A by 0.25 kcal/mol and conformer **17**B more stable than **17**A by 0.05 kcal/mol (shown as in Table 3). The small energy difference between these conformers made it difficult to determine which conformers bind to the receptor. One of our hypotheses is that, just as with **16**A and **17**B, the spatial positions of the carbonyl oxygen of amide in **5a** and in **5b** are the same. In Fig. 8, comparison of the model compounds **5a** and **5b** clearly shows good carbonyl oxygen and amide hydrogen overlap of their amide groups. These results support the three point interactions.

An amide bond moiety is often replaced with (*E*)-olefin as a bioisostere,[33] because this transformation does not change the spatial arrangement of the two pharmacophores neighboring the amide bond. However replacement of the amide group of **5b** with an (*E*)-olefin and a saturated ethylene unit afforded compounds **5c** (IC_{50}=1.25 μM) and **5d** (IC_{50}=2.05 μM), respectively. These transformations result in less favorable inhibition of *in vitro* platelet aggregation. The described activity of **5c** and **5d** compared with derivative **5b** indicates that the amide moiety is critical for inhibitory activity. We assumed that the lack of *in vitro* activity of olefin and ethylene derivatives was due to the following reasons: 1) Most of the possible conformations of olefin, ethylene, and amide derivatives are different. 2) **5a** and **5b** demonstrated a good overlap of their amide with almost the same *in vitro* activity, suggest a similar mode of binding, as shown in Fig. 8. Since the olefin and ethylene derivatives did not show any comparable activity as amide derivatives, hydrogen-bonding between ligand and receptor could be important.

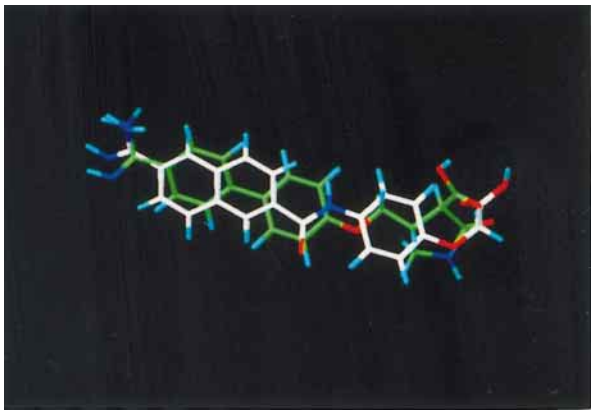


Fig. 3. Superimposition of BIBU-52 (Green) and **5b** (White)

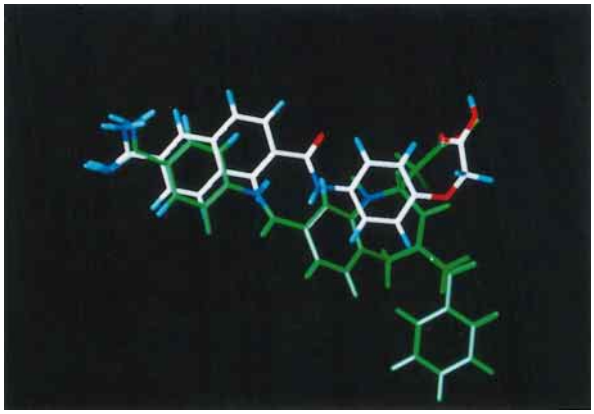


Fig. 4. Superimposition of SB207448 (Green) and **5b** (White)

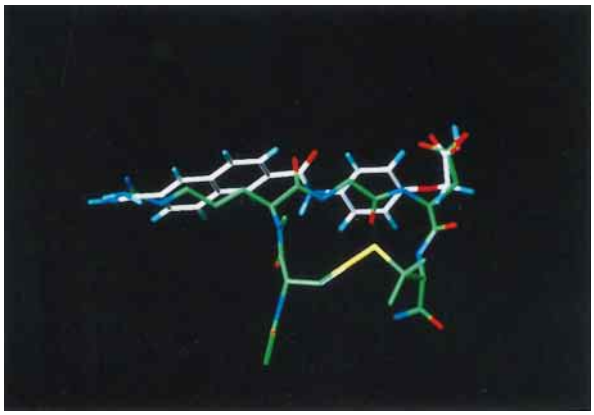


Fig. 5. Superimposition of the Naphthalene Derivative **5b** (White) and SK&F107260 (Green)

The carbonyl oxygen of the amide of **5b** was superimposed upon the carbonyl oxygen of SK&F107260.

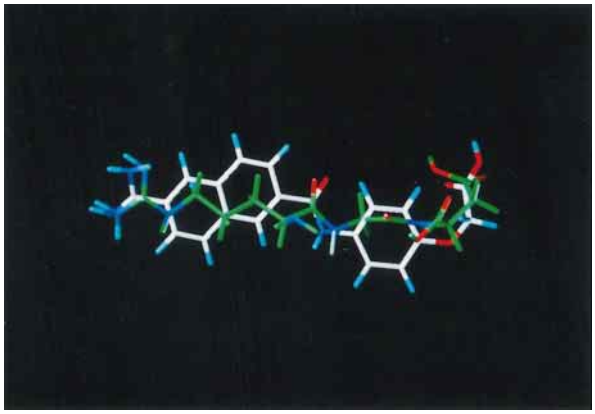


Fig. 6. Superimposition of the Naphthalene Derivative **5b** (White) and RGD Peptide (Green)

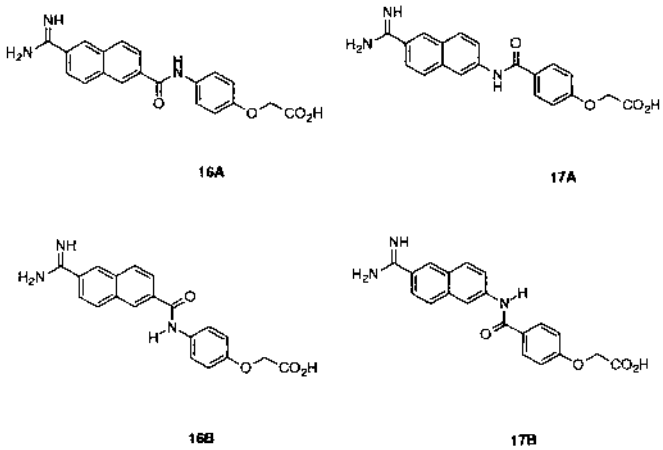


Fig. 7. Conformation of the Amide Moiety in **5a** and **5b**

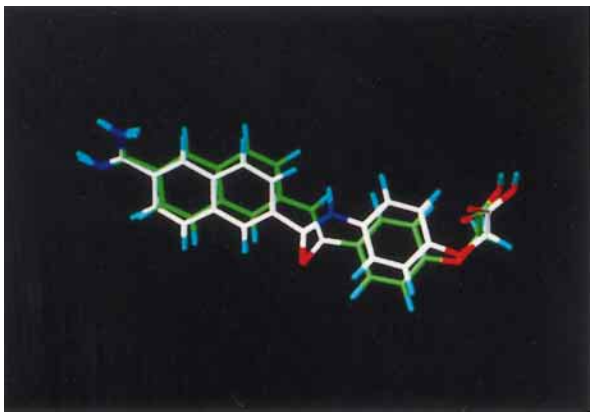


Fig. 8. Superimposition of **5b** (White) and **5a** (Green)

In the olefin derivative, the naphthalene, olefin, and phenyl groups share the same plane. In the ethylene derivative, the naphthalene and phenyl groups share a parallel plane. In the amide derivatives, the angle between the naphthalene and amide planes is 45 degrees, therefore, the angle between the naphthalene and phenyl groups is 45 degrees. This type of conformation indicated that most of the possible conformations of the olefin, ethylene, and amide-derivatives are different. The difference in activity between **5a** and **5c** is due to the position of the naphthalene and phenyl ring.

As shown above, the crucial position of the oxygen or hydrogen in the amide bond suggests that there is a corresponding hydrogen donor or acceptor in the receptor. It seems likely that the bound conformation of naphthalene compounds is a preferred alternative orientation when the carbonyl oxygen of the amide or amide hydrogen interacts with the receptor. High activity in a compound is due to the ability to present the relevant atoms to the receptor in the most appropriate spatial fashion. The arrangements of the amide bonds observed in such compounds are presumably those spatially most relevant to the receptor interaction. The difference in activity between **5a** and **5c** is due to the hydrogen

bonding interaction. These results suggest that a three point interaction is more favorable than a two point one, which involves only the amidine and carboxylic acid groups.

Recently, Gp IIb/IIIa antagonists with bicyclic 5-amidinoindoles have been reported by Su and co-workers.[34] The 10-fold difference in potency observed between the indoles and acyclic compounds suggested a conformational restriction in the indole part or a CH–π interaction effect in that region of the receptor. However, our acyclic compound **15** (Fig. 1) possessed similar inhibitory activity to the naphthalene **1**. This potency suggests that the naphthyl group does not provide an additional CH–π interaction effect compared with an acyclic compound within that region of Gp IIb/IIIa. We assumed that the marked *in vitro* inhibition was due to conformational restriction of the reported non-peptide antagonists.

Nafamostat, selected as our starting compound, acts in blood clotting disorders by suppressing the clotting proteases, including thrombin. As a side-effect, it is sometimes known to prolong the bleeding time. The specificity of the naphthalene compounds for inhibition of a variety of serine proteases, including thrombin, factor Xa, plasmin and trypsin, was appraised by measuring the apparent inhibition constant (Ki_{app}).[35] As shown in Table 4, **5a** and **5b** have lost their ability to inhibit these proteases while the ability of BIBU-52 and Ro 43-8857 was comparable with that of **5a** and **5b**.

In conclusion, carboxylic acids **5a** and **5b** were found to be potent antagonists of fibrinogen receptors. The naphthalene compounds may produce a three points interaction and conformational restriction.

Experimental

Chemistry. General Information Reagents were purchased from commercial suppliers and used without further purification. Reaction solvents were distilled from an appropriate drying agent before use. Melting points were measured on a Yanaco micromelting point apparatus and are uncorrected. IR and NMR spectra, which were in agreement with the structures cited, were recorded on a Shimadzu IR-420 instrument for IR and a Brucker AMX-500 spectrometer (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR) and a Brucker AC-200 spectrometer (200 MHz for ^{1}H-NMR and 50 MHz for ^{13}C-NMR) for NMR using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad). Electron impact (EI)-MS and secondary ion (SI)-MS were taken on a Hitachi M-2000 mass spectrometer.

The purity of the selected final compounds was determined by RP-HPLC using an Inertsil ODS-3 column (4.6 mm. i.d.×250 mm, 5 μm, GL Sciences Inc.): flow rate, 1 ml/min; temperature, 40 °C; sample size, 2 μg/ml; injection volume, 1 μl; detection, 270 nm; mobile phase A, 20% MeCN/0.05% TFA in water; mobile phase B, 23% MeCN/0.05% TFA in water; mobile phase C, 33% MeOH/0.05% TFA in water; mobile phase D, 47% MeOH/0.05% TFA in water (see suporting information).

Determination of Inhibition of ADP-Induced Aggregation of Human Platelets[31] Platelet rich plasma (PRP) was prepared from blood taken from healthy volunteers by centrifugation in the presence of 0.38% sodium citrate, and used for the determination.

Two minutes after the test compounds were added to the above PRP, ADP (1—5 μM) was added, at a concentration such that primary aggregation alone was observed. The suppression of ADP aggregation by these compounds was evaluated. The percentage suppression was determined by varying the concentration of the compounds and the concentration at which the aggregation was suppressed by 50% (IC_{50}) was calculated. This was taken as the activity of the compound.

Anti-protease Activity[35] The potential serine protease inhibition of Gp IIb/IIIa antagonists was assessed using human α-thrombin, human plasmin, human blood coagulation factor Xa and bovine β-trypsin. Briefly, 10 nM protease was mixed with 10^{-4} M Gp IIb/IIIa antagonist or DMSO in Tris–HCl buffered saline for 10 min at room temperature. Protease activity was measured following the addition of 2 mM of each synthetic substrate by monitoring the progressive absorbance at 405 nm at 25 °C on a DV-7400 spectrophotometer (Beckman). The synthetic substrates used were S-2303 for thrombin, S-2238 for factor Xa and S-2251 for plasmin and β-trypsin. The Ki_{app} value was obtained by plotting the percentage inhibition against the inhibitor concentration. Nafamostat mesylate (Futhan) was used as a respective protease inhibitor.

Computational Methods All molecular modeling studies were performed on Silicon Graphics R8000 graphic workstations using the molecular modeling software package SYBYL version 6.3 from TRIPOS Associates. Geometry optimization was carried out using Gaussian 94 and Spartan. As basic functions, B3LYP/6-31G*, B3LYP/6-31G, and RHF/4-31G in Gaussian 94 and Spartan were used for geometry optimization.

***tert*-Butyl 4-Aminophenoxyacetate** 4-Nitrophenol (13.9 g, 100 mmol) was dissolved in dimethylformamide (DMF) (20 ml), and *tert*-butyl bromoacetate (29.3 g, 150 mmol) and potassium carbonate (27.6 g, 200 mmol) were added, followed by stirring at 70 °C for 4 h. The reaction mixture was diluted with ethyl acetate, washed with water, and the aqueous layer was extracted with EtOAc. The mixture was washed with water and dried over anhydrous $MgSO_4$. After filtration, low boiling material was distilled from the filtrate under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) and recrystallized from a mixed solvent of EtOAc and *n*-hexane to give 21.8 g *tert*-butyl 4-nitrophenoxyacetate as pale-yellow crystals (86%): IR (KBr) cm^{-1}: 1740, 1590, 1500, 1330, 1240, 1160. ^{1}H-NMR (DMSO-d_6) δ: 1.43 (9H, s), 4.86 (2H, s), 7.13 (2H, d, J=7.1 Hz), 8.21 (2H, d, J=7.1 Hz).

tert-Butyl 4-nitrophenoxyacetate (19.3 g, 76.0 mmol) was dissolved in EtOH (100 ml) and 10% palladium–carbon (1.0 g) was added. The mixture was stirred at room temperature for 18 h under a hydrogen atmosphere. The reaction mixture was filtered and the low boiling material was distilled from the filtrate under reduced pressure to give 16.8 g of *tert*-butyl 4-aminophenoxyacetate as a pale-brown solid (99%): IR (neat) cm^{-1}: 3350, 2950, 1740, 1510, 1220, 1150. ^{1}H-NMR (DMSO-d_6) δ: 1.41 (9H, s), 4.43 (2H, s), 4.63 (2H, s), 6.49 (2H, d, J=6.6 Hz), 6.62 (2H, d, J=6.6 Hz).

Methyl 4-(6-Bromo-2-naphthylaminocarbonyl)phenoxyacetate (2). (Standard Procedure A) A solution of *p*-methoxycarbonylmethoxybenzoic acid (0.69 g, 3.30 mmol), CDMT (0.58 g, 3.30 mmol), and N-methylmorpholine (NMM) (0.36 ml, 3.30 mmol) in CH_2Cl_2 (10 ml) was stirred at 0 °C for 3 h. When CDMT could no longer be detected by TLC, a solution of 6-bromo-2-naphthylamine (0.68 g, 0.310 mmol) in CH_2Cl_2 (10 ml) was added. After 21 h at room temperature, the solvent was evaporated. The residue was dissolved in EtOAc and successively washed with 0.2 N HCl at 0 °C, H_2O, 5% aqueous $NaHCO_3$, H_2O, and brine. The crude material obtained after evaporation of the solvent was recrystallization from EtOAc and dried to give **2** (0.73 g, 58%): IR (KBr) cm^{-1}: 3230, 1750, 1635, 1215. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 3.73 (3H, s), 4.93 (2H, s), 7.10 (2H, d, J=6.9 Hz), 7.59 (1H, dd, J=2.1, 8.8 Hz), 7.82—7.90 (3 H, m), 7.99 (2 H, d, J=6.9 Hz,), 8.14 (1H, s), 8.47 (1H, s), 10.35 (1H, s).

Methyl 4-(6-Cyano-2-naphthylaminocarbonyl)phenoxyacetate (3a) CuCN (212 mg, 2.37 mmol) was added to a solution of **2** (653 mg, 1.58 mmol) in 1,3-dimethyl-2-imidazolidione (DMEU) (5 ml). The resulting mixture was stirred at 150 °C for 5 h, cooled with ice-water, poured into H_2O, and then extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by recrystallization (EtOAc–*n*-hexane) to give 260 mg (46%) of **3a** as a colorless solid: IR (KBr) cm^{-1}: 3350, 2200, 1745, 1670, 1250. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s), 4.94 (2H, s), 7.11 (2H, d, J=8.8 Hz), 7.74 (1H, d, J=8.0 Hz), 7.89—8.14 (5H, m), 8.49 (1H, s), 8.60 (1H, s), 10.50 (1H, s).

Methyl 4-(6-Amidino-2-naphthylaminocarbonyl)phenoxyacetate (4) In the same manner as in standard procedure B (*vide post*), the cyano group of **3a** (200 mg, 0.55 mmol) was converted to an amidino group to give 105 mg of **4** as a yellow solid (37% in 3 steps): IR (KBr) cm^{-1}: 3400, 1730, 1680, 1230. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s), 4.94 (2H, s), 7.11 (2H, d, J=8.6 Hz), 7.79 (1H, d, J=10.0 Hz), 7.98—8.10 (5H, m), 8.42 (1H, s), 8.62 (1H, s), 9.24 (4H, br s), 10.51 (1H, s).

4-(6-Amidino-2-naphthylaminocarbonyl)phenoxyacetic Acid (5a) A mixture of **4** (68 mg, 0.14 mmol), 1 N NaOH solution (1.0 ml, 1.0 mmol) and EtOH (10 ml) was stirred at room tempurature for 5 min. The solution was acidified with 1 N HCl to pH 2—3, and the precipitated solids were collected by filtration to give 32 mg (60%) of **5a** as a brown solid after drying: mp: >250 °C. IR (KBr) cm^{-1}: 3350, 1740, 1650, 1605, 1250. ^{1}H-NMR (DMSO-d_6) δ: 4.80 (2H, s), 7.08 (2H, d, J=8.9 Hz), 7.80 (1H, dd, J=1.8, 8.7 Hz), 7.99—8.05 (3H, m), 8.07 (2H, d, J=8.9 Hz), 8.44 (1H, d, J=1.2 Hz), 8.62 (1H, d, J=1.5 Hz), 9.13 (2H, s), 9.42 (2H, s), 10.53 (1H, s), 13.06 (1H, br s).

Anal. Calcd for $C_{20}H_{17}N_3O_4 \cdot HCl \cdot 1.1H_2O$: C, 57.24; H, 4.85; N, 10.01. Found: C, 57.38; H, 4.93; N, 9.76.

6-Cyano-2-naphthol (6) A mixture of 6-bromo-2-naphthol (16.0 g, 71.7 mmol), CuCN (7.70 g, 86.0 mmol) and DMEU (20 ml) was stirred at 160 °C for 3 h. To the resulting mixture was added 10% NaOH (100 ml), and then the insoluble material was removed by filtration and washed with water (100 ml). The filtrate and washings were combined, and filtered. The filtrate was acidified with 10% HCl to pH 2—3 with ice-salt cooling, and then stirred at the same temperature for 1 h. Precipitated solids were collected by filtration to give 12.5 g of **6** as a brown solid after drying. This compound was used in the next reaction without further purification.

6-Cyano-2-naphthyl Trifluoromethanesulfonate (7) To a solution of **6** (5.15 g, 30.4 mmol) in pyridine (16 ml) was added dropwise Tf_2O (5.63 ml 33.5 mmol) at 0—8 °C for 20 min. The resulting mixture was allowed to warm to 23 °C, stirred for 15 h, poured into water (80 ml), and then extracted with Et_2O. The extract was washed sequentially with water, 3 N HCl, water and brine, and dried over anhydrous $MgSO_4$. It was then concentrated and subjected to silica gel column chromatography ($CHCl_3$–*n*-hexane) give 6.57 g (72%) of **7** as a slightly yellow solid: mp: 93—95.5 °C; IR (KBr) cm^{-1}: 3050, 2200, 1620, 1600, 1415, 1240, 1225. ^{1}H-NMR ($CDCl_3$) δ: 7.52 (1H, dd, J=2.4, 9.1 Hz), 7.73 (1H, dd, J=1.5, 8.6 Hz), 7.83 (1H, d, J=2.4 Hz), 7.99 (1H, d, J=7.9 Hz), 8.03 (1H, d, J=8.5 Hz), 8.29 (1H, s). MS *m*/*z*: 301 (M^+).

Methyl 6-Cyano-2-naphthoate (8) To a solution of **7** (303 mg, 1.01 mmol), $Pd(OAc)_2$ (8.5 mg, 0.038 mmol) and PPh_3 (24.8 mg, 0.095 mmol) in DMF (2 ml)[36] were added Et_3N (0.28 ml, 2.0 mmol) and MeOH (0.81 ml, 20 mmol). The resulting solution was purged with CO gas for 10 min, stirred at 65 °C for 4 h, poured into water (10 ml), and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane) to afford 177 mg (83%) of **8** as a pale yellow solid: mp: 161—162.5 °C. IR (KBr) cm^{-1}: 2200, 1710, 1590, 1425, 1270. ^{1}H-NMR ($CDCl_3$) δ: 7.68 (1H, dd, J=8.5, 1.5 Hz), 7.96 (1H, d, J=8.7 Hz), 8.05 (1H, d, J=8.5 Hz), 8.19 (1H, dd, J=8.6, 1.6 Hz), 8.27 (1H, s), 8.64 (1H, s). MS *m*/*z*: 211 (M^+).

6-Cyano-2-naphthoic Acid (9) A mixture of **8** (79.2 mmol), LiI (253 mg, 1.89 mmol), NaCN (23.2 mg, 0.473 mmol) and DMF (0.9 ml) was stirred at 140 °C for 19 h. The resulting mixture was poured into 1 N NaOH (25 ml), and then extracted with CH_2Cl_2. The aqueous layer was acidified with 3 N HCl to pH 2—3, and then extracted with $CHCl_3$. The extract was washed with brine and dried over anhydrous $MgSO_4$. Concentration gave 25.0 mg (34%) of **9** as a pale yellow solid: ^{1}H-NMR (DMSO-d_6) δ: 7.88 (1H, d, J=8.6 Hz), 8.10 (1H, d, J=8.7 Hz), 8.17 (1H, d, J=8.7 Hz), 8.33 (1H, d, J=8.6 Hz), 8.68 (1H, s), 8.72 (1H, s).

***tert*-Butyl 4-(6-Cyano-2-naphthalenecarboxamido)phenoxyacetate (3b)** In the same manner as in standard procedure A, **9** (1.00 g, 5.07 mmol) and *tert*-butyl 4-aminophenoxyacetate (1.15 g, 5.20 mmol) were condensed to give 1.53 g of **3b** as a white solid (75%): IR (KBr) cm^{-1}: 3300, 1740, 1640, 1520. ^{1}H-NMR (DMSO-d_6) δ: 1.42 (9H, s), 4.63 (2H, s), 6.92 (2H, d, J=9.0 Hz), 7.68 (2H, d, J=9.0 Hz), 7.87 (1H, d, J=8.8 Hz), 8.11 (1H, d, J=8.8 Hz), 8.18 (1H, d, J=8.8 Hz), 8.26 (1H, d, J=8.8 Hz), 8.63 (1H, s), 8.66 (1H, s), 10.42 (1H, s). MS *m*/*z*: 402 (M^+).

***tert*-Butyl 4-(6-Amidino-2-naphthalenecarboxamido)phenoxyacetate (4b). (Standard Procedure B)** **3b** (1.22 g, 2.23 mmol) was dissolved in a mixed solution of pyridine (40 ml) and Et_3N (4 ml), and hydrogen sulfide gas was bubbled through it for 10 min at room temperature, followed by stirring for 16 h. Low boiling material was distilled from the reaction mixture under reduced pressure and the residue was dissolved in EtOAc. The mixture was washed with 2 N aqueous potassium hydrogensulfate solution, water and saturated brine, and then dried over anhydrous $MgSO_4$. After filtration, low boiling material was distilled from the filtrate under reduced pressure to give the corresponding thioamide as a yellow solid. The thioamide was dissolved in acetone (65 ml) and methyl iodide (6.5 ml) was added. The mixture was refluxed under heating for 45 min. Low boiling matters were distilled away from the reaction mixture under reduced pressure to give corresponding thioiminomethyl ester as a yellow solid. MeOH (20 ml) and ammonium acetate (450 mg, 5.80 mmol) were added, and the mixture was refluxed under heating for 3 h. Low boiling material was distilled from the reaction mixture under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to give 1.22 g of the hydriodide of **4b** as a yellow solid (98% in 3 steps): IR (KBr) cm^{-1}: 3700—2900, 1730, 1640, 1600. ^{1}H-NMR (DMSO-d_6) δ: 1.44 (9H, s), 4.65 (2H, s), 6.93 (2H, s), 7.69 (2H, d), 7.80—8.00 (3H, m), 8.32 (1H, s).

4-(6-Amidino-2-naphthalenecarboxamido)phenoxyacetic Acid (5b). (Standard Procedure C) CH_2Cl_2 (11 ml) was added to the hydriodide (1.22 g, 2.23 mmol) of **4b**, followed by TFA (11 ml) and stirring at room temperature for 2 h. Et_2O (100 ml) was added to the reaction mixture and the mixture was stirred for 10 min. The resulting precipitate was collected by filtration and washed with diethyl ether to give 1.07 g of the hydriodide of **5b** as a brown solid (98%): IR (KBr) cm^{-1}: 3300, 1640, 1510. ^{1}H-NMR (DMSO-d_6) δ: 4.68 (2H, s), 6.95 (2H, d, J=9.0 Hz), 7.71 (2H, d, J=9.0 Hz), 7.89 (1H, dd, J=8.5, 1.5 Hz), 8.15 (1H, dd, J=81.5, 8.5 Hz), 8.24 (1H, d, J=8.7 Hz), 8.32 (1H, d, J=8.7 Hz), 8.54 (1H, s), 8.68 (1H, s), 9.08 (2H, br s), 9.49 (2H, br s), 10.45 (1H, s), 12.6—13.4 (1H, br s). *Anal*. Calcd for $C_{20}H_{17}N_3O_4 \cdot 0.5C_2HO_2F_3 \cdot 1.1H_2O$: C, 44.40; H, 3.67; N, 7.40. Found: C, 44.08; H, 3.53; N, 7.73.

2-Cyano-6-vinylnaphthalene (11) To a solution of **7** (4.44 g, 14.7 mmol) in DMF (65 ml) were added vinyltributyltin (4.44 ml, 15.2 mmol), lithium chloride (1.90 g, 44.8 mmol), bis(triphenylphosphine)palladium chloride(II)[37] (210 mg, 0.299 mmol) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol. The resulting mixture was stirred at 70 °C for 2.5 h, cooled with ice-water, poured into water (180 ml), and then extracted with Et_2O. The extract was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was stirred with Et_2O and aqueous saturated potassium fluoride solution (75 ml) at 23 °C for 3 h. The precipitate was removed by filtration through Celite and washed with Et_2O. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography ($CHCl_3$/hexane) to give 2.44 g (93%) of **11** as a colorless solid: IR (KBr) cm^{-1}: 2200, 1620, 1585, 1490, 1415, 1370, 1300. ^{1}H-NMR ($CDCl_3$) δ: 5.45 (1H, d, J=10.9 Hz), 5.95 (1H, d, J=17.6 Hz), 6.89 (1H, dd, J=17.6, 10.9 Hz), 7.59 (1H, dd, J=8.5, 1.5 Hz), 7.70—7.93 (4H, m), 8.18 (1H, s).

6-Cyano-2-naphthaldehyde (12) To a solution of **11** (5.36 g, 29.9 mmol) in dioxane (300 ml) was added a solution of osmium tetroxide[38] in 1 : 1 dioxane–water (2 mg/ml, 42 ml, 0.33 mmol), followed by portionwise addition of a solution of sodium periodate (14.1 g, 66.0 mmol) in water (100 ml) for 30 min. The resulting mixture was stirred at 23 °C for 18 h, diluted with water (120 ml), and then extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. Concentration followed by silica gel column chromatography ($CHCl_3$) gave 4.54 g (84%) of **12** as a yellow solid: IR (KBr) cm^{-1}: 2200, 1620, 1585, 1490, 1415, 1370, 1270. ^{1}H-NMR ($CDCl_3$) δ: 5.45 (1H, d, J=10.9 Hz), 5.95 (1H, d, J=17.6 Hz), 6.89 (1H, dd, J=10.9, 17.6 Hz), 7.59 (1H, dd, J=1.5, 8.5 Hz), 7.70—7.93 (4H, m), 8.18 (1H, m), MS *m*/*z*: 179 (M^+).

(*E*)- and (*Z*)-2-Cyano-6-[2-(4-methoxyphenyl)vinyl]naphthalene (13a, 13b) To s suspension of *p*-methoxybenzyltriphenylphosphonium bromide (2.51 g, 5.99 mmol) in benzene (40 ml) was added dropwise a solution of *n*-BuLi in hexane (1.6 N, 5.0 ml 7.2 mmol) with ice-water cooling, and the resulting wine red solution was stirred at 23 °C for 2 h. To this solution was added dropwise a solution of **12** (1.13 g, 6.24 mmol) in benzene (30 ml) over 5 min. The reaction mixture was stirred at 23 °C for 4.5 h, poured into water (60 ml), and then extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. Concentration followed by silica gel column chromatography ($CHCl_3$/hexane) gave 1.19 g of a mixture of the *E* and *Z* isomers **13a** and **13b** as a yellow solid. The mixture was suspended in 85 : 15 EtOAc–hexane, refluxed for 1 h, and then allowed to cool to 23 °C for 16 h. The precipitate was collected by filtration to give 703 mg of **13a** as a pale yellow solid. The mother liquor was concentrated to give 442 mg of a 90 : 10 mixture of **13b** and **13a** as a yellow solid (67%). Spectral data for **13a**: IR (KBr) cm^{-1}: 2900, 2200, 1600, 1505, 1405, 1300 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (1H, d, J=12.2 Hz), 6.71 (1H, d, J=12.0 Hz), 6.75 (2H, d, J=8.8 Hz), 7.18 (2H, d, J=8.7 Hz), 7.49 (1H, dd, J=8.6, 1.5 Hz), 7.55 (1H, dd, J=8.6, 1.6 Hz), 7.64—7.86 (3H, m), 8.14 (1H, s). MS *m*/*z*: 286 (MH^+).

(*E*)-2-Cyano-6-[2-(4-hydroxyphenyl)vinyl]naphthalene (14) To a mixture of MeCN (100 ml) and CH_2Cl_2 (50 ml) were added sequentially aluminum chloride (3.33 g, 25.0 mmol), sodium iodide (3.75 g, 25.0 mmol) and **13a** (714 mg, 2.50 mmol) with ice-water cooling. The reaction mixture was refluxed for 23 h, cooled to 23 °C, poured into water, and then extracted with $CHCl_3$. The extract was washed successively with 30% aqueous sodium thiosulfate and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was suspended in 4 : 1 $CHCl_3$–hexane, refluxed for 1 h and allowed to cool to 23 °C for 16 h. The precipitate was collected by filtration, washed with 4 : 1 $CHCl_3$–hexane and dried to give 604 mg (purity 91%, 81%) of **14** as a yellow solid: IR (KBr) cm^{-1}: 3275, 2200, 1615, 1600, 1580, 1505, 1340. ^{1}H-NMR (DMSO-d_6) δ: 6.81 (1H, d, J=8.5 Hz), 7.22 (1H, d, J=16.4 Hz), 7.43 (1H, d, J=16.4 Hz), 7.51 (2H, d, J=8.6 Hz), 7.75 (1H, dd, J=8.6, 1.5 Hz), 7.94—8.10 (4H, m), 8.50 (1H, s), 9.15—10.10 (1H, br s). MS *m*/*z*: 271 (M^+).

(*E*)-*tert*-Butyl 4-[2-(6-Cyano-2-naphthyl)vinyl]phenoxyacetate (3c) To a mixture of **14** (purity 91 wt%, 583 mg, 1.96 mmol), potassium carbonate (543 mg, 3.93 mmol) and DMF (8 ml) was added dropwise *tert*-butyl bromoacetate (0.47 ml, 2.91 mmol) at 23 °C for 1 min. The resulting mixture was stirred at 23 °C for 19 h, poured into water, and then extracted with EtOAc. The extract was washed with brine and dried over anhydrous $MgSO_4$. Concentration followed by silica gel column chromatography ($CHCl_3$/*n*-hexane) gave 595 mg (79%) of **3c** as a colorless solid: IR (KBr) cm^{-1}: 2950, 2200, 1745, 1595, 1505, 1390, 1360. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s), 4.55 (2H, s), 6.93 (2H, d, J=8.7 Hz), 7.13 (1H, d, J=16.3 Hz), 7.25 (1H, d, J=16.2 Hz), 7.51 (2H, d, J=8.7 Hz), 7.58 (1H, dd, J=8.4, 1.5 Hz), 7.79—7.90 (4H, m), 8.17 (1H, s). MS *m*/*z*: 385 (M^+).

(*E*)-*tert*-Butyl 4-[2-(6-Amidino-2-naphthyl)vinyl]phenoxyacetate (4c) In the same manner as in standard procedure B, the cyano group of **3c** (316 mg, 0.820 mmol) was converted to an amidino group to give 256 mg of the hydriodide of **4c** as a yellow solid (62% in 3 steps): mp 162—163 °C (dec.). IR (KBr) cm^{-1}: 3200, 1740, 1660, 1595, 1505, 1360. ^{1}H-NMR (DMSO-d_6) δ: 1.44 (9 H, s), 4.71 (2 H, s), 6.96 (2 H, d, J=8.7 Hz), 7.33 (1H, d, J=16.4 Hz), 7.48 (1H, d, J=16.4 Hz), 7.63 (2H, d, J=8.7 Hz), 7.80 (1H, dd, J=8.7, 1.5 Hz), 7.96—8.19 (4H, m), 8.44 (1H, s), 9.18 (4H, br s).

(*E*)-4-[2-(6-Amidino-2-naphthyl)vinyl]phenoxyacetic Acid (5c) In the same manner as in standard procedure C, the hydriodide (237 mg, 0.447 mmol) of **4c** was treated with TFA (3.6 ml) to give 178 mg of the hydriodide of **5c** as a pale solid (86%): mp >300 °C. IR (KBr) cm^{-1}: 3300, 1750, 1640, 1505, 1190, 1170. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 4.73 (2H, s), 6.98 (2H, d, J=8.8 Hz), 7.33 (1H, d, J=16.4 Hz), 7.48 (1H, d, J=16.4 Hz), 7.63 (2H, d, J=8.8 Hz), 7.82 (1H, dd, J=8.6, 1.8 Hz), 8.01 (1H, dd, J=8.7, 1.3 Hz), 8.07 (1H, d, J=8.7 Hz), 8.10 (1H, d, J=9.1 Hz), 8.11 (1H, s), 8.45 (1H, s), 9.19 (2H, s), 9.41 (2H, s). *Anal*. Calcd for $C_{21}H_{18}N_2O_3 \cdot C_2HO_2F_3 \cdot 1.6H_2O$: C, 56.47; N, 4.57; N, 5.73. Found: C, 56.29; H, 4.11; N, 5.89.

***tert*-Butyl 4-[2-(6-Cyano-2-naphthyl)ethyl]phenoxy Acetate (3d)** To a solution of crude **3c** (189 mg, 0.490 mmol) in dioxane (2 ml) was added 10% Pd–C. The resulting mixture was stirred at 23 °C for 21 h under a hydrogen atmosphere. The catalyst was removed by filtration and washed with MeOH (30 ml). The filtrate and washings were combined and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane) to give 103 mg of **3d** as a colorless solid: mp 106.5—108 °C. IR (KBr) cm^{-1}: 2925, 2200, 1745, 1510, 1435, 1365, 1300. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.88—3.02 (2H, m), 3.02—3.15 (2H, m), 4.48 (2H, s), 7.08, 6.80 (4H, A_2B_2-q, J=8.7 Hz), 7.41 (1H, dd, J=8.4, 1.6 Hz), 7.57 (1H, dd, J=8.6, 1.6 Hz), 7.59 (1H, s), 7.80 (1H, d, J=8.4 Hz), 7.81 (1H, d, J=8.5 Hz), 8.18 (1H, s). MS *m*/*z*: 387 (M^+).

***tert*-Butyl 4-[2-(6-Amidino-2-naphthyl)ethyl]phenoxyacetate hydriodide (4d)** In the same manner as in standard procedure B, the cyano group of **3d** (92.4 mg, 0.238 mmol) was converted to an amidino group to give 95.7 mg of the hydriodide of **4d** as a pale solid (80% in 3 steps).: mp: 136.5 °C (dec.). IR (KBr) cm^{-1}: 3250, 1740, 1660, 1510, 1365, 1215. ^{1}H-NMR (DMSO-d_6) δ: 1.41 (9H, s), 2.87—3.18 (4H, m), 4.58 (2H, s), 6.79, 7.15 (4H, A_2B_2-q, J=8.6 Hz), 7.58 (1H, d, J=8.5 Hz), 7.77 (1H, dd, J=8.6, 1.7 Hz), 7.84 (1H, s), 8.00 (1H, d, J=7.5 Hz), 8.04 (1H, d, J=8.2 Hz), 8.42 (1H, s), 9.16 (4H, br s).

4-[2-(6-Amidino-2-naphthyl)ethyl]phenoxyacetic Acid (5d) In the same manner as in standard procedure C, the hydriodide (85.9 mg, 0.161 mmol) of **4d** was treated with TFA (1.3 ml) to give 63.0 mg of the hydriodide of **5d** as a pale brown solid (85%): mp: >300 °C. IR (KBr) cm^{-1}: 3300, 3050, 1665, 1510, 1435, 1230, 1200. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 2.91—2.98 (2H, m), 3.04—3.11 (2H, m), 4.61 (2H, s), 6.81, 7.15 (4H, A_2B_2-q, J=8.6 Hz), 7.59 (1H, dd, J=8.5, 1.4 Hz), 7.79 (1H, dd, J=8.6, 1.8 Hz), 7.84 (1H, s), 8.01 (1H, d, J=8.5 Hz), 8.04 (1H, d, J=8.7 Hz), 8.44 (1H, d, J=0.9 Hz), 9.18 (2H, s), 9.39 (2H, s). *Anal*. Calcd for $C_{21}H_{20}N_2O_3 \cdot C_2HO_2F_3 \cdot 0.2H_2O$: C, 59.28; H, 4.63; N, 6.01. Found: C, 59.27; H, 4.54; N, 6.09.

4-[2-(4-Amidinophenoxy)-1-oxoethylamino]phenoxyacetic Acid (15) 34% yield from benzyloxycarbonylamidinophenoxyacetic acid[39]: mp: >250 °C. IR (KBr) cm^{-1}: 1740, 1675, 1620, 1500, 1190. ^{1}H-NMR (DMSO-d_6) δ: 4.64 (2H, s), 4.84 (2H, s), 6.85—6.93 (2H, m), 7.18—7.22 (2H, m), 7.48—7.54 (2H, m), 7.79—7.82 (2H, m), 9.04—9.15 (4H, m), 10.09 (1H, bs). *Anal*. Calcd for $C_{17}H_{17}N_3O_5 \cdot HCl \cdot 0.35H_2O$: C, 52.88; H, 4.88; N, 10.88. Found; C, 53.20; H, 4.95; N, 10.36.

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Supporting Information Available: HPLC analyses for compounds **5a**—**d** (1 page). *Ab initio* molecular orbital calculations for **16**A, **16**B, **17**A, **17**B and *N*-formyl-4-methoxyaniline (model compound for the acidic part) (7 pages). Ordering information is given on any current masthead page.

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