Indoline Derivatives I: Synthesis and Factor Xa (FXa) Inhibitory Activities

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A series of bisamidine derivatives each having a ring structure in the center of the molecule was synthesized and their Factor Xa (FXa) inhibitory activities were evaluated. Among them, some indoline derivatives showed potent inhibitory activities *in vitro*. In particular, (*R*)-18a having an (*R*)-configuration at the 2-position of the indoline ring exhibited the most potent FXa inhibitory activity *in vitro*, more potent than DX-9065a. Furthermore, (*R*)-18a exhibited more potent anticoagulant activity than DX-9065a. We also succeeded in obtaining an X-ray crystal structure of FXa bound with (*R*)-18a.

Key words Facter Xa (FXa) inhibitory activity; indoline derivative; anticoagulant

Factor Xa (FXa), a serine protease in the blood coagulation cascade,[2)] is essential for the formation of thrombin, a key mediator of both fibrin formation and platelet activation. FXa plays an important role in the coagulation network at the common pathway that connects both the tissue factor-activated extrinsic pathway and the surface-activated intrinsic pathway. Inactivation of FXa does not influence preformed thrombin but does effectively prevent the generation of thrombin.[3,4)] Thus, FXa inhibitors are expected to be novel antithrombotics with potential for the treatment and prevention of thromboembolic diseases without risk of bleeding.[5)]

Several antithrombotic agents, low molecular weight heparins[6)] and synthetic pentasaccharide fondaparinux sodium (Arixtra[7)]), targeted to FXa, are known. These agents require antithrombin III (ATIII), variable from patient to patient, to produce antithrombotic effects. Some studies showed that ATIII-dependent agents were less potent toward clot-bound coagulation factors compared with coagulation enzymes present in the plasma because of a lower accessibility of agent-ATIII complexes to the clot-bound coagulation factors.[8,9)] Therefore, small molecule FXa inhibitors which produce anticoagulant action independent of ATIII are thought to be more promising anticoagulants than ATIII-dependent anticoagulants.[10)]

Many direct FXa inhibitors have been reported in the literature. Among them, we focused on the structure of DX-9065a[11,12)] and Yamanouchi compound[13)] (Fig. 1) which have amidino groups on each side of the molecules and side chains in the center of the molecules. Moreover, this moiety seems to have weak rigidity and results in loose binding to the FXa active site.[14)]

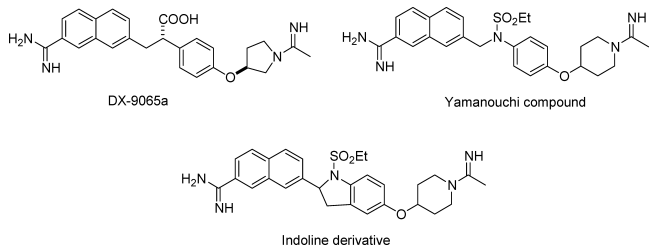

Fig. 1. Structures of DX-9065a, Yamanouchi Compound and Indoline Derivative

Thus, introduction of a cyclic moiety in the center of these structures was expected to increase the rigidity of the molecule and enhance affinity towards FXa. Using this strategy, we synthesized indoline compounds and their derivatives to find compounds which bind tightly to the active FXa site.

In this paper, we describe the synthesis and structure–activity relationships (SARs) of these compounds and the X-ray crystal structure of one of these compound bound to FXa.

Chemistry

Key intermediates **9a**—**j** were synthesized as shown in Chart 1. Protected nitrophenol **1** was introduced a trimethylsilylmethyl group to give compound **2**.[15)] Compound **2** was coupled with 2-cyano-7-naphthylaldehyde (**3**)[16)] by tetrabutylammonium fluoride (TBAF) to give alcohol **4**. After reduction of the nitro group of **4** by catalytic hydrogenation, aniline **5** was reacted with ethanesulfonyl chloride under basic conditions to give sulfonamide **6**. Intramolecular Mitsunobu reaction[17)] of **6** with *n*-Bu_3P and 1,1′-(azodicarbonyl)dipiperidine (ADDP) afforded corresponding indoline **7**. After removing the methoxymethyl (MOM) group of **7** by treatment with HCl, phenol **8** was converted to intermediates **9a**—**j** by means of the Mitsunobu reaction with alcohols (method A), or by alkylation with the tosylate (method B).

Intermediates **16a** and **16b** were synthesized as shown in Chart 2. 1-Fluoro-4-nitrobenzene (**10**) was converted to ether **11a** and **11b** by reaction with alcohols. Compounds **11a** and **11b** were subjected to the similar procedures as Chart 1 to give the corresponding intermediates **16a** and **16b**.

The syntheses of the amidine derivatives from intermediates **9a**—**j** are outlined in Chart 3. Compounds **9a**—**j** were converted to the corresponding amidines **17a**—**j** by bubbling HCl gas into an alcohol solution of nitriles, followed by amination of the resulting imidates (method C), or by treatment with hydroxylamine, followed by acetylation and hydrogenation of the resulting amidoximes (method D). The treatment of **17a**, **f**—**j** having the non-substituted amine moieties with ethyl acetimidate and triethylamine afforded corresponding bisamidines **18a**, **f**—**j**.

The synthesis of compound **21** is outlined in Chart 4. After

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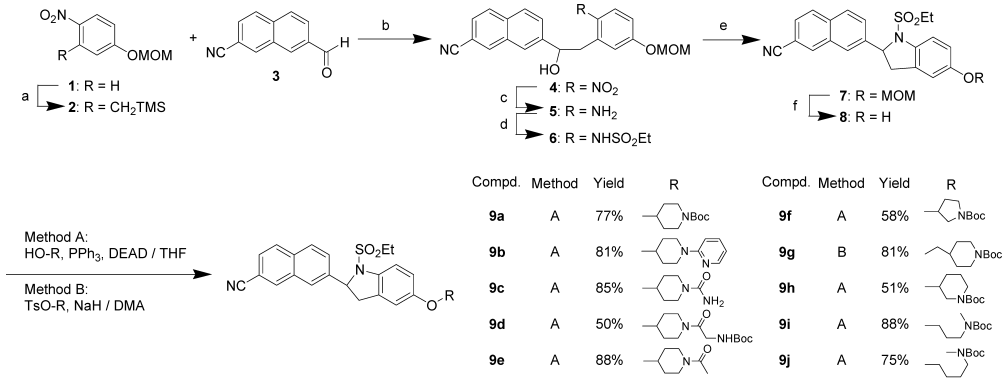
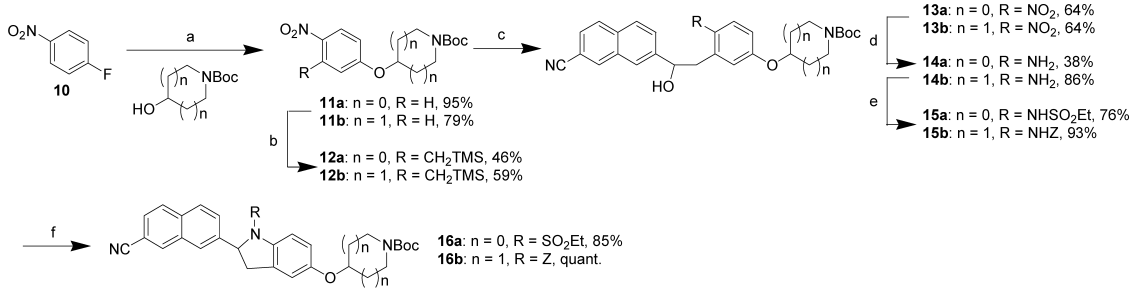


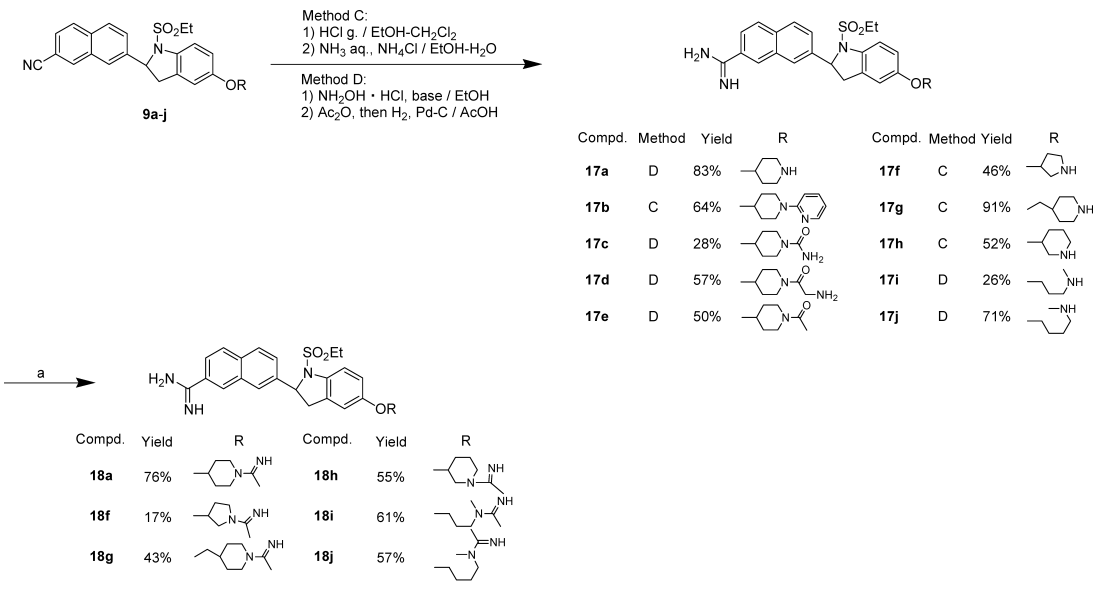
[a] Reagents: a) $TMSCH_2MgCl$, then DDQ / THF, 74%; b) TBAF / THF, 58%; c) H_2, Pd-C / EtOH-THF, 76%; d) $EtSO_2Cl$, Pyr. / CH_2Cl_2, 84%; e) *n*-Bu_3P, ADDP / THF, 98%; f) HCl / AcOEt, 97%.

Chart 1



[a] Reagents: a) NaH / DMA; b) $TMSCH_2MgCl$, then DDQ / THF; c) **3**, TBAF / THF; d) H_2, Pd-C / EtOH-THF; e) $EtSO_2Cl$ or ZCl, Pyr. / CH_2Cl_2; f) *n*-Bu_3P, ADDP / THF.

Chart 2

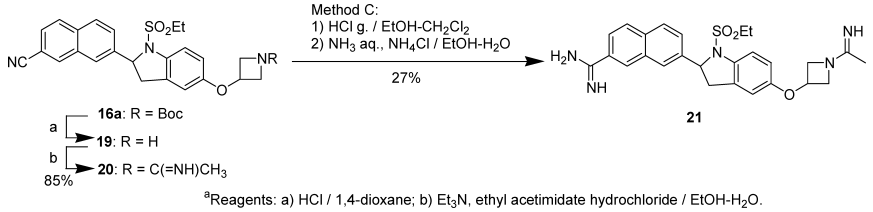


[a] Reagents: a) Et_3N, ethyl acetimidate hydrochloride / EtOH-H_2O.

Chart 3

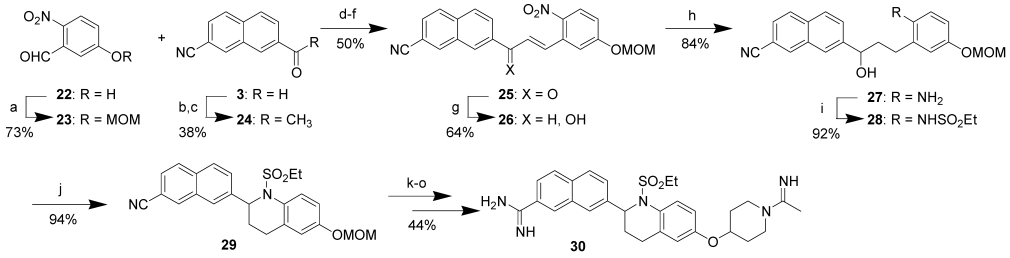
removing the *t*-butoxycarbonyl (Boc) group of **16a** under acidic conditions, compound **19** was converted into acetimidate **20**. Compound **21** was synthesized from **20** by the same method (method C) described above.

Tetrahydroquinoline derivative **30** was synthesized as shown in Chart 5. Phenol **22** was protected to give compound **23**, and aldehyde **3** was converted to ketone **24** in 2 steps. After aldol reaction of aldehyde **23** and ketone **24**, the resulting alcohol was treated with acid, followed by reprotection of the phenolic hydroxyl group to give unsaturated ketone **25**. Reduction of the carbonyl group of **25**, followed by hydrogenation of alcohol **26** afforded aniline **27**. Compound **27** was converted to the corresponding sulfonamide **28**, which was cyclized by means of intramolecular Mitsunobu reaction



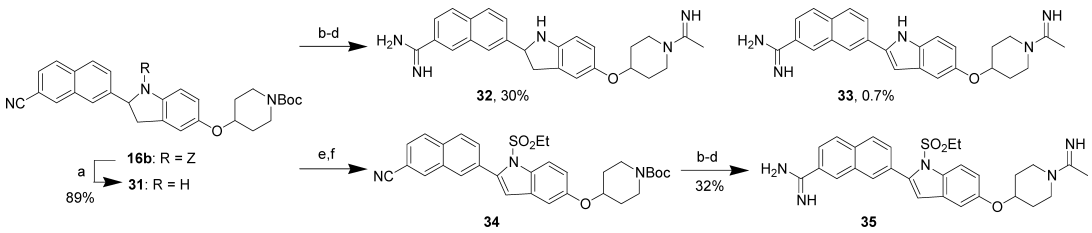
[a]Reagents: a) HCl / 1,4-dioxane; b) Et_3N, ethyl acetimidate hydrochloride / EtOH-H_2O.

Chart 4



[a] Reagents: a) MOMCl, Et_3N / $PhCH_3$-CH_2Cl_2-DMA; b) CH_3MgBr / THF; c) MnO_2 / CH_2Cl_2; d) LDA / THF; e) *p*-TsOH・H_2O / $Cl(CH_2)_2Cl$; f) MOMCl, Et_3N / DMA; g) $NaBH_4$ / EtOH-CH_2Cl_2; h) H_2, Pd-C / EtOH-THF; i) $EtSO_2Cl$, Pyr. / CH_2Cl_2; j) *n*-Bu_3P, ADDP / THF; k) HCl / AcOEt; l) 1-Boc-4-hydroxypiperidine, PPh_3, DEAD / THF; m) KO*t*-Bu, NH_2OH・HCl / MeOH-$PhCH_3$; n) Ac_2O, then H_2, Pd-C / AcOH; o) Et_3N, ethyl acetimidate hydrochloride / EtOH.

Chart 5



[a] Reagents: a) H_2, Pd-C / EtOH-THF; b) HCl g. / EtOH-CH_2Cl_2; c) NH_3 aq., NH_4Cl / EtOH-H_2O; d) Et_3N, ethyl acetimidate hydrochloride / EtOH; e) MnO_2 / CH_2Cl_2; f) $EtSO_2Cl$, NaH, DMAP / DMF.

Chart 6

to give tetrahydroquinoline **29**. Compound **30** was synthesized from **29** by the same methods (methods A and D) described above.

Non-substituted indoline derivative **32** and indole derivatives **33** and **35** were synthesized as shown in Chart 6. The benzyloxycarbonyl (*Z*) group of intermediate **16b** was removed to give compound **31** and this compound was converted to the corresponding non-substituted indoline compound **32** and indole compound **33**, an oxidized form of **32** by the similar procedures described above. Moreover, compound **31** was oxidized by MnO_2,[18] followed by treatment with ethanesulfonyl chloride to give compound **34** having an ethanesulfonyl group on the indole ring. Compound **34** was converted to the corresponding ethanesulfonylindole **35** by the same procedures as above.

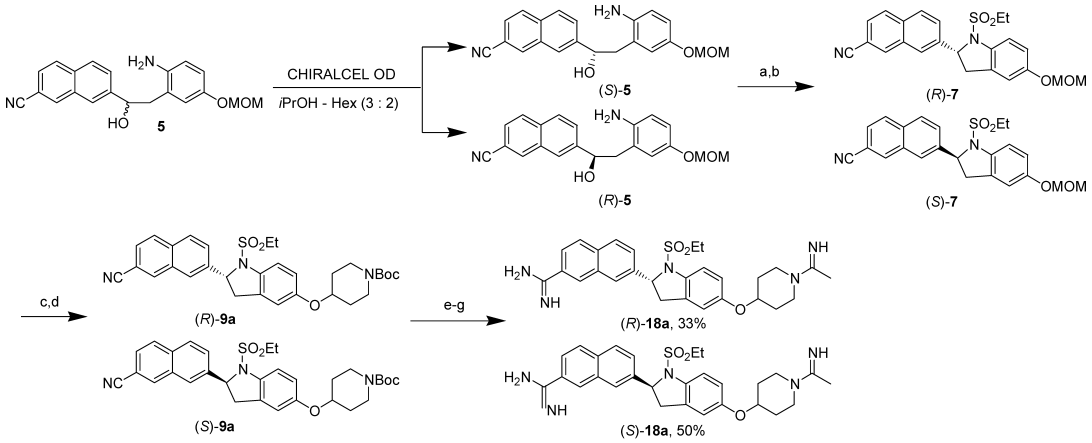
The syntheses of optically active (*R*)-**18a** and (*S*)-**18a** are outlined in Chart 7. Racemic alcohol **5** was separated by chiral column chromatography into optically pure (*S*)-**5** and (*R*)-**5**, respectively. After reaction of (*S*) and (*R*)-**5** with ethanesulfonyl chloride, ether (*R*) and (*S*)-**9a**, respectively, were obtained *via* stereochemically inversed indoline (*R*) and (*S*)-**7**, respectively, by the same procedure as that for **9a**. Optically active bisamidines (*R*)-**18a** and (*S*)-**18a** were synthesized from (*R*) and (*S*)-**9a**, respectively, by the same method as described in Chart 3. The stereochemistry of the optically active indoline moiety was confirmed by X-ray crystallographic analysis of (*R*)-**9a** (Fig. 2).

Results and Discussion

The *in vitro* FXa inhibitory activities of all compounds synthesized were evaluated and are expressed as IC_{50} values.

As described above, we considered that introduction of the ring structure into the center of the molecule to enhance rigidity would give higher FXa inhibitory activity. So we studied the influence of the ring structure (Table 1). Regarding the indoline compounds, compound **18a** having an ethanesulfonyl moiety on the nitrogen atom exhibited more potent FXa inhibitory activity than no-substituent compound **32**. This tendency was also observed for the indole compounds (**35** *vs*. **33**). Regarding the ring structure, indoline compound **18a** exhibited much higher FXa inhibitory activity than indole compound **35**. Moreover, indoline compound **18a** exhibited 5-fold higher FXa inhibitory activity than that of tetrahydroquinoline compound **30**. Among these ring structures, the indoline structure having a substituent was found to be suitable as the center of the molecule.

Next, the effect of the substituent on the nitrogen atom of the piperidine ring was examined (Table 2). No-substituent compound **17a** and 2-pyridyl compound **17b** had significantly (11-fold) low inhibitory activity compared to the ace-



[a] Reagents: a) $EtSO_2Cl$, Pyr. / CH_2Cl_2; b) *n*-Bu_3P, ADDP / THF; c) HCl / AcOEt; d) 1-Boc-4-hydroxypiperidine, PPh_3, DEAD / THF; e) HCl g. / EtOH-CH_2Cl_2, f) NH_3 aq., NH_4Cl / EtOH-H_2O, g) Et_3N, ethyl acetimidate hydrochloride / EtOH.

Chart 7

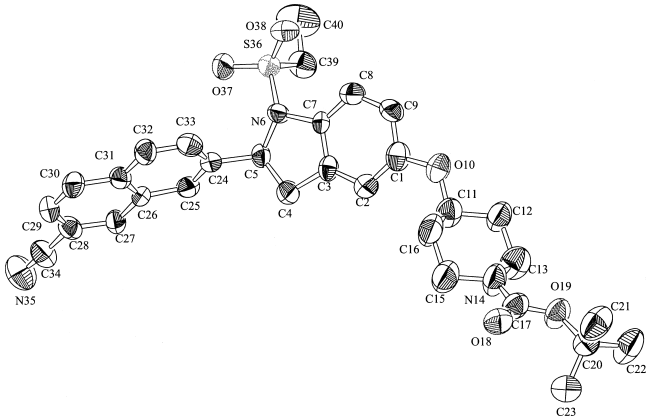
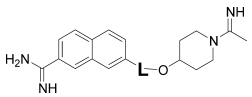
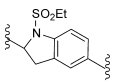
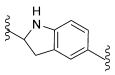
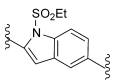
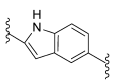
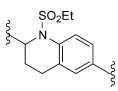


Fig. 2. View of the (*R*)-**9a** Molecule

H atoms have been omitted for clarity.

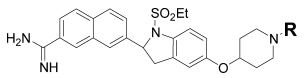
Table 1. FXa Inhibitory Activity of Compounds **18a**, **32**, **35**, **33** and **30**



Compd.[a)]	L	IC_{50} (nM)
18a		11
32		180
35		3600
33		7100
30		51

a) All compounds were synthesized and evaluated as their hydrochlorides.

Table 2. FXa Inhibitory Activity of Compounds **18a** and **17a**—**e**



Compd.[a)]	R	IC_{50} (nM)
18a		11
17a		120
17b		120
17c		29
17d		53
17e		34

a) All compounds were synthesized and evaluated as their hydrochlorides.

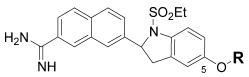
timidoyl compound **18a**. Regarding the acyl-type compounds, urea compound **17c**, glycyl compound **17d**, and acetyl compound **17e** were tested. Among them, **17c** and **17e** exhibited moderate activity, but lower than that of **18a**. These results indicate that an acetimidoyl group is favorable as a substituent on the nitrogen atom of the piperidine ring.

To further optimize this basic moiety, we focused on the amine structure attached to the acetimidoyl group (Table 3). In regard to ring size, 4-piperdine compound **18a** showed potent inhibitory activity similar to that of 3-pyrrolidine compound **18f** having the same moiety as DX-9065a, whereas 3-azetidine compound **21** exhibited weak activity. Introduction of one carbon atom between the piperidine ring and the oxygen atom decreased FXa inhibitory activity (**18a** *vs*. **18g**). A compound substituted at the 3-position of the piperidine ring (**18h**) showed 3-fold less inhibitory activity compared to that at the 4-position (**18a**). On the other hand, introduction of an acyclic amine structure (**18i**, **j**) instead of the piperidine ring resulted in a decline of inhibitory activity. According to these results, a 4-piperidine or 3-pyrrolidine moiety turned out to be the most appropriate as the amine structure. However, we

thought that **18a** was more favorable than **18f** because **18a** has no asymmetric carbon on the ring structure.

All indoline derivatives discussed above are racemates having an asymmetric carbon atom at the 2-position of the indoline ring. Therefore, each of the enantiomers of **18a** was prepared to examine their FXa inhibitory activities (Table 4). The compound with the (*R*)-configuration, (*R*)-**18a**, exhibited 20-fold higher inhibitory activity than that with the (*S*)-configuration, (*S*)-**18a**. The result indicates that (*R*)-**18a** is the active enantiomer for FXa inhibitory activity. We compared this activity to that of DX-9065a which is in clinical trial at present. (*R*)-**18a** showed more potent activity than that of DX-9065a.

Table 3. FXa Inhibitory Activity of Compounds **18a**—**f** and **21**



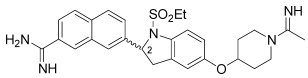
Compd.[a)]	R	IC_{50} (nM)
18a		11
18f[b)]		17
21		43
18g		31
18h[b)]		34
18i		71
18j		61

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) A mixture of four diastereoisomers.

To further understand the SARs of these compounds, the crystal structure of FXa complexed with (*R*)-**18a** was determined by X-ray crystallography at 2.3 Å resolution (Fig. 3). The crystal structure revealed that (*R*)-**18a** binds to FXa in an L-shaped conformation with the naphthamidine moiety deep in the S1 pocket and the acetimidoylpiperidine moiety at the aryl binding site consisting of residues Tyr-99, Phe-174 and Trp-215. Indole compound **35**, having an sp^2 carbon atom corresponding to the asymmetric carbon atom at the 2-position of the indoline ring in (*R*)-**18a**, has a relatively flat structure and does not form the L-shaped conformation peculiar to (*R*)-**18a**. Therefore, the surface of **35** would not be complementary to that of FXa. The crystal structure shows that (*R*)-**18a** binds to FXa in an L-shaped conformation with good surface complementarity, resulting in much higher FXa inhibitory activity of (*R*)-**18a** than that of **35**.

Moreover, the complex structure of FXa and (*R*)-**18a** was compared to that of FXa and DX-9065a[14] in order to understand the difference in FXa inhibitory activity (Table 4). DX-9065a binds to FXa in a similar L-shaped conformation to that of (*R*)-**18a**, with the naphthylamidine moiety in the S1 pocket and the pyrrolidine moiety at the aryl binding site (Fig. 3). However, there are two remarkable differences between these two compounds. First, although the terminal acetimidoyl group of DX-9065a points to Glu-97, the acetimi-

Table 4. FXa Inhibitory Activity of Compounds (*RS*)-**18a**, (*R*)-**18a**, (*S*)-**18a** and DX-9065a



Compd.[a)]	IC_{50} (nM)
(*RS*)-**18a**	11
(*R*)-**18a**	7.6
(*S*)-**18a**	150
DX-9065a	64

a) All compounds were synthesized and evaluated as their hydrochlorides.

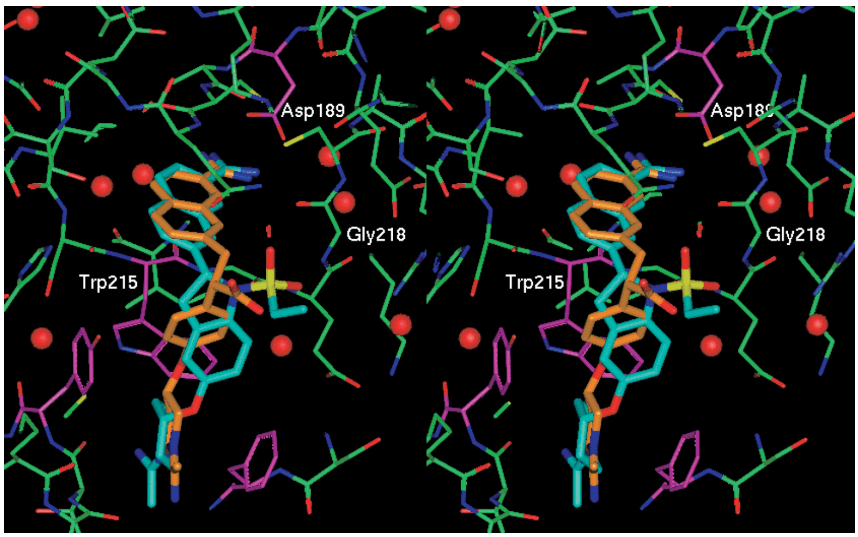


Fig. 3. Stereoview of Binding Mode of (*R*)-**18a** with FXa

The structure of FXa complexed with (*R*)-**18a** is shown in stick representation. Water molecules are represented as red balls. Where the complex structure of FXa and DX-9065a is superposed on that of FXa and (*R*)-**18a**, only DX-9065a is shown in stick representation. The color scheme is as follows: nitrogen atoms, blue; oxygen atoms, red; sulfur atoms, yellow; carbon atoms of (*R*)-**18a**, cyan; carbon atoms of DX-9065a, orange; carbon atoms of Asp-189 (in S1 pocket), Tyr-99, Phe-174 and Trp-215 (at the aryl binding site), magenta; and other carbon atoms of FXa, green.

doyl group of (*R*)-**18a** extends to the space between Thr-98 and Ile-175, contributing to the good surface complementarity of (*R*)-**18a**. Secondly, the carboxyl group of DX-9065a between the S1 pocket and the aryl binding site makes a hydrogen bond with Gln-192 with a length of 3.1 Å, while the ethanesulfonyl group of (*R*)-**18a** makes a hydrogen bond with Gly-218 with a length of 2.9 Å, a more optimum length for a hydrogen bond. The comparison of the complex structures suggests that these conformational differences likely contribute to the higher FXa inhibitory activity of (*R*)-**18a** than that of DX-9065a.

We evaluated the effect of the anticoagulant activity of (*R*)-**18a** on prothrombin time (PT) and expressed it as a CT_2 value, the concentration required to achieve 200% relative clotting time. Table 5 shows the CT_2 values of (*R*)-**18a** and DX-9065a in hamsters and humans (*in vitro*). (*R*)-**18a** exhibited potent anticoagulant activity and its activity was much higher than that of DX-9065a in both hamsters and humans.

In conclusion, we synthesized many bisamidine derivatives each having a ring structure in the center of the molecule and evaluated their FXa inhibitory activities. According to the results, we found that some novel indoline derivatives have high FXa inhibitory activities. Among them, (*R*)-**18a**, having an (*R*)-configuration at the 2-position of the indoline ring, exhibited more potent FXa inhibitory activity and anticoagulant activity than those of DX-9065a *in vitro*. (*R*)-**18a** and some indoline derivatives are currently under further evaluation and we are continuing synthetic efforts to explore novel compounds having more potent FXa inhibitory activity and safety.

Table 5. Anticoagulant Activity of Compounds (*R*)-**18a** and DX-9065a

Compd.	CT_2 (μM)[a]	
	Hamster	Human
(*R*)-**18a**	1.1	0.52
DX-9065a	8.3	2.7

a) The concentration required to double clotting time (PT).

Experimental

^{1}H-NMR spectra were obtained on a JEOL EX 270 or 400 MHz spectrometer and were reported as δ values relative to Me_4Si as the internal standard. Abbreviations of the ^{1}H-NMR peak patterns are as follows: br s=broad singlet, s=singlet, d=doublet, dd=double doublet, t=triplet, br t=broad triplet, q=quartet, and m=multiplet. Merck Silica gel 60 (230—400 mesh) was used in the column chromatography. Tetrahydrofuran, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, and dimethylsulfoxide are abbreviated as THF, DMF, DMA and DMSO, respectively.

4-(Methoxymethoxy)-1-nitro-2-(trimethylsilylmethyl)benzene (2) To a solution of 4-(methoxymethoxy)-1-nitrobenzene **1** (41.9 g, 229 mmol) in THF (50 ml) was slowly added (trimethylsilylmethyl)magnesium chloride (1.0 M in Et_2O, 252 ml, 252 mmol) and the mixture was stirred at −30 °C for 30 min. Then a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (52 g, 229 mmol) in THF (300 ml) was added slowly and the mixture was stirred at −30 °C for 2 h. The mixture was concentrated and the resulting residue was dissolved in EtOAc. The mixture was filtered through a silica gel column and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=5/1) to give **2** (45.9 g, 170 mmol, 74%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (9H, s), 2.64

Table 6. Physical Data for Indoline Derivatives

Compd.	Formula	Analysis (%), Calcd (Found)				
		C	H	N	Cl	S
17a	$C_{26}H_{30}N_4O_3S \cdot 1.9HCl \cdot 2.5H_2O$	52.67 (52.90)	6.27 (5.96)	9.45 (9.13)	11.36 (11.62)	5.41 (5.09)
17b	$C_{31}H_{33}N_5O_3S \cdot 2.5HCl \cdot 1.0H_2O$	56.00 (56.19)	5.69 (5.67)	10.53 (10.33)	13.33 (13.22)	4.82 (4.73)
17c	$C_{27}H_{31}N_5O_4S \cdot 1.7HCl \cdot 1.4H_2O$	53.26 (53.57)	5.88 (5.99)	11.50 (11.25)	9.90 (9.85)	5.27 (5.15)
17d	$C_{28}H_{33}N_5O_4S \cdot 2.0HCl \cdot 1.3H_2O$	53.21 (52.95)	6.00 (5.95)	11.08 (10.75)	11.22 (11.56)	5.07 (5.47)
17e	$C_{28}H_{32}N_4O_4S \cdot 1.0HCl \cdot 1.0H_2O$	58.48 (58.23)	6.13 (5.98)	9.74 (9.44)	6.16 (6.60)	5.58 (5.36)
18a	$C_{28}H_{33}N_5O_3S \cdot 2.3HCl \cdot 1.3H_2O$	53.64 (53.59)	6.09 (6.04)	11.17 (11.09)	13.01 (13.31)	5.11 (5.05)
18f	$C_{27}H_{31}N_5O_3S \cdot 2.6HCl \cdot 2.2H_2O$	50.67 (50.32)	5.98 (6.08)	10.94 (11.17)	14.40 (14.68)	5.01 (5.05)
18g	$C_{29}H_{35}N_5O_3S \cdot 2.0HCl \cdot 1.2H_2O$	55.44 (55.19)	6.32 (6.56)	11.15 (11.07)	11.29 (11.66)	5.10 (5.08)
18h	$C_{28}H_{33}N_5O_3S \cdot 2.0HCl \cdot 1.2H_2O$	54.76 (54.68)	6.14 (6.40)	11.40 (11.38)	11.54 (11.82)	5.22 (5.05)
18i	$C_{27}H_{33}N_5O_3S \cdot 2.1HCl \cdot 2.7H_2O$	51.24 (51.20)	6.45 (6.10)	11.07 (11.20)	11.76 (11.83)	5.07 (5.10)
18j	$C_{28}H_{35}N_5O_3S \cdot 1.9HCl \cdot 2.5H_2O$	52.88 (53.00)	6.64 (6.35)	11.01 (11.22)	10.59 (10.47)	5.04 (5.05)
21	$C_{26}H_{29}N_5O_3S \cdot 2.0HCl \cdot 1.9H_2O$	52.16 (52.01)	5.86 (5.59)	11.70 (11.86)	11.84 (12.29)	5.35 (5.39)
30	$C_{29}H_{35}N_5O_3S \cdot 2.0HCl \cdot 2.0H_2O$	54.20 (54.05)	6.43 (6.44)	10.90 (10.75)	11.03 (11.41)	4.99 (5.15)
32	$C_{26}H_{29}N_5O \cdot 3.3HCl \cdot 3.9H_2O$	50.52 (50.65)	6.54 (6.41)	11.33 (11.29)	18.93 (19.21)	—
33	$C_{26}H_{27}N_5O \cdot 2.0HCl \cdot 2.3H_2O$	57.84 (57.82)	6.27 (6.36)	12.97 (12.71)	13.13 (13.21)	—
35	$C_{28}H_{31}N_5O_3S \cdot 2.0HCl \cdot 3.4H_2O$	51.60 (51.53)	6.15 (5.78)	10.74 (10.55)	10.88 (11.10)	4.92 (4.99)

Table 7. Physical Data for Indoline Derivatives

Compd.	^{1}H-NMR δ (DMSO-d_6)
17a	1.18 (3H, t, J=7.5 Hz), 1.74—1.90 (2H, m), 2.04—2.15 (2H, m), 2.95—3.37 (7H, m), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.50—4.61 (1H, m), 5.78 (1H, dd, J=2.5, 10.0 Hz), 6.92 (1H, dd, J=2.5, 9.0 Hz), 6.99 (1H, br s), 7.34 (1H, d, J=9.0 Hz), 7.64 (1H, dd, J=1.5, 8.5 Hz), 7.83 (1H, dd, J=1.5, 8.5 Hz), 7.96 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.50 (1H, br s)
17b	1.19 (3H, t, J=7.5 Hz), 1.64—1.84 (2H, m), 2.00—2.16 (2H, m), 2.96—3.37 (3H, m), 3.62—3.78 (2H, m), 3.89—4.12 (3H, m), 4.58—4.72 (1H, m), 5.73—5.85 (1H, m), 6.88—7.05 (3H, m), 7.36 (1H, d, J=8.5 Hz), 7.38—7.49 (1H, m), 7.61—7.71 (1H, m), 7.81—7.91 (1H, m), 7.94—8.19 (5H, m), 8.52 (1H, br s)
17c	1.18 (3H, t, J=7.5 Hz), 1.35—1.55 (2H, m), 1.79—1.94 (2H, m), 2.94—3.37 (5H, m), 3.58—3.73 (2H, m), 3.95 (1H, dd, J=10.5, 17.0 Hz), 4.37—4.50 (1H, m), 5.77 (1H, dd, J=2.5, 10.0 Hz), 6.88 (1H, dd, J=2.5, 9.0 Hz), 6.95 (1H, d, J=2.5 Hz), 7.33 (1H, d, J=9.0 Hz), 7.65 (1H, dd, J=1.5, 8.5 Hz), 7.82 (1H, dd, J=1.5, 8.5 Hz), 7.95 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, br s)
17d	1.19 (3H, t, J=7.5 Hz), 1.41—1.67 (2H, m), 1.82—2.02 (2H, m), 2.94—4.04 (10H, m), 4.45—4.65 (1H, m), 5.72—5.82 (1H, m), 6.86—7.00 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.60—7.69 (1H, m), 7.78—7.88 (1H, m), 7.96 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, br s)
17e	1.18 (3H, t, J=7.5 Hz), 1.35—1.66 (2H, m), 1.77—2.04 (2H, m), 2.00 (3H, s), 3.00 (1H, dd, J=2.5, 17.0 Hz), 3.06—3.38 (4H, m), 3.57—4.09 (2H, m), 3.95 (1H, dd, J=10.0, 17.0 Hz), 4.45—4.57 (1H, m), 5.77 (1H, dd, J=2.5, 10.0 Hz), 6.90 (1H, dd, J=2.5, 8.5 Hz), 6.93 (1H, br s), 7.33 (1H, d, J=8.5 Hz), 7.65 (1H, dd, J=1.5, 8.5 Hz), 7.82 (1H, dd, J=1.5, 8.5 Hz), 7.96 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, br s)
18a	1.18 (3H, t, J=7.5 Hz), 1.63—1.83 (2H, m), 1.93—2.14 (2H, m), 2.29 (3H, s), 3.02 (1H, dd, J=2.5, 17.0 Hz), 3.07—3.18 (1H, m), 3.25—3.41 (1H, m), 3.45—3.62 (2H, m), 3.67—3.87 (2H, m), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.57—4.68 (1H, m), 5.78 (1H, dd, J=2.5, 10.0 Hz), 6.92 (1H, dd, J=2.5, 9.0 Hz), 6.99 (1H, d, J=2.0 Hz), 7.35 (1H, d, J=9.0 Hz), 7.64 (1H, d, J=8.5 Hz), 7.84 (1H, dd, J=2.0, 8.5 Hz), 7.96 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.50 (1H, br s)
18f	1.19 (3H, t, J=7.5 Hz), 2.14—2.33 (2H, m), 2.25, 2.29 (together 3H, each singlet), 2.94—3.20 (2H, m), 3.34—4.03 (6H, m), 5.05—5.21 (1H, m), 5.73—5.84 (1H, m), 6.84—7.00 (2H, m), 7.30—7.41 (1H, m), 7.58—7.69 (1H, m), 7.76—7.87 (1H, m), 7.96 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, br s)
18g	1.18 (3H, t, J=7.5 Hz), 1.25—1.50 (2H, m), 1.80—1.95 (2H, m), 2.03—2.21 (1H, m), 2.29 (3H, s), 2.94—3.45 (5H, m), 3.82 (2H, d, J=6.0 Hz), 3.87—4.04 (2H, m), 4.11—4.26 (1H, m), 5.73—5.84 (1H, m), 6.82—6.95 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.59—7.69 (1H, m), 7.80—7.89 (1H, m), 7.95 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.50 (1H, br s)
18h	1.11—1.25 (3H, m), 1.51—2.00 (4H, m), 2.19, 2.33 (together 3H, each singlet), 2.93—4.05 (8H, m), 4.50—4.69 (1H, m), 5.74—5.86 (1H, m), 6.85—7.01 (2H, m), 7.30—7.41 (1H, m), 7.57—7.69 (1H, m), 7.78—7.90 (1H, m), 7.95 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.51 (1H, br s)
18i	1.18 (3H, t, J=7.3 Hz), 1.94—2.09 (2H, m), 2.25, 2.27 (together 3H, each singlet), 2.97—3.02 (1H, m), 3.04, 3.12 (together 3H, each singlet), 3.07—3.17 (2H, m), 3.23—3.34 (2H, m), 3.59 (2H, br t, J=6.3 Hz), 3.91—4.05 (3H, m), 5.78 (1H, dd, J=2.5, 9.9 Hz), 6.85—6.89 (1H, m), 6.92 (1H, d, J=2.8 Hz), 7.35 (1H, d, J=8.7 Hz), 7.63 (1H, dd, J=1.6, 10.1 Hz), 7.84 (1H, dd, J=1.6, 8.7 Hz), 7.95 (1H, s), 8.07 (1H, d, J=8.7 Hz), 8.12 (1H, d, J=8.7 Hz), 8.50 (1H, s)
18j	1.18 (3H, t, J=7.4 Hz), 1.61—1.78 (4H, br s), 2.24, 2.28 (together 3H, each singlet), 3.01 (1H, dd, J=1.7, 17.0 Hz), 3.04, 3.11 (together 3H, each singlet), 3.11 (1H, dd, J=7.3, 14.2 Hz), 3.22—3.40 (1H, m), 3.44—3.53 (2H, m), 3.90—4.02 (3H, m), 5.78 (1H, dd, J=2.5, 10.0 Hz), 6.86 (1H, dd, J=2.5, 8.8 Hz), 6.91 (1H, s), 7.34 (1H, d, J=8.8 Hz), 7.64 (1H, d, J=8.6 Hz), 7.84 (1H, dd, J=1.8, 8.6 Hz), 7.95 (1H, s), 8.07 (1H, d, J=8.7 Hz), 8.12 (1H, d, J=8.7 Hz), 8.51 (1H, s)
21	1.18 (3H, t, J=7.5 Hz), 2.08, 2.09 (together 3H, each singlet), 3.02 (1H, d, J=17.0 Hz), 3.07—3.19 (1H, m), 3.24—3.42 (1H, m), 3.97 (1H, dd, J=10.0, 17.0 Hz), 4.03—4.14 (1H, m), 4.28—4.37 (1H, m), 4.56—4.66 (1H, m), 4.69—4.79 (1H, m), 5.02—5.13 (1H, m), 5.80 (1H, dd, J=2.5, 10.0 Hz), 6.81 (1H, dd, J=2.5, 9.0 Hz), 6.87 (1H, br s), 7.38 (1H, d, J=9.0 Hz), 7.63 (1H, dd, J=1.5, 8.5 Hz), 7.84 (1H, dd, J=2.0, 8.5 Hz), 7.95 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.51 (1H, br s)
30	1.17 (3H, t, J=7.5 Hz), 1.64—1.82 (2H, m), 1.88—2.12 (3H, m), 2.30 (3H, s), 2.52—2.69 (2H, m), 2.72—2.84 (1H, m), 2.99—3.13 (1H, m), 3.28—3.43 (1H, m), 3.45—3.62 (2H, m), 3.65—3.90 (2H, m), 4.61—4.72 (1H, m), 5.61 (1H, t, J=7.0 Hz), 6.86 (1H, d, J=3.0 Hz), 6.93 (1H, dd, J=3.0, 9.0 Hz), 7.60—7.69 (2H, m), 7.81 (1H, d, J=8.5 Hz), 7.93 (1H, br s), 8.03 (1H, d, J=8.5 Hz), 8.10 (1H, d, J=8.5 Hz), 8.45 (1H, br s)
32	1.69—1.87 (2H, m), 2.00—2.15 (2H, m), 2.31 (3H, s), 3.32—3.90 (6H, m), 4.66—4.79 (1H, m), 5.40—5.52 (1H, m), 6.95—7.30 (3H, m), 7.85—7.96 (3H, m), 8.10—8.28 (2H, m), 8.54 (1H, s)
33	1.68—1.90 (2H, m), 1.95—2.14 (2H, m), 2.33 (3H, s), 3.50—3.93 (4H, m), 4.61—4.71 (1H, m), 6.88 (1H, dd, J=2.5, 8.0 Hz), 7.05 (1H, s), 7.20 (1H, d, J=2.0 Hz), 7.40 (1H, d, J=8.5 Hz), 7.84 (1H, dd, J=2.0, 8.5 Hz), 8.10—8.27 (3H, m), 8.48 (1H, s), 8.55 (1H, s)
35	0.90 (3H, t, J=7.0 Hz), 1.73—1.92 (2H, m), 2.02—2.18 (2H, m), 2.32 (3H, s), 3.26 (2H, q, J=7.0 Hz), 3.50—3.92 (4H, m), 4.72—4.83 (1H, m), 6.93 (1H, s), 7.12 (1H, dd, J=2.5, 8.5 Hz), 7.37 (1H, d, J=2.5 Hz), 7.84—7.94 (3H, m), 8.10 (1H, d, J=8.5 Hz), 8.19—8.28 (2H, m), 8.59 (1H, s)

(2H, s), 3.48 (3H, s), 5.21 (2H, s), 6.75 (1H, d, J=2.5 Hz), 6.83 (1H, dd, J=2.5, 9.0 Hz), 8.03 (1H, d, J=9.0 Hz).

7-{1-Hydroxy-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile (4) To a solution of 4-(methoxymethoxy)-1-nitro-2-(trimethylsilylmethyl)benzene **2** (27.00 g, 100.2 mmol) and 7-formylnaphthalene-2-carbonitrile **3** (19.00 g, 104.9 mmol) in THF (250 ml) was slowly added a solution of TBAF monohydrate (2.61 g, 9.34 mmol) in THF (15 ml) and the mixture was stirred at −10 °C for 30 min. TBAF (75% in H_2O, 15 ml, 41.00 mmol) was then added and the mixture was stirred at room temperature for 1 h. NH_4Cl solution (250 ml) was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **4** (22.07 g, 58.33 mmol, 58%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 3.22 (1H, dd, J=9.0, 13.5 Hz), 3.41 (3H, s), 3.57 (1H, dd, J=3.5, 13.5 Hz), 5.15 (1H, d, J=7.0 Hz), 5.18 (1H, d, J=7.0 Hz), 5.23—5.31 (1H, m), 6.91 (1H, d, J=2.5 Hz), 7.03 (1H, dd, J=2.5, 9.0 Hz), 7.57—7.64 (1H, m), 7.74—7.80 (1H, m), 7.88—7.96 (3H, m), 8.09 (1H, d, J=9.0 Hz), 8.19—8.24 (1H, m).

7-{2-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile (5) A solution of 7-{1-hydroxy-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile **4** (24.00 g, 63.43 mmol) in THF (100 ml) and EtOH (100 ml) was hydrogenated over 10% Pd–C (2.4 g) at room temperature for 4 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/2) to give **5** (16.85 g, 48.36 mmol, 76%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 2.96—3.05 (2H, m), 3.38 (3H, s), 5.00 (2H, s), 5.18 (1H, dd, J=4.5, 7.5 Hz), 6.65 (1H, d, J=2.5 Hz), 6.69 (1H, d, J=8.5 Hz), 6.80 (1H, dd, J=2.5, 8.5 Hz), 7.58

(1H, dd, J=1.5, 8.5 Hz), 7.65 (1H, dd, J=1.5, 8.5 Hz), 7.82—7.94 (2H, m), 8.19 (1H, br s).

7-{2-[2-(Ethanesulfonyl)amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile (6) To a suspension of 7-{2-[2-amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile **5** (3.00 g, 8.61 mmol) in CH_2Cl_2 (60 ml) were added $EtSO_2Cl$ (1.08 ml, 11.4 mmol) and pyridine (0.96 ml, 11.9 mmol), and the mixture was stirred overnight at room temperature. The mixture was concentrated and the resulting residue was diluted with EtOAc and washed with H_2O. The organic layer was dried and concentrated. The resulting residue was dissolved in hexane and EtOAc (2/1), and stirred. The precipitate formed was collected by filtration to give **6** (3.20 g, 7.26 mmol, 84%) as a solid. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.5 Hz), 3.07—3.24 (4H, m), 3.36 (3H, s), 5.02 (1H, d, J=7.0 Hz), 5.06 (1H, d, J=7.0 Hz), 5.18—5.28 (1H, m), 6.70 (1H, d, J=3.0 Hz), 6.91 (1H, dd, J=3.0, 9.0 Hz), 7.40 (1H, d, J=9.0 Hz), 7.57—7.69 (2H, m), 7.82 (1H, br s), 7.86—7.96 (2H, m), 8.20 (1H, br s).

2-(7-Cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(methoxymethoxy)-indoline (7) To a solution of 7-{2-[2-(ethanesulfonyl)amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile **6** (3.20 g, 7.26 mmol) in THF (60 ml) were added n-Bu_3P (2.10 ml, 8.43 mmol) and ADDP (2.20 g, 8.72 mmol), and the mixture was stirred at 0 °C for 1 h. H_2O (100 ml) was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was suspended in hexane and EtOAc (1/1), and the mixture was filtered. The filtrate was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=2/3) to give **7** (3.00 g, 7.10 mmol, 98%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 2.93—3.13 (3H, m), 3.49 (3H, s), 3.87 (1H, dd, J=10.0, 16.5 Hz), 5.14 (2H, s), 5.64 (1H, dd, J=3.0, 10.0 Hz), 6.91—6.98 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.54—7.62 (2H, m), 7.81—7.90 (3H, m), 8.21 (1H, br s).

2-(7-Cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-hydroxyindoline (8) To a suspension of 2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(methoxymethoxy)indoline **7** (3.00 g, 7.10 mmol) in EtOAc (80 ml) was added a 4 N solution of hydrogen chloride in EtOAc (20 ml, 80 mmol) and the mixture was stirred at room temperature for 6 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=2/3) to give **8** (2.60 g, 6.87 mmol, 97%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 2.93—3.11 (3H, m), 3.84 (1H, dd, J=10.0, 16.5 Hz), 5.62 (1H, dd, J=3.0, 10.0 Hz), 6.69—6.78 (2H, m), 7.36 (1H, d, J=8.5 Hz), 7.53—7.62 (2H, m), 7.82—7.92 (3H, m), 8.17 (1H, br s).

5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (9a) (Method A) Diethyl azodicarboxylate (DEAD) (0.94 ml, 5.97 mmol) was added to a solution of 2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-hydroxyindoline **8** (1.50 g, 3.96 mmol), 1-(*t*-butoxycarbonyl)-4-hydroxypiperidine (1.20 g, 5.96 mmol) and PPh_3 (1.56 g, 5.95 mmol) in THF (60 ml), and the mixture was stirred at room temperature for 4 h. After adding DEAD (0.19 ml, 1.21 mmol), 1-(*t*-butoxycarbonyl)-4-hydroxypiperidine (0.239 g, 1.19 mmol) and PPh_3 (0.312 g, 1.19 mmol), the mixture was stirred at room temperature for 2 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/5) to give **9a** (1.72 g, 3.06 mmol, 77%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.47 (9H, s), 1.68—1.80 (2H, m), 1.85—1.98 (2H, m), 2.92—3.13 (2H, m), 3.08 (1H, dd, J=3.0, 17.0 Hz), 3.26—3.39 (2H, m), 3.63—3.77 (2H, m), 3.86 (1H, dd, J=10.0, 17.0 Hz), 4.34—4.44 (1H, m), 5.63 (1H, dd, J=3.0, 10.0 Hz), 6.77—6.88 (2H, m), 7.42 (1H, d, J=8.5 Hz), 7.53—7.64 (2H, m), 7.82—7.92 (3H, m), 8.20 (1H, br s).

Similarly, compounds **9b**—**f**, **9h**—**j** were prepared.

9b: ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.75—2.15 (4H, m), 2.91—3.14 (3H, m), 3.35—3.52 (2H, m), 3.79—4.02 (3H, m), 4.41—4.54 (1H, m), 5.55—5.70 (1H, m), 6.56—6.66 (1H, m), 6.69 (1H, d, J=8.5 Hz), 6.74—6.90 (2H, m), 7.41—7.65 (4H, m), 7.79—7.96 (3H, m), 8.15—8.28 (2H, m).

9c: ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.75—2.04 (4H, m), 2.89—3.10 (2H, m), 3.08 (1H, dd, J=3.0, 16.5 Hz), 3.25—3.45 (2H, m), 3.56—3.71 (2H, m), 3.87 (1H, dd, J=10.5, 16.5 Hz), 4.39—4.50 (1H, m), 5.64 (1H, dd, J=3.0, 10.5 Hz), 6.75—6.90 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.52—7.66 (2H, m), 7.80—7.95 (3H, m), 8.20 (1H, br s).

9d: ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.45 (9H, s), 1.71—1.98 (4H, m), 2.92—3.22 (3H, m), 3.25—3.42 (1H, m), 3.56—3.70 (1H, m), 3.72 (2H, d, J=5.5 Hz), 3.87 (1H, dd, J=10.0, 16.5 Hz), 3.98 (2H, d, J=3.0 Hz), 4.40—4.58 (1H, m), 5.64 (1H, dd, J=3.0, 10.0 Hz), 6.76—6.88 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.55—7.65 (2H, m), 7.80—7.94 (3H, m), 8.19 (1H, br s).

9e: ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.71—2.08 (4H, m), 2.12 (3H, s), 2.90—3.11 (2H, m), 3.08 (1H, dd, J=3.0, 16.5 Hz), 3.28—3.49 (1H, m), 3.54—3.85 (3H, m), 3.87 (1H, dd, J=10.5, 16.5 Hz), 4.38—4.55 (1H, m), 5.64 (1H, dd, J=3.0, 10.5 Hz), 6.70—6.91 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.49—7.63 (2H, m), 7.81—7.93 (3H, m), 8.20 (1H, br s).

9f: ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.47 (9H, s), 1.98—2.29 (2H, m), 2.92—3.13 (3H, m), 3.42—3.67 (4H, m), 3.86 (1H, dd, J=10.0, 16.0 Hz), 4.75—4.90 (1H, m), 5.58—5.68 (1H, m), 6.71—6.85 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.50—7.64 (2H, m), 7.79—7.93 (3H, m), 8.21 (1H, br s).

9h: ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.28—2.20 (4H, m), 1.41 (9H, s), 2.92—4.01 (8H, m), 4.05—4.28 (1H, m), 5.58—5.70 (1H, m), 6.69—6.88 (2H, m), 7.42 (1H, d, J=8.5 Hz), 7.50—7.68 (2H, m), 7.80—7.95 (3H, m), 8.21 (1H, br s).

9i: ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.42 (9H, s), 1.89—2.09 (2H, m), 2.87 (3H, s), 2.88—3.03 (2H, m), 3.07 (1H, dd, J=3.0, 16.5 Hz), 3.40 (2H, t, J=7.0 Hz), 3.86 (1H, dd, J=10.0, 16.5 Hz), 3.94 (2H, t, J=6.0 Hz), 5.62 (1H, dd, J=3.0, 10.0 Hz), 6.73—6.81 (2H, m), 7.42 (1H, d, J=8.5 Hz), 7.57 (1H, dd, J=1.5, 8.5 Hz), 7.58 (1H, dd, J=1.5, 8.5 Hz), 7.83—7.93 (3H, m), 8.20 (1H, br s).

9j: ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.45 (9H, s), 1.66—1.78 (4H, m), 2.85 (3H, s), 2.93—3.07 (2H, m), 3.07 (1H, dd, J=3.0, 16.5 Hz), 3.28 (2H, t, J=7.0 Hz), 3.86 (1H, dd, J=10.0, 16.5 Hz), 3.95 (2H, t, J=6.0 Hz), 5.62 (1H, dd, J=3.0, 10.0 Hz), 6.77—6.81 (2H, m), 7.42 (1H, d, J=8.5 Hz), 7.57 (1H, dd, J=1.5, 8.5 Hz), 7.59 (1H, dd, J=1.5, 8.5 Hz), 7.84—7.90 (3H, m), 8.20 (1H, br s).

5-[1-(*t*-Butoxycarbonyl)piperidin-4-ylmethyloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (9g) (Method B) A solution of 2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-hydroxyindoline **8** (1.00 g, 2.64 mmol) in DMA (20 ml) was treated with NaH (130 mg, 2.98 mmol, as a 55% w/w dispersion in mineral oil) under cooling conditions and the mixture was stirred at room temperature for 10 min. 1-(*t*-Butoxycarbonyl)-4-(*p*-toluenesulfonyloxymethyl)piperidine (1.20 g, 3.25 mmol) was added and the whole was stirred overnight at room temperature. The mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=2/3) to give **9g** (1.24 g, 2.15 mmol, 81%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.46 (9H, s), 1.72—2.03 (5H, m), 2.63—2.83 (2H, m), 2.92—3.14 (3H, m), 3.77 (2H, d, J=6.0 Hz), 3.87 (1H, dd, J=10.0, 16.5 Hz), 4.07—4.23 (2H, m), 5.63 (1H, dd, J=3.0, 10.0 Hz), 6.73—6.84 (2H, m), 7.43 (1H, d, J=8.5 Hz), 7.53—7.63 (2H, m), 7.81—7.92 (3H, m), 8.20 (1H, br s).

***t*-Butyl 3-(4-Nitrophenoxy)azetidine-1-carboxylate (11a)** A solution of *t*-butyl 3-hydroxyazetidine-1-carboxylate (4.89 g, 28.2 mmol) in DMA (90 ml) was treated with NaH (1.29 g, 29.6 mmol, as a 55% w/w dispersion in mineral oil) under cooling conditions and the mixture was stirred at room temperature for 15 min. Then a solution of 4-fluoro-1-nitrobenzene **10** (5.18 g, 36.7 mmol) in DMA (20 ml) was added and the whole was stirred at room temperature for 4 h. NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **11a** (7.86 g, 26.7 mmol, 95%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 4.03 (2H, dd, J=3.5, 9.5 Hz), 4.36 (2H, dd, J=6.5, 10.0 Hz), 4.94—5.01 (1H, m), 6.82 (2H, d, J=9.0 Hz), 8.22 (2H, d, J=9.0 Hz).

***t*-Butyl 3-[4-Nitro-3-(trimethylsilylmethyl)phenoxy]azetidine-1-carboxylate (12a)** To a solution of *t*-butyl 3-(4-nitrophenoxy)azetidine-1-carboxylate **11a** (10.4 g, 35.3 mmol) in THF (200 ml) was slowly added (trimethylsilylmethyl)magnesium chloride (1.0 M in Et_2O, 37.2 ml, 37.2 mmol) and the mixture was stirred at −5 °C for 1 h. Then a solution of DDQ (10.8 g, 47.6 mmol) in THF (30 ml) was added slowly and the mixture was stirred at 0 °C for 3.5 h. NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=13/7) to give **12a** (6.25 g, 16.4 mmol, 46%) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 0.01 (9H, s), 1.45 (9H, s), 2.63 (2H, s), 4.01 (2H, dd, J=4.0, 9.5 Hz), 4.32 (2H, dd, J=7.0, 9.5 Hz), 4.86—4.95 (1H, m), 6.42 (1H, d, J=2.5 Hz), 6.54 (1H, dd, J=2.5, 9.0 Hz), 8.04 (1H, d, J=9.0 Hz).

***t*-Butyl 3-{3-[2-(7-Cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-nitrophenoxy}azetidine-1-carboxylate (13a)** To a solution of *t*-butyl 3-[4-nitro-3-

(trimethylsilylmethyl)phenoxy]azetidine-1-carboxylate **12a** (6.23 g, 16.4 mmol) and 7-formylnaphthalene-2-carbonitrile **3** (3.26 g, 18.0 mmol) in THF (120 ml) was slowly added a solution of TBAF monohydrate (0.46 g, 1.65 mmol) in THF (20 ml) and the mixture was stirred at −10 °C for 1 h. TBAF (75% in H_2O, 3.06 g, 8.78 mmol) in THF (10 ml) was then added and the mixture was stirred at room temperature for 1 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The crystals that appeared were filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **13a** (5.13 g, 10.5 mmol, 64%) as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.16 (1H, dd, J=9.0, 13.0 Hz), 3.58 (1H, dd, J=3.5, 13.0 Hz), 3.92—4.01 (2H, m), 4.25—4.35 (2H, m), 4.84—4.91 (1H, m), 5.26 (1H, dd, J=3.0, 9.0 Hz), 6.67—6.76 (2H, m), 7.62 (1H, dd, J=1.5, 8.5 Hz), 7.77 (1H, dd, J=1.5, 8.5 Hz), 7.90—7.97 (3H, m), 8.10 (1H, d, J=9,0 Hz), 8.23 (1H, br s).

***t*-Butyl 3-{4-Amino-3-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-phenoxy}azetidine-1-carboxylate (14a)** A solution of *t*-butyl 3-{3-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-nitrophenoxy}azetidine-1-carboxylate **13a** (5.40 g, 11.0 mmol) in THF (60 ml) and EtOH (60 ml) was hydrogenated over 10% Pd-C (0.81 g) at room temperature for 8 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The crystals that appeared were filtered off, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/4) to give **14a** (1.91 g, 4.16 mmol, 38%) as yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.92—3.10 (2H, m), 3.83—3.95 (2H, m), 4.08—4.21 (2H, m), 4.63—4.71 (1H, m), 5.18 (1H, dd, J=4.0, 8.5 Hz), 6.41 (1H, d, J=3.0 Hz), 6.49 (1H, dd, J=3.0, 8.5 Hz), 6.69 (1H, d, J=8.5 Hz), 7.60 (1H, dd, J=1.5, 8.5 Hz), 7.65 (1H, dd, J=1.5, 8.5 Hz), 7.86 (1H, br s), 7.89 (1H, d, J=8.5 Hz), 7.92 (1H, d, J=8.5 Hz), 8.19 (1H, br s).

***t*-Butyl 3-{3-[2-(7-Cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-(ethanesulfonyl)aminophenoxy}azetidine-1-carboxylate (15a)** To a suspension of *t*-butyl 3-{4-amino-3-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]phenoxy}azetidine-1-carboxylate **14a** (1.86 g, 4.05 mmol) in CH_2Cl_2 (15 ml) and DMA (15 ml) were added $EtSO_2Cl$ (0.50 ml, 5.3 mmol) and pyridine (0.43 ml, 5.32 mmol), and the mixture was stirred at room temperature for 7 h. H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=7/13) to give **15a** (1.69 g, 3.06 mmol, 76%) as a brown solid. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7.5 Hz), 1.43 (9H, s), 3.04—3.24 (4H, m), 3.79—3.95 (2H, m), 4.10—4.26 (2H, m), 4.66—4.76 (1H, m), 5.21 (1H, dd, J=3.0, 8.5 Hz), 6.46 (1H, d, J=3.0 Hz), 6.59 (1H, dd, J=3.0, 9.0 Hz), 7.40 (1H, d, J=9.0 Hz), 7.58—7.68 (2H, m), 7.83 (1H, br s), 7.91 (1H, d, J=8.5 Hz), 7.93 (1H, d, J=8.5 Hz), 8.19 (1H, br s).

5-[1-(*t*-Butoxycarbonyl)azetidin-3-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (16a) To a solution of *t*-butyl 3-{3-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-(ethanesulfonyl)aminophenoxy}azetidine-1-carboxylate **15a** (1.67 g, 3.03 mmol)in THF (35 ml) were added *n*-Bu_3P (1.16 ml, 4.66 mmol) and ADDP (1.07 g, 4.24 mmol) in THF (15 ml), and the mixture was stirred at room temperature for 2 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was suspended in hexane and EtOAc (1/1), and the mixture was filtered. The filtrate was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **16a** (1.38 g, 2.59 mmol, 85%) as a brown amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.5 Hz), 1.45 (9H, s), 2.92—3.08 (2H, m), 3.09 (1H, dd, J=3.0, 17.0 Hz), 3.87 (1H, dd, J=10.0, 17.0 Hz), 3.99 (2H, dd, J=4.0, 9.5 Hz), 4.22—4.35 (2H, m), 4.77—4.90 (1H, m), 5.64 (1H, dd, J=3.0, 10.0 Hz), 6.57—6.67 (2H, m), 7.42 (1H, d, J=8.5 Hz), 7.56 (1H, dd, J=2.0, 8.5 Hz), 7.59 (1H, dd, J=1.5, 8.5 Hz), 7.82—7.94 (3H, m), 8.20 (1H, br s).

Similarly, the benzyloxycarbonyl derivative **16b** was prepared.

16b: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.64—1.80 (2H, m), 1.83—1.98 (2H, m), 3.00 (1H, dd, J=2.5, 17.0 Hz), 3.25—3.38 (2H, m), 3.63—3.83 (3H, m), 4.33—4.44 (1H, m), 4.89—5.25 (2H, m), 5.56—5.70 (1H, m), 6.73—7.25 (7H, m), 7.39—7.64 (3H, m), 7.76— 7.92 (3H, m), 8.04 (1H, br s).

2-(7-Amidinonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(piperidin-4-ylmethyloxy)indoline Dihydrochloride (17g) (Method C) HCl gas was bubbled through a solution of 5-[1-(*t*-butoxycarbonyl)piperidin-4-ylmethoxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **9g** (1.24 g, 2.15 mmol) in CH_2Cl_2 (10 ml) and EtOH (10 ml) at 0 °C. Then the mixture was stirred at room temperature for 3 h and concentrated. The resulting residue was dissolved in EtOH (20 ml) and H_2O (5 ml). The solution was neutralized with NH_3 solution and treated with NH_4Cl (180 mg, 3.37 mmol). The mixture was allowed to stand overnight at room temperature and concentrated. The resulting residue was chromatographed on a silica gel column (Cosmosil 75C18-PREP^{TM}, Nacalai Tesque Inc., MeCN/H_2O=1/19) to give the free base of **17g** (0.960 g, 1.95 mmol, 91%) as an amorphous solid. This amorphous solid (250 mg) was dissolved in EtOAc (10 ml) and treated with a 4 N solution of hydrogen chloride in EtOAc (0.4 ml, 1.6 mmol). The mixture was concentrated and the resulting residue was lyophilized to give **17** (0.287 g, 0.507 mmol) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 1.39—1.62 (2H, m), 1.79—2.11 (3H, m), 2.79—3.45 (7H, m), 3.81 (2H, d, J=6.0 Hz), 3.96 (1H, dd, J=10.0, 17.0 Hz), 5.72—5.83 (1H, m), 6.81—6.97 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.60—7.68 (1H, m), 7.80—7.90 (1H, m), 7.95 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.51 (1H, br s).

Similarly, compounds **17b**, **17f**—**h** were prepared.

17f: ^{1}H-NMR (DMSO-d_6) δ: 1.12—1.31 (3H, m), 1.70—2.48 (2H, m), 2.82—4.09 (8H, m), 4.72—5.20 (1H, m), 5.66—5.85 (1H, m), 6.77—7.02 (2H, m), 7.25—7.42 (1H, m), 7.50—8.51 (6H, m).

17g: ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 1.39—1.64 (2H, m), 1.80—2.17 (3H, m), 2.78—3.51 (7H, m), 3.81 (2H, d, J=6.0 Hz), 3.96 (1H, dd, J=10.0, 17.0 Hz), 5.71—5.83 (1H, m), 6.80—6.97 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.58—7.69 (1H, m), 7.81—7.90 (1H, m), 7.95 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.51 (1H, br s).

17h: ^{1}H-NMR (DMSO-d_6) δ: 1.16—1.26 (3H, m), 1.55—1.99 (4H, m), 2.81—3.38 (7H, m), 3.90—4.02 (1H, m), 4.45—4.57 (1H, m), 5.76—5.87 (1H, m), 6.90—6.98 (2H, m), 7.26 (1H, d, J=8.0 Hz), 7.60—7.68 (1H, m), 7.81—7.90 (1H, m), 7.95 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, br s).

2-(7-Amidinonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(piperidin-4-yloxy)indoline Dihydrochloride (17a) (Method D) To a solution of 5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **9a** (208 mg, 0.370 mmol) in MeOH (5 ml) and toluene (2 ml) were added hydroxylamine hydrochloride (28 mg, 0.40 mmol) and KO*t*-Bu (42 mg, 0.37 mmol). The mixture was stirred at 70 °C for 3 h. After adding hydroxylamine hydrochloride (28 mg, 0.40 mmol) and KO*t*-Bu (42 mg, 0.37 mmol), the mixture was stirred at 70 °C for 5 h. The deposit was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=23/2) to give a colorless solid. This solid was dissolved in AcOH (5 ml) and treated with Ac_2O (0.050 ml, 0.53 mmol). After stirring at room temperature for 15 min, the mixture was hydrogenated over 10% Pd-C (50 mg) at room temperature for 6 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was dissolved in MeOH (4 ml) and treated with a 4 N solution of hydrogen chloride in dioxane (3.0 ml, 12 mmol). The mixture was stirred at room temperature for 1.5 h. The mixture was concentrated and the resulting residue was purified by preparative HPLC (YMC-pack ODS, YMC, H_2O/MeCN=17/3) to give the free base of **17a** (148 mg, 0.309 mmol) as an amorphous solid. This amorphous solid (6.0 mg) was dissolved in a 1 N solution of hydrogen chloride (1 ml) and stored at room temperature for 5 min. The mixture was concentrated to give **17a** (6.6 mg, 0.012 mmol, 83%) as an amorphous solid.

Similarly, compounds **17c**—**e**, **17i** and **17j** were prepared.

17i: ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 2.01—2.08 (2H, m), 2.54 (3H, s), 2.93—3.00 (3H, m), 3.12 (1H, dd, J=7.0, 14.5 Hz), 3.22—3.31 (1H, m), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.02 (2H, t, J=6.0 Hz), 5.78 (1H, dd, J=2.5, 10.0 Hz), 6.86 (1H, dd, J=2.5, 8.5 Hz), 6.92 (1H, d, J=1.5 Hz), 7.35 (1H, d, J=8.5 Hz), 7.63 (1H, d, J=9.0 Hz), 7.82 (1H, dd, J=1.5, 8.5 Hz), 7.95 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.12 (1H, d, J=8.5 Hz), 8.49 (1H, br s).

17j: ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 1.76 (4H, br s), 2.50 (3H, s), 2.90 (2H, br s), 3.03 (1H, dd, J=2.5, 10.5 Hz), 3.10—3.21 (1H, m), 3.27—3.35 (1H, m), 3.94—4.02 (3H, m), 5.78 (1H, dd, J=2.5, 10.5 Hz), 6.86 (1H, dd, J=2.0, 9.0 Hz), 6.92 (1H, s), 7.35 (1H, d, J=8.5 Hz), 7.64 (1H, d, J=8.5 Hz), 7.86 (1H, d, J=8.5 Hz), 7.95 (1H, br s), 8.07 (1H, d, J=8.5 Hz), 8.12 (1H, d, J=8.5 Hz), 8.52 (1H, br s).

5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline Dihydrochloride (18a) To a solution of 2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(piperidin-4-yloxy)indoline dihydrochloride **17a** (142 mg, 0.297 mmol) in EtOH (6 ml) were added ethyl acetimidate hydrochloride (81 mg, 0.66 mmol) and Et_3N (0.14 ml, 1.0 mmol). The mixture was stirred overnight at room temperature. The mixture was concentrated and the resulting residue was purified by preparative

HPLC (YMC-pack ODS, YMC, H_2O/MeCN=4/1) to give the free base of **18a** (135 mg, 0.234 mmol) as an amorphous solid. This amorphous solid (135 mg) was dissolved in MeOH (4 ml) and treated with a 4 N solution of hydrogen chloride in dioxane (0.19 ml, 0.76 mmol). The mixture was allowed to stand at room temperature for 5 min and then concentrated. The resulting residue was lyophilized to give **18a** (134 mg, 0.226 mmol, 76%) as an amorphous solid.

Similarly, compounds **18f**—**j** were prepared.

5-[1-(Acetimidoyl)azetidin-3-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (20) To a solution of 5-[1-(*t*-butoxycarbonyl)-azetidin-3-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **16a** (390 mg, 0.731 mmol) in dioxane (4 ml) was added a 4 N solution of hydrogen chloride in dioxane (4 ml) and the mixture was stirred at room temperature for 3.5 h. The mixture was concentrated and the resulting residue (**19**) was dissolved in EtOH (5 ml) and CH_2Cl_2 (5 ml). After adding ethyl acetimidate hydrochloride (198 mg, 1.60 mmol) and Et_3N (0.34 ml, 2.45 mmol), the mixture was stirred overnight at room temperature. After adding ethyl acetimidate hydrochloride (99 mg, 0.80 mmol) and Et_3N (0.17 ml, 1.2 mmol), the mixture was stirred at room temperature for 4 h. The mixture was concentrated and the resulting residue was purified by preparative HPLC (YMC-pack ODS, YMC, H_2O/MeCN=1/1) to give **20** (294 mg, 0.619 mmol, 85%) as a pale yellow solid. ^{1}H-NMR (DMSO-d_6) δ: 1.18 (3H, t, J=7.5 Hz), 2.08 and 2.09 (together 3H, each singlet), 3.01 (1H, dd, J=3.0, 17.0 Hz), 3.06—3.17 (1H, m), 3.23—3.38 (1H, m), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.04—4.15 (1H, m), 4.28—4.38 (1H, m), 4.55—4.65 (1H, m), 4.68—4.79 (1H, m), 5.05—5.13 (1H, m), 5.77 (1H, dd, J=3.0, 10.0 Hz), 6.81 (1H, dd, J=2.5, 9.0 Hz), 6.87 (1H, br s), 7.37 (1H, d, J=9.0 Hz), 7.62 (1H, d, J=8.5 Hz), 7.78 (1H, dd, J=1.5, 8.5 Hz), 7.95 (1H, br s), 8.06 (1H, d, J=8.5 Hz), 8.09 (1H, d, J=8.5 Hz), 8.60 (1H, br s).

5-[1-(Acetimidoyl)azetidin-3-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline Dihydrochloride (21) (Method C) HCl gas was bubbled through a solution of 5-[1-(acetimidoyl)azetidin-3-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **20** (280 mg, 0.590 mmol) in CH_2Cl_2 (8 ml) and EtOH (5 ml) at 0 °C. Then the mixture was stirred at room temperature for 8.5 h and concentrated. The resulting residue was dissolved in EtOH (9 ml) and treated with NH_4Cl (57.0 mg, 1.07 mmol) in H_2O (3 ml) and NH_3 solution (0.120 ml, 1.97 mmol). The mixture was stirred overnight at room temperature and allowed to stand overnight at 0 °C. The mixture was concentrated and the resulting residue was purified by preparative HPLC (YMC-pack ODS, YMC, H_2O/MeCN=4/1) to give the free base of **21** (94 mg) as an amorphous solid. This amorphous solid (94 mg) was dissolved in MeOH (5 ml) and treated with a 4 N solution of hydrogen chloride in dioxane (0.14 ml, 0.56 mmol) at 0 °C. The mixture was concentrated and the resulting residue was lyophilized to give **21** (90 mg, 0.16 mmol, 27%) as an amorphous solid.

2-Formyl-4-(methoxymethoxy)-1-nitrobenzene (23) To a solution of 2-formyl-4-hydroxy-1-nitrobenzene **22** (15.91 g, 95.20 mmol) in $PhCH_3$ (50 ml) and CH_2Cl_2 (100 ml) and DMA (50 ml) were added MOMCl (7.88 ml, 104 mmol) and Et_3N (14.59 ml, 104.7 mmol) at 0 °C. The mixture was stirred overnight at room temperature. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/1) to give **23** (14.66 g, 69.42 mmol, 73%) as a pale green solid. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (3H, s), 5.30 (2H, s), 7.31 (1H, dd, J=3.0, 9.0 Hz), 7.49 (1H, d, J=3.0 Hz), 8.16 (1H, d, J=9.0 Hz), 10.47 (1H, s).

7-Acetylnaphthalene-2-carbonitrile (24) To a solution of 7-formylnaphthalene-2-carbonitrile **3** (3.00 g, 16.6 mmol) in THF (80 ml) was added CH_3MgBr (1.0 M in THF, 17.4 ml, 17.4 mmol) at −70 °C and the mixture was stirred at −70 °C for 2 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give 7-(1-hydroxyethyl)naphthalene-2-carbonitrile (1.64 g, 8.31 mmol, 50%) as a pale yellow oil. This oil (236 mg, 1.20 mmol) was dissolved in CH_2Cl_2 (10 ml) and treated with MnO_2 (1.04 g, 12.0 mmol). The mixture was stirred overnight at room temperature. The mixture was filtered, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=7/3) to give **24** (177 mg, 0.906 mmol, 76%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 2.76 (3H, s), 7.74 (1H, dd, J=1.5, 9.0 Hz), 7.96—8.00 (2H, m), 8.20 (1H, dd, J=1.5, 9.0 Hz), 8.37 (1H, br s), 8.51 (1H, br s).

7-{3-[5-(Methoxymethoxy)-2-nitrophenyl]acryloyl}naphthalene-2-carbonitrile (25) To a solution of 7-acetylnaphthalene-2-carbonitrile **24** (5.87 g, 30.1 mmol) in THF (250 ml) was added lithium diisopropylamide (LDA) (2.0 M in *n*-heptane/THF/ethylbenzene, 22.6 ml, 45.2 mmol) at −65 °C and the mixture was stirred at −65 °C for 15 min. 2-Formyl-4-(methoxymethoxy)-1-nitrobenzene **23** (9.52 g, 45.1 mmol) in THF (50 ml) was added and the mixture was stirred at −65 °C for 3 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2—1/1) to give 7-{3-hydroxy-3-[5-(methoxymethoxy)-2-nitrophenyl]propionyl}naphthalene-2-carbonitrile (7.26 g, 17.9 mmol, 59%) as a colorless solid. This solid (7.25 g, 17.8 mmol) was dissolved in $ClCH_2CH_2Cl$ (200 ml) and treated with *p*-toluenesulfonic acid (TsOH) monohydrate (0.68 g, 3.57 mmol) at 40 °C. The solution was refluxed for 2 h, then cooled to give colorless crystals. The crystals were filtered off and then dissolved in DMA (200 ml). The solution was treated with MOMCl (1.68 ml, 22.1 mmol) and Et_3N (3.10 ml, 22.4 mmol) at 0 °C, and stirred for 4 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=7/3) to give **25** (5.32 g, 13.7 mmol, 92%, 2 steps) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, s), 5.32 (2H, s), 7.20 (1H, dd, J=2.5, 9.0 Hz), 7.26—7.33 (2H, m), 7.76 (1H, dd, J=1.5, 8.5 Hz), 7.99—8.05 (2H, m), 8.18 (1H, d, J=9.0 Hz), 8.21—8.28 (2H, m), 8.41 (1H, br s), 8.61 (1H, br s).

7-{1-Hydroxy-3-[5-(methoxymethoxy)-2-nitrophenyl]-2-propene-1-yl}naphthalene-2-carbonitrile (26) To a solution of 7-{3-[5-(methoxymethoxy)-2-nitrophenyl]acryloyl}naphthalene-2-carbonitrile **25** (4.35 g, 11.2 mmol) in EtOH (65 ml) and CH_2Cl_2 (65 ml) was added $NaBH_4$ (0.42 g, 11.1 mmol) and the mixture was stirred at room temperature for 3 h. H_2O was added, and the mixture was concentrated. The resulting residue was extracted with EtOAc and the organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **26** (2.81 g, 7.20 mmol, 64%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.46 (3H, s), 5.22 (2H, s), 5.61—5.67 (1H, m), 6.31 (1H, dd, J=6.5, 15.5 Hz), 7.02 (1H, dd, J=2.5, 9.0 Hz), 7.12 (1H, d, J=2.5 Hz), 7.35 (1H, d, J=15.5 Hz), 7.61 (1H, dd, J=1.5, 8.5 Hz), 7.74 (1H, dd, J=1.5, 8.5 Hz), 7.92 (2H, d, J=8.5 Hz), 7.99 (1H, br s), 8.04 (1H, d, J=9.0 Hz), 8.24 (1H, br s).

7-{3-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxypropyl}naphthalene-2-carbonitrile (27) A solution of 7-{1-hydroxy-3-[5-(methoxymethoxy)-2-nitrophenyl]-2-propene-1-yl}naphthalene-2-carbonitrile **26** (3.68 g, 9.43 mmol) in THF (30 ml) and EtOH (30 ml) was hydrogenated over 10% Pd–C (0.74 g) at room temperature for 5 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/4) to give **27** (2.87 g, 7.92 mmol, 84%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 2.02—2.16 (2H, m), 2.61—2.81 (2H, m), 3.48 (3H, s), 4.79 (1H, dd, J=4.0, 9.0 Hz), 5.09 (2H, s), 6.67 (1H, d, J=8.5 Hz), 6.75—6.85 (2H, m), 7.58 (1H, dd, J=1.5, 8.5 Hz), 7.62 (1H, dd, J=2.0, 8.5 Hz), 7.81—7.92 (3H, m), 8.18 (1H, br s).

7-{3-[2-(Ethanesulfonyl)amino-5-(methoxymethoxy)phenyl]-1-hydroxypropyl}naphthalene-2-carbonitrile (28) To a solution of 7-{3-[2-amino-5-(methoxymethoxy)phenyl]-1-hydroxypropyl}naphthalene-2-carbonitrile **27** (2.09 g, 5.77 mmol) in CH_2Cl_2 (60 ml) were added $EtSO_2Cl$ (0.71 ml, 7.49 mmol) and pyridine (0.61 ml, 7.54 mmol), and the mixture was stirred at room temperature for 8 h. H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=2/3) to give **28** (2.41 g, 5.30 mmol, 92%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, t, J=7.5 Hz), 2.01—2.18 (2H, m), 2.78—2.90 (1H, m), 2.94—3.06 (1H, m), 3.12 (2H, q, J=7.5 Hz), 3.48 (3H, s), 4.74—4.81 (1H, m), 5.15 (2H, s), 6.87—6.96 (2H, m), 7.35—7.43 (1H, m), 7.54—7.63 (2H, m), 7.81 (1H, br s), 7.85 (1H, d, J=8.5 Hz), 7.88 (1H, d, J=8.5 Hz), 8.15 (1H, br s).

2-(7-Cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydroquinoline (29) To a solution of 7-{3-[2-(ethanesulfonyl)amino-5-(methoxymethoxy)phenyl]-1-hydroxypropyl}naphthalene-2-carbonitrile **28** (2.38 g, 5.24 mmol) in THF (50 ml) were added *n*-Bu_3P (1.87 ml, 7.51 mmol) and ADDP (1.72 g, 6.82 mmol) in THF (20 ml) at 0 °C, and the mixture was stirred at room temperature for 7 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2—1/1) to give **29** (2.15 g, 4.93 mmol, 94%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$)

δ: 1.33 (3H, t, J=7.5 Hz), 2.05—2.18 (1H, m), 2.52—2.80 (3H, m), 2.95—3.19 (2H, m), 3.48 (3H, s), 5.15 (2H, s), 5.63 (1H, t, J=7.0 Hz), 6.81 (1H, d, J=3.0 Hz), 6.96 (1H, dd, J=3.0, 9.0 Hz), 7.53—7.59 (2H, m), 7.75 (1H, d, J=9.0 Hz), 7.78 (1H, br s), 7.83 (1H, d, J=8.5 Hz), 7.86 (1H, d, J=8.5 Hz), 8.16 (1H, br s).

6-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)-1,2,3,4-tetrahydroquinoline Dihydrochloride (30) 2-(7-Cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydroquinoline **29** was converted to **30** by the same procedure as that for **18a**. Compound **30** was obtained (44%, 5 steps) as an amorphous solid.

5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline (31) A solution of benzyl 5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline-1-carboxylate **16b** (6.00 g, 9.94 mmol) in THF (30 ml) and EtOH (30 ml) was hydrogenated over 10% Pd–C (1.20 g) at room temperature for 4 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=20/1—0/1) to give **31** (4.16 g, 8.86 mmol, 89%) as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.63—1.99 (4H, m), 3.01 (1H, dd, J=10.0, 15.0 Hz), 3.21—3.34 (2H, m), 3.50 (1H, dd, J=9.0, 15.0 Hz), 3.65—3.80 (2H, m), 4.22—4.33 (1H, m), 5.15 (1H, dd, J=9.0, 10.0 Hz), 6.61—6.78 (3H, m), 7.60 (1H, dd, J=2.0, 8.5 Hz), 7.74 (1H, dd, J=2.0, 8.5 Hz), 7.86—7.94 (3H, m), 8.20 (1H, br s).

5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indoline Dihydrochloride (32) and 5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indole Trihydrochloride (33) 5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline **31** was converted to **32** and **33** by the same procedure as that for **18a**. Compound **32** was obtained (30%, 3 steps) as a yellow amorphous solid and compound **33** was obtained (0.7%, 3 steps) as a yellow amorphous solid.

5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indole (34) To a solution of 5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline **31** (500 mg, 1.06 mmol) in CH_2Cl_2 (10 ml) was added MnO_2 (926 mg, 10.7 mmol) and the mixture was refluxed for 9 h. Then the mixture was stirred overnight at room temperature, and the mixture was filtered. The filtrate was concentrated to give 5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indole (438 mg, 0.936 mmol, 88%) as a yellow solid. This solid (338 mg) was dissolved in DMF (6 ml) and treated with NaH (58 mg, 1.33 mmol, as a 55% w/w dispersion in mineral oil) under cooling conditions. The mixture was stirred at room temperature for 0.5 h. $EtSO_2Cl$ (0.140 ml, 1.48 mmol) and 4-dimethylaminopyridine (4.4 mg, 0.036 mmol) were added and the whole was stirred overnight at room temperature. H_2O was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1—1/4) to give **34** (326 mg, 0.583 mmol, 81%) as a brown amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.0 Hz), 1.48 (9H, s), 1.74—1.87 (2H, m), 1.91—2.03 (2H, m), 2.97 (2H, q, J=7.0 Hz), 3.27—3.43 (2H, m), 3.67—3.82 (2H, m), 4.47—4.57 (1H, m), 6.73 (1H, s), 6.87—7.14 (3H, m), 7.66 (1H, d, J=8.5 Hz), 7.85—8.09 (4H, m), 8.28 (1H, s).

2-(7-Amidinonaphthalen-2-yl)-1-(ethanesulfonyl)-5-(piperidin-4-yloxy)indole Dihydrochloride (35) 5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indole **34** was converted to **35** by the same procedure as that for **18a**. Compound **35** was obtained (32%, 3 steps) as a pale purple amorphous solid.

(*R*)-7-{2-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile ((*R*)-5) and (*S*)-7-{2-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile ((*S*)-5) 7-{2-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile **5** (2.20 g, 6.31 mmol) was separated into less polar (*R*)-**5** and more polar (*S*)-**5** by preparative HPLC (CHIRALCEL OD, Daicel Chemical Industries, Ltd., hexane/*i*-PrOH=2/3). (*R*)-**5** was obtained (1.16 g, quant., 99%ee) as a solid and (*S*)-**5** was obtained (1.14 g, quant., 99%ee) as a solid.

Optically active bisamidine derivatives ((*R*)-**18a** and (*S*)-**18a**) were similarly prepared as racemates from (*S*)-**5** and (*R*)-**5**, respectively.

(*R*)-**18a**: 33%, $[\alpha]_D$ −44° (c=0.53, MeOH), 99%ee.

(*S*)-**18a**: 50%, $[\alpha]_D$ +44° (c=0.60, MeOH), 99%ee.

X-Ray Crystallographic Analysis of (*R*)-33 The reflection data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromated Cu$K\alpha$ radiation (λ=1.5418 Å). The structure was solved by a direct method using the SIR92 program.[19] The structure was then refined by the full-matrix least-squares procedure with anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms. Crystal data: $C_{31}H_{35}N_3O_5S$; M=561.69; monoclinic, space group $P2_1$, a=5.778(4) Å, b=8.012(4) Å, c=31.454(4) Å, β=91.43(4)°; V=1455.8(10) Å^3, Z=2, D_C=1.281 g/cm^3, R=0.056, R_W=0.091 for 2862 reflections with $I>3\sigma$.

X-Ray Crystallographic Analysis of FXa Complexed with (*R*)-18a Human FXa was purchased from Enzyme Research Laboratories, Inc., IN, U.S.A. and purified as described.[20] Briefly, FXa was treated with α-chymotrypsin to remove the first 44 amino acids of the light chain (Gla domain), resulting in des-Gla-FXa. Then des-Gla-FXa was purified on an anion-exchange column and concentrated to 15 mg/ml. Crystals were obtained at 295 K using the hanging-drop vapour-diffusion technique, equilibrated against a reservoir solution of 20% PEG3350, 0.5 M sodium acetate, 8 mM calcium chloride and 0.1 M imidazole-malic acid (pH 5.5) by the microseeding technique. X-ray diffraction data were collected in a glass capillary with the wavelength set to 1.0 Å at the BL-6B station (Photon Factory, Tsukuba, Japan). The crystal belongs to the $P2_12_12_1$ space group, with a=57.0 Å, b=73.1 Å and c=79.8 Å. The diffraction data were integrated and scaled with the programs Denzo and Scalepack (HKL Research, Inc.),[21] with an $R_{sym}(I)$ of 4.8% and a completeness of 96.3% to the highest resolution of 2.3 Å. The FXa structure from the complex structure of FXa and DX-9065a (PDB code: 1FAX)[14] was used as a starting model for refinement. The electron density of (*R*)-**18a** was clearly defined in the initial electron density map. The model of FXa with (*R*)-**18a** was rebuilt with the program O[22] and refined with X-PLOR and CNX[23]. Residues 45—87 of the light chain were not built due to weak electron densities. The final structure gave R_{cryst}=22.3% and R_{free}=26.2% at 2.3 Å resolution with good stereochemistry, root mean square (RMS) deviation from ideal bond length of 0.004 Å and RMS deviation from ideal bond angles of 1.1°. The geometry of the model was checked with the program PROCHECK[24]; there were no residues in the disallowed regions of the Ramachandran plot. The figures were produced with InsightII (Molecular Simulations Inc.).

Biology. Anti-FXa Assay The hydrolysis of the chromogenic substrates was assayed by continuously measuring absorbance at 405 nm at 37 °C with a microplate reader (SPECTRA max PLUS 384, Molecular Devices, CA, U.S.A.). Reaction mixtures (90 μl) were prepared in 96-well plates containing human FXa (0.5 IU, Enzyme Research Laboratories, Inc., IN, U.S.A.) and compounds in reaction buffer (50 mM Tris–HCl–150 mM NaCl, pH 8.4). Reactions were initiated by the addition of 10 μl of S-2222 (4 mM, Daiichi Pure Chemical, Japan) and monitored for 5 min. The concentration required to inhibit enzyme activity by 50% (IC_{50}) was estimated from dose-response curves.

Coagulation Assay Citrated blood samples were collected from healthy male volunteers and male hamsters (Japan SLC). Platelet-poor plasma was prepared by centrifugation at 2000×***g*** for 10 min and stored at −20 °C until use. Plasma clotting times were determined using a COAGMASTER II (Sankyo, Japan). Prothrombin time (PT) was measured using SIMPLASTIN EXCEL (Organon Teknika, NC, U.S.A.). Coagulation times for each compound were compared with coagulation times measured using distilled water as a control. Each measurement was performed three times. The concentration required to double the clotting time (CT_2) was estimated by linear regression analysis using two data points, the two mean values of the concentrations closest to the predicted 2-fold PT on either side.

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