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

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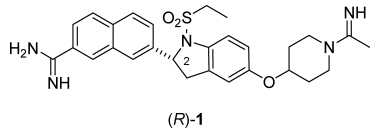
Factor Xa (FXa) is well known to play a pivotal role in blood coagulation, so FXa inhibitor is a promising drug candidate for prophylaxis and treatment of thromboembolic diseases. In the course of our research, we have found that (*R*)-5-[1-(acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline ((*R*)-1) showed potent FXa inhibitory activity *in vitro*. However, single oral administation (*RS*)-1 showed high toxicity in mice. Among newly synthesized compounds, ({(*RS*)-5-[1-(acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetic acid ((*RS*)-11d) showed more potent FXa inhibitory activity and higher safety than (*RS*)-1. The *R*-isoform of compound 11d ((*R*)-11d) exhibited potent *in vitro* anticoagulant activity in human and hamster plasma. Orally administered (*R*)-11d also showed dose-dependent potent anticoagulant activity in hamsters, marmosets and cynomolgus monkeys. Compound (*R*)-11d with potent anticoagulant activity and high safety is therefore favorable as a novel oral FXa inhibitor.

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

Intravascular clot formation is a serious event which leads to a number of ischemic diseases, such as myocardial infarction, stroke and venous thromboembolism. At present, warfarin is the sole oral anticoagulant that is being widely used for prophylaxis and treatment of thrombosis. However, many reports have mentioned the limitations of warfarin.[2—4)] Indeed, warfarin requires frequent international normalized ratio (INR) monitoring because of its narrow therapeutic window and the large inter- and intraindividual variability in its effect. In addition, its onset of anticoagulant action is considerably slow and it interacts with many foods and conventional agents. Accordingly, novel oral anticoagulants with high efficacy and without INR monitoring are desired.

Factor Xa (FXa) has been thought of as a particularly promising target for effective anticoagulation because it acts at the convergence point of the intrinsic and extrinsic coagulation pathways. Moreover, one molecule of FXa generates more than 100 thrombin molecules.[5)] It is thought that inhibition of FXa effectively blocks thrombin formation, thereby diminishing thrombin-mediated fibrin clot formation. Recent research has focused on the identification of orally available small-molecule FXa inhibitors that do not require routine coagulation monitoring.[6,7)]

In a previous paper, we reported that compound (*R*)-**1** (Fig. 1), which has the (*R*)-configuration at the 2-position of the indoline ring, showed potent inhibitory activity against FXa *in vitro*.[8)] However, orally administered (*RS*)-**1** had high toxicity in mice. We intended to explore new indoline compounds with potent FXa inhibitory activity and diminished toxicity by further structural optimization of (*RS*)-**1**. In this study, we examined substituents on the indoline ring in order to identify more desirable compounds. Herein, we describe the synthesis and structure-activity relationships (SARs) of these compounds.



(*R*)-**1**

Fig. 1. Structure of the Indoline Derivative (*R*)-**1**

Chemistry

Key intermediates **8a**—**g** and **i** were synthesized as shown in Chart 1. After reduction of the nitro group of alcohol **2** by catalytic hydrogenation,[8)] aniline **3** was reacted with acyl reagents or sulfonyl reagents to give anilides **4a**—**g**. An intramolecular Mitsunobu reaction[9)] of **4a**—**g** with *n*-Bu_3P and 1,1′-(azodicarbonyl)dipiperidine (ADDP) afforded corresponding indolines **5a**—**g**. After removing the methoxymethyl (MOM) group of **5a**—**g** by treatment with HCl, phenols **6a**—**g** was converted to intermediates **8a**—**g** by means of a Mitsunobu reaction[10)] with alcohol **7**. Furthermore, after removing the benzyloxycarbonyl (Z) group of compound **8h**[8)] by catalytic hydrogenation, the resulting indoline derivative was acylated with ethyl malonyl chloride to give ethyl malonate intermediate **8i**.

The syntheses of the amidine derivatives from intermediates **8a**—**g**, **i** are outlined in Chart 2. Compounds **8a**—**g**, **i** were converted to the corresponding amidines **9a**—**g**, **i** by bubbling HCl gas into a mixture of ethanol and dichloromethane, followed by amination of the resulting imidates (Method A), or by treatment with hydroxylamine, followed by acylation and hydrogenation of the resulting amidoximes (Method B).[11)] The treatment of **9a**—**g**, **i** having amine moieties with ethyl acetimidate and triethylamine afforded corresponding bisamidines **10a**—**g**, **i**. The ester moieties of **10d**—**f**, **i** were hydrolyzed under acidic conditions to give corresponding carboxylic acids **11d**—**f**, **i**.

4 or 6-Substituted indoline derivatives (**21**, **22**) were synthesized as shown in Chart 3. 3-Nitrophenol (**12**) was converted to intermediate **13** according to a method similar to

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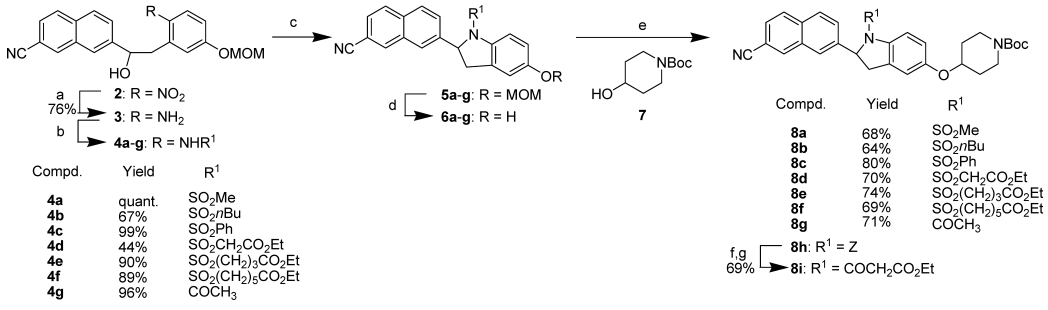
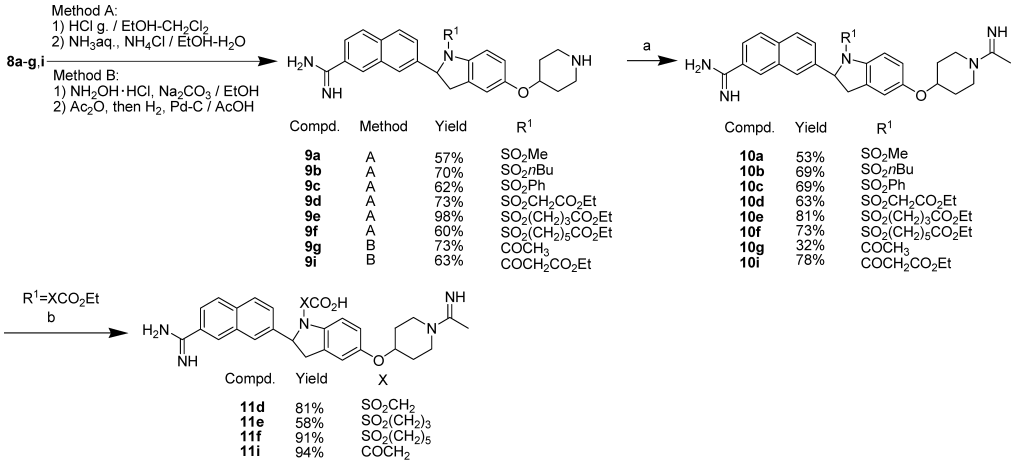


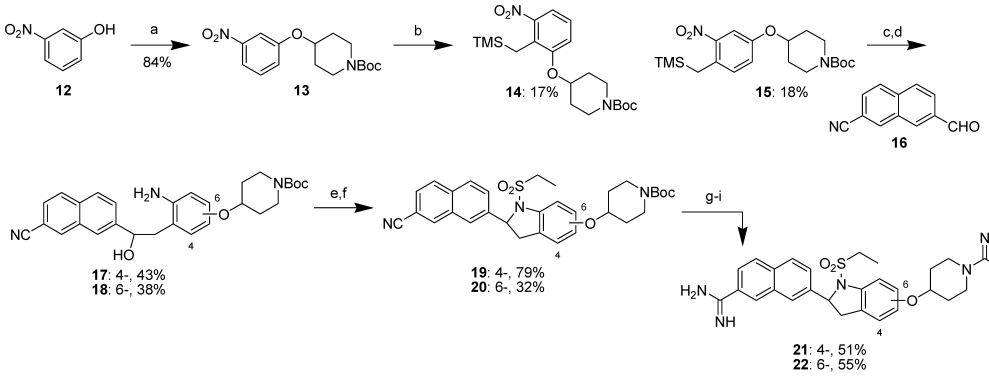
Reagents: a) H_2, Pd-C / EtOH-THF; b) R^1Cl or $R^1{}_2O$, Pyr. or Et_3N / CH_2Cl_2; c) nBu$_3$P, ADDP / THF; d) HCl / AcOEt; e) PPh_3, DEAD / THF; f) H_2, Pd-C / EtOH-THF; g) $ClCOCH_2CO_2Et$, Pyr. / CH_2Cl_2.

Chart 1



Reagents: a) Et_3N, ethyl acetimidate·HCl / EtOH-H_2O; b) 1N HCl / H_2O.

Chart 2

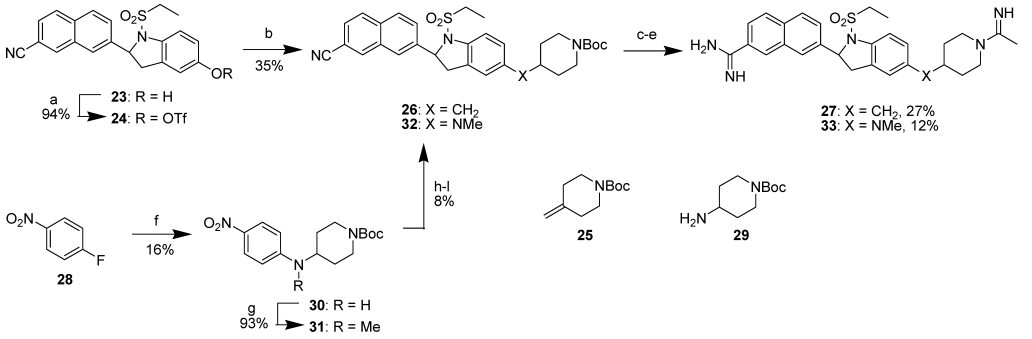


Reagents: a) **7**, PPh_3, DIAD / THF; b) $TMSCH_2MgCl$, then DDQ / THF; c) **16**, TBAF / THF; d) Sn / AcOH; e) $EtSO_2Cl$, Pyr. / CH_2Cl_2; f) nBu$_3$P, ADDP / THF; g) HCl g. / EtOH-CH_2Cl_2; h) NH_3aq., NH_4Cl / EtOH-H_2O; i) Et_3N, ethyl acetimidate·HCl / EtOH.

Chart 3

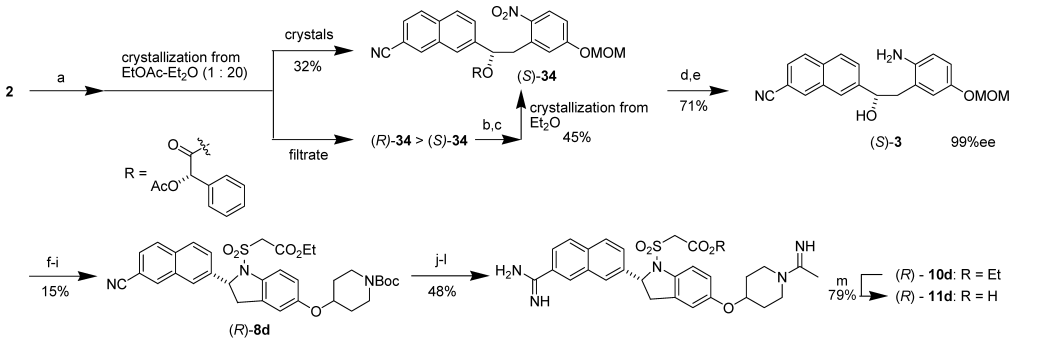
that for **8a**—**g**. Then, intermediate **13** was introduced to a trimethylsilylmethyl group to give two regioisomers (**14**, **15**)[12] which were separable from each other by using silica gel column chromatography.[13] These two compounds (**14**, **15**) were coupled with 2-cyano-7-naphthylaldehyde (**16**)[14] by tetrabutylammonium fluoride (TBAF), followed by reduction of the nitro group by catalytic hydrogenation to give anilines **17** and **18**, respectively. By the same method as described in Charts 1 and 2, anilines **17** and **18** were converted to corresponding compounds **21** and **22**, which have 4 and 6-substituted indoline structures, respectively.

5-Alkyl or 5-(methyl)aminoindoline derivatives (**27**, **33**) were synthesized as shown in Chart 4. 5-Hydroxyindoline compound (**23**)[8] was converted to its trifluoromethanesulfonate **24**.[15] This compound was subjected to a Suzuki–Miyaura cross coupling reaction[16,17] with *N*-Boc-4-methyl-



Reagents: a) Tf_2O / Pyr.; b) **25**, 9-BBN, then K_2CO_3, $PdCl_2(dppf)\cdot CH_2Cl_2$ / DMF-H_2O; c) HCl g. / EtOH-CH_2Cl_2; d) NH_3aq., NH_4Cl / EtOH-H_2O; e) Et_3N, ethyl acetimidate·HCl / EtOH: f) **29**, NaH / DMF; g) MeI, NaH / DMF; h) $TMSCH_2MgCl$, then DDQ / THF; i) **16**, TBAF / THF; j) Sn / AcOH; k) $EtSO_2Cl$, Pyr. / CH_2Cl_2; l) $n$$Bu_3P$, ADDP / THF.

Chart 4



Reagents: a) RCl, Pyr. / CH_2Cl_2; b) K_2CO_3 / MeOH; c) PPh_3, DEAD, R-OH / CH_2Cl_2; d) K_2CO_3 / MeOH; e) H_2, Pd-C / EtOH-THF; f) $EtO_2CCH_2SO_2Cl$, Pyr. / CH_2Cl_2; g) $n$$Bu_3P$, ADDP / THF; h) HCl / AcOEt; i) 7, PPh_3, DEAD / THF; j) KOt-Bu, NH_2OH / EtOH; k) Ac_2O then H_2, Pd-C / AcOH; l) Et_3N, ethyl acetimidate HCl / EtOH; m) 4NHCl / H_2O.

Chart 5

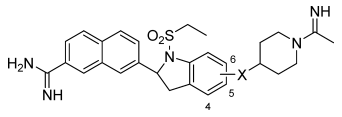
enepiperidine (**25**)[18] to give compound **26**, which has a methylene chain between the indoline ring and piperidine ring. By the same method as described in Chart 2, compound **26** was converted to corresponding 5-alkylindoline derivative **27**. Regarding the 5-(methyl)aminoindoline derivative,[19] 4-fluoro-1-nitrobenzene (**28**) was reacted with *N*-Boc-4-aminopiperidine (**29**) under basic conditions, followed by the introduction of a methyl group on the nitrogen atom to give intermediate **31**. Compound **31** was converted to the corresponding 5-(methyl)aminoindoline derivative **33** by the same procedures as described in Charts 1 and 2.

The effective and practical synthesis of enantiomerically pure intermediate (*S*)-**3** without using chiral column chromatography is outlined in Chart 5. Racemate **2** was reacted with (*S*)-*O*-acetylmandel chloride[20] to give mandelate **34** as a diastereomixture. The diastereomixture was subjected to crystallization (solvent: EtOAc/Et_2O=1/20) to give optically pure mandelate (*S*)-**34** having an *S*-configuration. Furthermore, to provide more (*S*)-**34** we attempted to perform a stereochemical inversion of the diastereomixture containing mainly (*R*)-**34**, rather than (*S*)-**34** in the filtrate. The diastereomixture given from the filtrate was subjected to alcohol hydrolysis under basic conditions and a subsequent Mitsunobu reaction with (*S*)-*O*-acetylmandelic acid afforded the diastereomixture containing (*S*)-**34**. The diastereomixture was subjected to crystallization (solvent: Et_2O) to achieve an additional synthesis of mandelate (*S*)-**34**. After alcohol hydrolysis of mandelate (*S*)-**34**, the nitro group was reduced to give enantiomerically pure (>99% ee) alcohol (*S*)-**3**. At this point, we had succeeded in a multi-gram (*ca.* 10 g) synthesis of (*S*)-**3**. Therefore, we considered that this synthetic route was applicable to the scale-up synthesis of (*S*)-**3**. The stereochemistry of (*S*)-**3** was confirmed by a comparison with the same compound reported in the previous paper.[21] After the reaction of (*S*)-**3** with ethyl chlorosulfonylacetate,[22] stereochemically inversed intermediate (*R*)-**8d** was obtained according to the same procedure as that for **8d**. Optically active bisamidine (*R*)-**10d** was synthesized from (*R*)-**8d** by the same method as described in Chart 2. Moreover, carboxylic acid (*R*)-**11d** was synthesized by the acidic hydrolysis of (*R*)-**10d**.

Results and Discussion

The *in vitro* FXa inhibitory activities of all the compounds synthesized were evaluated and expressed as IC_{50} values. Based on the results of our previous report, we attempted further optimization for each moiety of our indoline derivative. At first, we compared the effects of the position and the linker atom of the piperidine ring to racemate (*RS*)-**1** (Table 1). Regarding for the substitution pattern of the central indoline ring, 5-substituted indoline compound (*RS*)-**1** showed higher FXa inhibitory activity than 4-substituted one **21** and 6-substituted one **22**. In these three regioisomers, it seemed that 5-substituted compound is more favorable than the other two compounds. Regarding the linker structure of 5-substituted indoline compounds, we synthesized compounds having a methylene group (**27**) or methylamino group (**33**) instead of an oxygen atom. Although both compounds showed good FXa inhibitory activities, the potencies were a little

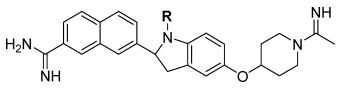
Table 1. FXa Inhibitory Activity of Compounds (*RS*)-**1**, **21**, **22**, **27** and **33**



Compd.[a]	Position	X	IC_{50} (nM)
(*RS*)-**1**	5-	O	11
21	4-	O	27
22	6-	O	140
27	5-	CH_2	22
33	5-	NMe	17

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

Table 2. FXa Inhibitory Activity of Compounds (*RS*)-**1**, **10a**—**d**, **10g**, **11d**—**f** and **11i**



Compd.[a]	R	IC_{50} (nM)
(*RS*)-**1**	SO_2Et	11
10a	SO_2Me	23
10b	SO_2nBu	20
10c	SO_2Ph	19
10d	$SO_2CH_2CO_2Et$	18
11d	$SO_2CH_2CO_2H$	8.2
11e	$SO_2(CH_2)_3CO_2H$	20
11f	$SO_2(CH_2)_5CO_2H$	21
10g	$COCH_3$	16
11i	$COCH_2CO_2H$	39

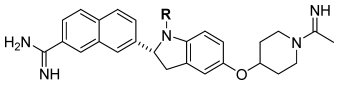
a) All compounds were synthesized and evaluated as their hydrochlorides.

lower than that of (*RS*)-**1**. From these results, it seems that 5-*O*-substitution is suitable for the linker structure between the indoline ring and the piperidine ring.

Next, we focused on the substituent attached to the nitrogen atom on the indoline ring and introduced various substituents other than the ethanesulfonyl group and examined their FXa inhibitory activities (Table 2). Regarding the sulfonyl derivatives, both alkylsulfonyl compounds (**10a**, **10b**) showed potent FXa inhibitory activities. Compound **10c** with an aromatic ring also showed similar inhibitory activity to compounds **10a** and **10b**, though the activity was a slightly lower than (*RS*)-**1**. Then compounds with a polar functional group introduced into the terminal carbon chain moieties (**10d**, **11d**) were synthesized. Both compounds showed potent FXa inhibitory activities superior to non-polar alkyl- or arylsulfonyl compounds. Furthermore, we studied the influence of the length of the alkylene between the sulfonamide group and the carboxyl group in **11d**. Compounds **11e** and **11f** with longer carbon chains than that of **11d** exhibited lower inhibitory activity than **11d**. In these three compounds (**11d**—**f**), monomethylene compound **11d** exhibited a favorable result. The introduction of an acyl group instead of a sulfonyl group exhibited similar or lower FXa inhibitory activities (**10g** *vs.* **10a** and **11i** *vs.* **11d**). These results suggest that ethanesulfoyl ((*RS*)-**1**) and carboxymethysulfonyl (and its ester form) side chains are appropriate as substituents on the nitrogen atom.

Among the newly synthesized compounds, **11d** showed more potent FXa inhibitory activity than (*RS*)-**1**. We attempted an acute toxicity test against these two compounds and **10d** (an ester form of **11d**) in mice. All the mice died immediately after administration of the compound (*RS*)-**1** at 600 mg/kg (*p.o.*). This result suggests that the ethanesulfonyl compound (*RS*)-**1** has a serious adverse reaction. On the other hand, all the mice survived with no lethal adverse reactions after administration of **10d** or **11d** (600 mg/kg, *p.o.*, respectively).[23] This result indicates that the substituent on the nitrogen atom of the indoline ring is highly important not only for efficacy but also for safety. Among the above compounds, **10d** and **11d** with polar functional groups on the nitrogen atom showed favorable results in efficacy and safety.

Table 3. FXa Inhibitory Activity of Compounds (*R*)-**1**, (*R*)-**10d** and (*R*)-**11d**



Compd.[a]	R	IC_{50} (nM)
(*R*)-**1**	SO_2Et	7.6
(*R*)-**10d**	$SO_2CH_2CO_2Et$	8.8
(*R*)-**11d**	$SO_2CH_2CO_2H$	3.9

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

Table 4. Anticoagulant Activity of Compounds (*R*)-**1** and (*R*)-**11d**

Compd.	CT_2 (μM)[a]	
	Hamster	Human
(*R*)-**1**	1.1	0.52
(*R*)-**11d**	0.80	0.48

a) The concentration required to double clotting time.

We have reported that chiral compound (*R*)-**1** showed more potent FXa inhibitory activity than the stereoisomer (*S*)-**1**. Based on this result, we synthesized the (*R*)-forms of **10d** and **11d** ((*R*)-**10d** and (*R*)-**11d**), to examine their inhibitory activities (Table 3). Both the two (*R*)-forms of **10d** and **11d** showed more potent inhibitory activities than their racemates. This result also suggests that the (*R*)-form is the active form. Moreover, the activity of carboxylic acid (*R*)-**11d** was superior to that of (*R*)-**1**. Therefore, (*R*)-**11d** is the best candidate of all the compounds described above.

We examined the effect of the *in vitro* anticoagulant activity of prothrombin time (PT) in hamster and human plasma. Table 4 shows the CT_2 values, the concentrations required to achieve 200% relative clotting time, of (*R*)-**11d** and (*R*)-**1** in hamster and human plasma (*in vitro*). Between these two compounds, (*R*)-**11d** exhibited nearly equal or slightly more potent activity in both hamster and human plasma than that of (*R*)-**1**. In these *in vitro* tests, (*R*)-**11d** showed comparable activity to (*R*)-**1** in FXa inhibition and anticoagulation.

We further evaluated the oral anticoagulant activity of (*R*)-**11d**. Table 5 shows the anticoagulant effect of (*R*)-**11d** in hamsters, marmosets and cynomolgus monkeys (*ex vivo*, *p.o.*). In each case, oral administration of (*R*)-**11d** prolonged the prothrombin time in a dose-dependent manner. In particular, administration to marmosets showed a highly potent

anticoagulant effect. The CT_2 values, the dose required to achieve 200% relative clotting time, of (*R*)-**11d** against hamsters, marmosets and cynomolgus monkeys were 38, 6.9 and 18 mg/kg, respectively (*ex vivo*, 1 h). These results suggest that (*R*)-**11d** exhibited potent anticoagulant activity both *in vitro* and *ex vivo*.

In conclusion, we synthesized many indoline compounds and evaluated their FXa inhibitory activities. As a result, we found some novel *N*-sulfonylindoline derivatives with high FXa inhibitory activities. Among them, enantiomerically pure (*R*)-**11d** with carboxymethylsulfonyl group on the nitrogen atom exhibited potent anticoagulant activities both *in vitro* and *ex vivo*. Moreover, (*R*)-**11d** exhibited no lethal adverse reaction after oral administration in mice (600 mg/kg, *p.o.*). The substituent on the nitrogen atom of the indoline ring is important for efficacy and safety. Compound (*R*)-**11d** and some indoline derivatives are currently undergoing further evaluation and synthetic efforts to explore novel compounds having more potent FXa inhibitory activities and greater safety is underway.

Table 5. Anticoagulant Activity of Compound (*R*)-**11d** (*ex vivo*, *p.o.*)

Dose (mg/kg)	PT (fold)		
	1 h	3 h	6 h
Hamster[a]			
30	1.5	1.2	1.0
100	3.7	2.1	1.2
Marmoset[a]			
10	2.3	1.8	1.5
30	8.7	6.9	4.1
Cynomolgus monkey[b]			
10	1.6	1.7	1.3
30	2.6	3.0	2.3

a) $n=4$. *b*) $n=3$.

Experimental

^{1}H-NMR spectra were obtained on a JEOL EX 270 or 400 MHz spectrometer and are 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, 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.

Ethyl ({[2-[2-(7-Cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-(methoxymethoxy)phenyl]amino}sulfonyl)acetate (4d: $R^1=SO_2CH_2CO_2Et$) To a solution of 7-{2-[2-amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile **3** (8.48 g, 24.4 mmol) in CH_2Cl_2 (180 ml) was added $EtO_2CCH_2SO_2Cl$ (5.00 g, 26.8 mmol) in CH_2Cl_2 (20 ml) and pyridine (2.17 ml, 26.8 mmol) and the mixture was stirred at room temperature for 1 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=1/1) to give **4d** (5.40 g, 10.8 mmol, 44%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz), 3.12—3.21 (1H, m), 3.29—3.38 (1H, m), 3.35 (3H, s), 4.02 (1H, d, J=15.0 Hz), 4.07 (1H, d, J=15.0 Hz), 4.27 (2H, q, J=7.0 Hz), 5.03 (1H, d, J=7.0 Hz), 5.07 (1H, d, J=7.0 Hz), 5.17—5.24 (1H, m), 6.75 (1H, d, J=3.0 Hz), 6.93 (1H, dd, J=3.0, 9.0 Hz), 7.49 (1H, d, J=9.0 Hz), 7.60 (1H, dd, J=1.5, 8.5 Hz), 7.70 (1H, dd, J=1.5, 8.5 Hz), 7.81—7.92 (3H, m), 8.19 (1H, br s).

Ethyl {[2-(7-Cyanonaphthalen-2-yl)-5-(methoxymethoxy)indolin-1-yl]-sulfonyl}acetate (5d: $R^1=SO_2CH_2CO_2Et$) To a solution of ethyl ({[2-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-4-(methoxymethoxy)phenyl]amino}-sulfonyl)acetate **4d** (5.39 g, 10.8 mmol) in THF (110 ml) was added n-Bu_3P (4.45 ml, 17.9 mmol) and ADDP (4.09 g, 16.2 mmol) in THF (40 ml) at 0 °C and the mixture was stirred at room temperature for 1.5 h. The mixture was allowed to stand overnight, and the precipitate was filtered away. NH_4Cl (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 chromatographed on a silica gel column (hexane/EtOAc=11/9) to give **5d** (4.85 g, 10.1 mmol, 93%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ 1.28 (3H, t, J=7.0 Hz), 3.05 (1H, dd, J=2.5, 16.0 Hz), 3.49 (3H, s), 3.92—

Table 6. Physical Data for Indoline Derivatives

Compd.	Formula	Analysis (%) Calcd (Found)				
		C	H	N	Cl	S
10a	$C_{27}H_{31}N_5O_3S\cdot 2.0HCl\cdot 2.0H_2O$	52.77 (53.08)	6.07 (6.28)	11.40 (11.10)	11.54 (11.25)	5.22 (5.08)
10b	$C_{30}H_{37}N_5O_3S\cdot 2.0HCl\cdot 2.5H_2O$	54.13 (54.32)	6.66 (6.70)	10.52 (10.25)	10.65 (10.68)	4.82 (4.66)
10c	$C_{32}H_{33}N_5O_3S\cdot 1.9HCl\cdot 1.9H_2O$	57.26 (57.45)	5.81 (6.07)	10.45 (10.13)	10.04 (9.87)	4.78 (4.72)
10d	$C_{30}H_{35}N_5O_5S\cdot 2.0HCl\cdot 3.0H_2O$	51.13 (51.00)	6.15 (5.76)	9.94 (9.99)	10.06 (10.18)	4.55 (4.90)
10g	$C_{28}H_{31}N_5O_2\cdot 2.0HCl\cdot 1.7H_2O$	58.68 (58.32)	6.40 (6.77)	12.22 (12.31)	12.37 (12.70)	—
11d	$C_{28}H_{31}N_5O_5S\cdot 2.0HCl\cdot 0.8H_2O$	52.80 (53.08)	5.48 (5.81)	10.99 (11.02)	11.13 (11.12)	5.03 (5.05)
11e	$C_{30}H_{35}N_5O_5S\cdot 1.7HCl\cdot 3.5H_2O$	51.28 (51.04)	6.27 (6.01)	9.97 (10.06)	8.58 (8.39)	4.56 (4.94)
11f	$C_{32}H_{39}N_5O_5S\cdot 2.1HCl\cdot 1.1H_2O$	54.60 (54.28)	6.23 (6.01)	9.95 (10.15)	10.58 (10.60)	4.55 (4.38)
11i	$C_{29}H_{31}N_5O_4\cdot 2.8HCl\cdot 1.8H_2O$	53.74 (53.43)	5.82 (6.00)	10.81 (11.16)	15.32 (15.50)	—
21	$C_{28}H_{33}N_5O_3S\cdot 2.5HCl\cdot 2.3H_2O$	51.56 (51.53)	6.20 (6.17)	10.74 (10.67)	13.59 (13.58)	4.92 (4.95)
22	$C_{28}H_{33}N_5O_3S\cdot 2.5HCl\cdot 2.5H_2O$	51.28 (51.38)	6.22 (6.28)	10.68 (10.69)	13.51 (13.22)	4.89 (5.15)
27	$C_{29}H_{35}N_5O_2S\cdot 2.3HCl\cdot 3.0H_2O$	53.13 (53.22)	6.66 (6.56)	10.68 (10.62)	12.44 (12.48)	4.89 (4.88)
33	$C_{29}H_{36}N_6O_2S\cdot 3.7HCl\cdot 2.9H_2O$	48.39 (48.37)	6.37 (6.05)	11.67 (11.68)	18.22 (18.29)	4.45 (4.61)

Table 7. Physical Data for Indoline Derivatives

Compd.	^{1}H-NMR δ (DMSO-d_6)
10a	1.63—1.83 (2H, m), 1.93—2.11 (2H, m), 2.30 (3H, s), 2.95—3.08 (1H, m), 3.02 (3H, s), 3.44—3.64 (2H, m), 3.66—3.87 (2H, m), 3.96 (1H, dd, *J*=10.0, 17.0 Hz), 4.59—4.69 (1H, m), 5.77 (1H, dd, *J*=2.5, 10.0 Hz), 6.94 (1H, dd, *J*=2.0, 9.0 Hz), 7.01 (1H, d, *J*=2.0 Hz), 7.36 (1H, d, *J*=9.0 Hz), 7.65 (1H, dd, *J*=1.5, 8.5 Hz), 7.84 (1H, dd, *J*=2.0, 8.5 Hz), 7.97 (1H, br s), 8.08 (1H, d, *J*=9.0 Hz), 8.13 (1H, d, *J*=8.5 Hz), 8.52 (1H, br s)
10b	0.82 (3H, t, *J*=7.5 Hz), 1.28—1.40 (2H, m), 1.55—1.80 (4H, m), 1.95—2.09 (2H, m), 2.30 (3H, s), 2.95—3.12 (2H, m), 3.19—4.05 (5H, m), 3.92 (1H, dd, *J*=10.0, 16.5 Hz), 4.56—4.68 (1H, m), 5.79 (1H, dd, *J*=3.0, 10.0 Hz), 6.93 (1H, dd, *J*=2.0, 9.0 Hz), 7.00 (1H, d, *J*=2.0 Hz), 7.35 (1H, d, *J*=9.0 Hz), 7.64 (1H, dd, *J*=1.0, 8.5 Hz), 7.79—7.88 (1H, m), 7.96 (1H, br s), 8.08 (1H, d, *J*=8.5 Hz), 8.13 (1H, d, *J*=8.5 Hz), 8.51 (1H, br s)
10c	1.57—1.79 (2H, m), 1.93—2.07 (2H, m), 2.28 (3H, s), 2.86 (1H, dd, *J*=2.5, 17.0 Hz), 3.25 (1H, dd, *J*=10.0, 17.0 Hz), 3.15—3.88 (4H, m), 4.52—4.65 (1H, m), 5.77 (1H, dd, *J*=2.5, 10.0 Hz), 6.84 (1H, d, *J*=2.0 Hz), 6.95 (1H, dd, *J*=2.0, 8.5 Hz), 7.52—7.90 (8H, m), 8.05 (1H, br s), 8.08 (1H, d, *J*=8.5 Hz), 8.14 (1H, d, *J*=8.5 Hz), 8.52 (1H, br s)
10d	1.12 (3H, t, *J*=7.0 Hz), 1.62—1.82 (2H, m), 1.96—2.12 (2H, m), 2.30 (3H, s), 2.96—3.07 (1H, m), 3.32—4.11 (7H, m), 4.38 (1H, d, *J*=14.0 Hz), 4.52 (1H, d, *J*=14.0 Hz), 4.59—4.69 (1H, m), 5.88 (1H, d, *J*=10.0 Hz), 6.95 (1H, d, *J*=9.0 Hz), 7.02 (1H, br s), 7.35 (1H, d, *J*=9.0 Hz), 7.64 (1H, d, *J*=8.5 Hz), 7.86 (1H, d, *J*=8.5 Hz), 7.94 (1H, br s), 8.08 (1H, d, *J*=8.5 Hz), 8.13 (1H, d, *J*=8.5 Hz), 8.52 (1H, br s)
10g	1.60—1.80 (2H, m), 1.89—2.10 (2H, m), 1.95 (3H, s), 2.30 (3H, s), 2.91 (1H, d, *J*=16.0 Hz), 3.45—3.94 (5H, m), 4.55—4.67 (1H, m), 5.91 (1H, d, *J*=9.0 Hz), 6.86—6.96 (2H, m), 7.59 (1H, dd, *J*=1.5, 8.5 Hz), 7.76 (1H, br s), 7.85 (1H, d, *J*=8.5 Hz), 8.04—8.19 (3H, m), 8.48 (1H, br s)
11d	1.63—1.85 (2H, m), 1.96—2.15 (2H, m), 2.30 (3H, s), 3.00 (1H, d, *J*=16.0 Hz), 3.44—4.23 (5H, m), 4.12 (1H, d, *J*=14.0 Hz), 4.42 (1H, d, *J*=14.0 Hz), 4.58—4.72 (1H, m), 5.85 (1H, d, *J*=8.5 Hz), 6.95 (1H, d, *J*=8.5 Hz), 7.00 (1H, br s), 7.36 (1H, d, *J*=8.5 Hz), 7.64 (1H, d, *J*=8.5 Hz), 7.85 (1H, d, *J*=8.5 Hz), 7.95 (1H, br s), 8.08 (1H, d, *J*=8.5 Hz), 8.13 (1H, d, *J*=8.5 Hz), 8.52 (1H, br s)
11e	1.63—2.15 (6H, m), 2.29 (3H, s), 2.35 (2H, t, *J*=7.0 Hz), 2.93—3.89 (7H, m), 3.97 (1H, dd, *J*=10.0, 17.0 Hz), 4.56—4.69 (1H, m), 5.76 (1H, dd, *J*=2.5, 10.0 Hz), 6.85—7.05 (2H, m), 7.35 (1H, d, *J*=9.0 Hz), 7.65 (1H, dd, *J*=1.0, 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)
11f	1.24—1.84 (8H, m), 1.94—2.20 (2H, m), 2,14 (2H, t, *J*=7.0 Hz), 2.29 (3H, s), 2.94—3.89 (7H, m), 3.96 (1H, dd, *J*=10.0, 16.5 Hz), 4.55—4.69 (1H, m), 5.79 (1H, dd, *J*=2.5, 10.0 Hz), 6.92 (1H, dd, *J*=2.0, 9.0 Hz), 6.98 (1H, br s), 7.35 (1H, d, *J*=8.5 Hz), 7.64 (1H, dd, *J*=1.5, 8.5 Hz), 7.84 (1H, d, *J*=8.5 Hz), 7.96 (1H, br s), 8.07 (1H, d, *J*=8.5 Hz), 8.13 (1H, d, *J*=8.5 Hz), 8.50 (1H, br s)
11i	1.63—1.81 (2H, m), 1.95—2.10 (2H, m), 2.30 (3H, s), 2.92 (1H, d, *J*=16.0 Hz), 3.27—3.92 (6H, m), 4.34 (1H, d, *J*=16.0 Hz), 4.58—4.67 (1H, m), 5.89 (1H, d, *J*=9.5 Hz), 6.92—6.98 (2H, m), 7.57 (1H, d, *J*=8.5 Hz), 7.76 (1H, br s), 7.86 (1H, d, *J*=8.5 Hz), 8.06—8.22 (3H, m), 8.47 (1H, br s)
21	1.17 (3H, t, *J*=7.5 Hz), 1.61—1.80 (2H, m), 1.89—2.08 (2H, m), 2.25, 2.27 (together 3H, each singlet), 2.85—2.97 (1H, m), 3.05—3.90 (7H, m), 4.69—4.79 (1H, m), 5.81 (1H, dd, *J*=2.0, 10.0 Hz), 6.86 (1H, d, *J*=8.0 Hz), 7.06 (1H, d, *J*=8.0 Hz), 7.26 (1H, t, *J*=8.0 Hz), 7.63 (1H, d, *J*=8.5 Hz), 7.85 (1H, d, *J*=8.5 Hz), 7.94 (1H, br s), 8.04—8.14 (2H, m), 8.52 (1H, br s)
22	1.17 (3H, t, *J*=7.0 Hz), 1.69—1.87 (2H, m), 1.96—2.12 (2H, m), 2.30 (3H, s), 2.90—2.99 (1H, m), 3.11—3.91 (7H, m), 4.62—4.72 (1H, m), 5.78 (1H, dd, *J*=2.0, 10.5 Hz), 6.76 (1H, d, *J*=8.5 Hz), 7.01 (1H, br s), 7.18 (1H, d, *J*=8.5 Hz), 7.61 (1H, d, *J*=8.5 Hz), 7.82 (1H, d, *J*=8.0 Hz), 7.93 (1H, br s), 8.06 (1H, d, *J*=8.5 Hz), 8.11 (1H, d, *J*=8.5 Hz), 8.48 (1H, br s)
27	1.09—1.31 (5H, m), 1.60—1.92 (3H, m), 2.24 (3H, s), 2.94—3.46 (7H, m), 3.80—4.15 (3H, m), 5.78 (1H, dd, *J*=3.0, 10.5 Hz), 7.06—7.12 (2H, m), 7.35 (1H, d, *J*=8.5 Hz), 7.62 (1H, d, *J*=8.5 Hz), 7.83 (1H, d, *J*=8.5 Hz), 7.95 (1H, br s), 8.04—8.15 (2H, m), 8.49 (1H, br s)
33	1.19 (3H, t, *J*=7.5 Hz), 1.63—1.95 (4H, m), 2.28 (3H, s), 2.75—4.05 (11H, m), 4.18—4.32 (1H, m), 5.76—5.84 (1H, m), 7.27—7.50 (3H, m), 7.65 (1H, d, *J*=8.5 Hz), 7.84 (1H, d, *J*=8.5 Hz), 7.97 (1H, br s), 8.06—8.16 (2H, m), 8.50 (1H, br s)

4.27 (3H, m), 3.99 (1H, d, *J*=14.5 Hz), 4.06 (1H, d, *J*=14.5 Hz), 5.14 (2H, s), 5.80 (1H, dd, *J*=2.5, 10.0 Hz), 6.90—7.01 (2H, m), 7.45 (1H, d, *J*=9.0 Hz), 7.57 (1H, dd, *J*=1.5, 8.5 Hz), 7.58 (1H, dd, *J*=1.5, 8.5 Hz), 7.81—7.92 (3H, m), 8.15 (1H, br s).

Ethyl {[2-(7-Cyanonaphthalen-2-yl)-5-hydroxyindolin-1-yl]sulfonyl}-acetate (6d: R^1=$SO_2CH_2CO_2Et$) To a suspension of ethyl {[2-(7-cyanonaphthalen-2-yl)-5-(methoxymethoxy)indoline-1-yl]sulfonyl}acetate **5d** (4.83 g, 10.1 mmol) in EtOAc (40 ml) was added a 4 N solution of hydrogen chloride in EtOAc (20 ml, 80 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. The mixture was allowed to stand overnight and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **6d** (4.21 g, 9.65 mmol, 96%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J*=7.0 Hz), 3.03 (1H, dd, *J*=2.5, 16.0 Hz), 3.89—4.23 (3H, m), 3.99 (1H, d, *J*=14.5 Hz), 4.05 (1H, d, *J*=14.5 Hz), 5.78 (1H, dd, *J*=2.5, 10.0 Hz), 6.69—6.80 (2H, m), 7.40 (1H, d, *J*=9.5 Hz), 7.48—7.59 (2H, m), 7.76—7.87 (3H, m), 8.19 (1H, br s).

Ethyl ({5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetate (8d: R^1=$SO_2CH_2CO_2Et$) Diethyl azodicarboxylate (DEAD) (0.54 ml, 3.43 mmol) was added to a solution of ethyl {[2-(7-cyanonaphthalen-2-yl)-5-hydroxyindoline-1-yl]sulfonyl}acetate **6d** (1.00 g, 2.29 mmol), 1-(*t*-butoxycarbonyl)-4-hydroxypiperidine **7** (692 mg, 3.44 mmol) and PPh_3 (901 mg, 3.43 mmol) in THF (20 ml), and the resulting mixture was stirred overnight at room temperature. To the reaction mixture were added DEAD (0.360 ml, 2.29 mmol), **7** (461 mg, 2.29 mmol) and PPh_3 (601 mg, 2.29 mmol), and the resulting mixture was stirred at room temperature for 2 h and stored overnight. 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=3/2) to give **8d** (1.11 g, 1.79 mmol, 78%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J*=7.0 Hz), 1.47 (9H, s), 1.67—1.80 (2H, m), 1.85—1.96 (2H, m), 3.04 (1H, dd, *J*=2.5, 16.0 Hz), 3.27—3.38 (2H, m), 3.65—3.75 (2H, m), 3.98 (1H, d, *J*=14.0 Hz), 4.01—4.12 (1H, m), 4.05 (1H, d, *J*=14.0 Hz), 4.15—4.25 (2H, m), 4.36—4.44 (1H, m), 5.79 (1H, dd, *J*=2.5, 10.0 Hz), 6.78—6.86 (2H, m), 7.44 (1H, d, *J*=8.5 Hz), 7.54—7.62 (2H, m), 7.82—7.91 (3H, m), 8.20 (1H, br s).

Similarly, compounds **8a**—**c**, **8e**—**g** were prepared.

8a: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.59—2.01 (4H, m), 2.81 (3H, s), 3.10 (1H, dd, *J*=3.5, 16.5 Hz), 3.25—3.39 (2H, m), 3.61—3.80 (2H, m), 3.86 (1H, dd, *J*=10.0, 16.5 Hz), 4.34—4.48 (1H, m), 5.56 (1H, dd, *J*=3.5, 10.0 Hz), 6.75—6.92 (2H, m), 7.45 (1H, d, *J*=8.5 Hz), 7.54—7.67 (2H, m), 7.79—7.96 (3H, m), 8.20 (1H, br s).

8b: ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, *J*=7.5 Hz), 1.18—2.01 (8H, m), 1.47 (9H, s), 2.80—3.05 (2H, m), 3.08 (1H, dd, *J*=3.0, 16.5 Hz), 3.25—3.39 (2H, m), 3.61—3.80 (2H, m), 3.86 (1H, dd, *J*=10.0, 16.5 Hz), 4.31—4.49 (1H, m), 5.61 (1H, dd, *J*=3.0, 10.0 Hz), 6.73—6.91 (2H, m), 7.42 (1H, d, *J*=8.5 Hz), 7.51—7.65 (2H, m), 7.80—7.93 (3H, m), 8.21 (1H, br s).

8c: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.54—1.98 (4H, m), 2.84 (1H, dd, *J*=3.0, 16.5 Hz), 3.11—3.42 (3H, m), 3.58—3.79 (2H, m), 4.27—4.43 (1H, m), 5.64 (1H, dd, *J*=3.0, 10.0 Hz), 6.62 (1H, d, *J*=2.5 Hz), 6.85 (1H, dd, *J*=2.5, 9.0 Hz), 7.33—7.45 (2H, m), 7.48—7.64 (3H, m), 7.66—7.75 (3H, m), 7.78—7.90 (3H, m), 8.19 (1H, br s).

8e: ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, *J*=7.0 Hz), 1.45 (9H, s), 1.47—2.00 (6H, m), 2.02—2.22 (2H, m), 2.30—2.51 (2H, m), 2.94—3.15 (3H, m), 3.23—3.40 (2H, m), 3.59—3.79 (2H, m), 3.88 (1H, dd, *J*=10.5, 16.5 Hz), 4.12 (2H, q, *J*=7.0 Hz), 4.32—4.48 (1H, m), 5.61 (1H, dd, *J*=3.0, 10.5 Hz), 6.75—6.91 (2H, m), 7.42 (1H, d, *J*=8.5 Hz), 7.50—7.65 (2H, m), 7.79—

7.96 (3H, m), 8.21 (1H, br s).

8f: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz), 1.32—1.99 (10H, m), 1.47 (9H, s), 2.24 (2H, t, J=7.5 Hz), 2.78—3.11 (2H, m), 3.08 (1H, dd, J=3.0, 16.5 Hz), 3.27—3.42 (2H, m), 3.61—3.79 (2H, m), 3.85 (1H, dd, J=10.0, 16.5 Hz), 4.11 (2H, t, J=7.0 Hz), 4.32—4.44 (1H, m), 5.60 (1H, dd, J=3.0, 10.0 Hz), 6.76—6.90 (2H, m), 7.41 (1H, d, J=8.5 Hz), 7.55—7.66 (2H, m), 7.79—7.94 (3H, m), 8.20 (1H, br s).

8g: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.59—1.98 (4H, m), 2.05 (3H, s), 2.97 (1H, dd, J=1.5, 16.0 Hz), 3.21—3.40 (2H, m), 3.60—3.78 (2H, m), 3.87 (1H, dd, J=9.5, 16.0 Hz), 4.35—4.43 (1H, m), 5.49—5.64 (1H, m), 6.65—6.88 (2H, m), 7.46 (1H, d, J=8.5 Hz), 7.61 (1H, d, J=8.5 Hz), 7.66 (1H, br s), 7.80—7.93 (2H, m), 8.17 (1H, br s), 8.27 (1H, d, J=8.5 Hz).

Ethyl 3-{5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indolin-1-yl}-3-oxopropionate (8i) A solution of 1-(benzyloxycarbonyl)-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline **8h** (6.00 g, 9.94 mmol) in THF (30 ml) and EtOH (30 ml) was hydrogenated over 10% Pd–C (1.2 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) to give 5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline (4.16 g, 8.86 mmol, 89%) as pale yellow crystals. This crystal (1.50 g, 3.19 mmol) was dissolved in CH_2Cl_2 (20 ml) and treated with ethyl malonyl chloride (0.49 ml, 3.83 mmol) and pyridine (0.26 ml, 3.21 mmol) at −10 °C. The resulting mixture was stirred at the same temperature for 2 h and at room temperature for 1 h. The reaction mixture was concentrated and to the resulting residue was added H_2O. The mixture was extracted 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=1/1) to give **8i** (1.46 g, 2.50 mmol, 78%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.0 Hz), 1.46 (9H, s), 1.67—1.77 (2H, m), 1.84—1.95 (2H, m), 2.99 (1H, dd, J=1.5, 16.0 Hz), 3.19 (1H, d, J=15.0 Hz), 3.27—3.36 (2H, m), 3.42 (1H, d, J=15.0 Hz), 3.64—3.73 (2H, m), 3.89 (1H, dd, J=10.0, 16.0 Hz), 4.08 (2H, q, J=7.0 Hz), 4.36—4.45 (1H, m), 5.67 (1H, dd, J=1.5, 10.0 Hz), 6.72 (1H, d, J=2.0 Hz), 6.86 (1H. dd, J=2.0, 9.0 Hz), 7.45 (1H, dd, J=1.5, 8.5 Hz), 7.62 (1H, dd, J=1.5, 8.5 Hz), 7.67 (1H, br s), 7.89 (1H, d, J=8.5 Hz), 7.90 (1H, d, J=8.5 Hz), 8.18 (1H, br s), 8.28 (1H, d, J=9.0 Hz).

Ethyl {[2-(7-Amidinonaphthalen-2-yl)-5-(piperidin-4-yloxy)indolin-1-yl]sulfonyl}acetate Dihydrochloride (9d: R^1=$SO_2CH_2CO_2Et$) (Method A) Into a solution of ethyl ({5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetate **8d** (790 mg, 1.27 mmol) in CH_2Cl_2 (10 ml) and EtOH (10 ml) was bubbled hydrogen chloride under ice-cooling, and the resulting mixture was stirred at room temperature under tightly sealed condition for 3 h. The reaction mixture was concentrated. The resulting residue was dissolved in EtOH (15 ml) and the solution was treated with NH_4Cl (123 mg, 2.30 mmol) in H_2O (5 ml) and NH_3 solution (0.260 ml, 4.27 mmol). The mixture was allowed to stand at room temperature overnight and concentrated. The resulting residue was chromatographed on a silica gel column (Cosmosil 75C_{18}-PREP™, Nacalai Tesque Inc., MeCN/H_2O=3/97—1/9) to give the free base of **9d**, (528 mg, 0.983 mmol, 77%) as an amorphous solid. This amorphous solid (49 mg, 0.091 mmol) was dissolved in EtOH (3 ml) and treated with a 4 N solution of hydrogen chloride in EtOAc (0.068 ml, 0.27 mmol). The mixture was concentrated and the resulting residue was dried at 70 °C to give **9d** (53 mg, 0.087 mmol) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, J=7.0 Hz), 1.73—1.88 (2H, m), 2.02—2.14 (2H, m), 2.97—3.39 (5H, m), 3.88—4.10 (3H, m), 4.37 (1H, d, J=14.0 Hz), 4.47—4.62 (1H, m), 4.51 (1H, d, J=14.0 Hz), 5.87 (1H, d, J=10.0 Hz), 6.94 (1H, d, J=9.0 Hz), 7.00 (1H, br s), 7.35 (1H, d, J=9.0 Hz), 7.64 (1H, d, J=8.5 Hz), 7.83 (1H, d, J=8.5 Hz), 7.94 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.50 (1H, br s).

Similarly, compounds **9a**—**c**, **9e** and **9f** were prepared.

9a: ^{1}H-NMR (DMSO-d_6) δ: 1.76—1.95 (2H, m), 1.99—2.19 (2H, m), 2.78—3.41 (5H, m), 3.01 (3H, s), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.50—4.65 (1H, m), 5.76 (1H, dd, J=3.0, 10.0 Hz), 6.89—7.03 (2H, m), 7.35 (1H, d, J=8.5 Hz), 7.65 (1H, d, J=8.5 Hz), 7.82 (1H, d, J=8.5 Hz), 7.97 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.50 (1H, br s).

9b: ^{1}H-NMR (DMSO-d_6) δ: 0.81 (3H, t, J=7.5 Hz), 1.25—1.45 (2H, m), 1.54—1.70 (2H, m), 1.75—1.88 (2H, m), 1.98—2.15 (2H, m), 2.97—3.41 (7H, m), 3.96 (1H, dd, J=10.0, 17.0 Hz), 4.48—4.65 (1H, m), 5.70—5.82 (1H, m), 6.85—7.02 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.64 (1H, d, J=8.5 Hz), 7.83 (1H, d, J=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).

9c: ^{1}H-NMR (DMSO-d_6) δ: 1.72—1.87 (2H, m), 1.95—2.11 (2H, m), 2.78—3.40 (6H, m), 4.45—4.57 (1H, m), 5.77 (1H, dd, J=3.0, 10.0 Hz), 6.83 (1H, d, J=2.0 Hz), 6.94 (1H, dd, J=2.0, 9.0 Hz), 7.48—7.61 (3H, m), 7.65—7.88 (5H, m), 8.05 (1H, br s), 8.08 (1H, d, J=8.5 Hz), 8.14 (1H, d, J=8.5 Hz), 8.52 (1H, br s).

9e: ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7.0 Hz), 1.71—2.23 (6H, m), 2.42 (2H, t, J=7.0 Hz), 2.79—3.39 (7H, m), 3.90—4.11 (1H, m), 4.02 (2H, q, J=7.0 Hz), 4.45—4.63 (1H, m), 5.67—5.84 (1H, m), 6.85—7.03 (2H, m), 7.34 (1H, d, J=9.0 Hz), 7.61—7.70 (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), 8.49 (1H, br s).

9f: ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7.0 Hz), 1.25—1.98 (8H, m), 1.99—2.18 (2H, m), 2.21 (2H, t, J=7.0 Hz), 2.78—3.40 (7H, m), 3.95 (1H, dd, J=10.5, 17.0 Hz), 4.03 (2H, q, J=7.0 Hz), 4.48—4.62 (1H, m), 5.78 (1H, dd, J=2.5, 10.5 Hz), 6.86—6.98 (2H, m), 7.34 (1H, d, J=8.5 Hz), 7.64 (1H, dd, J=1.5, 8.5 Hz), 7.82 (1H, dd, J=1.5, 8.5 Hz), 7.95 (1H, d, J=1.5 Hz), 8.07 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.5 Hz), 8.49 (1H, d, J=1.5 Hz).

1-Acetyl-2-(7-amidinonaphthalen-2-yl)-5-(piperidin-4-yloxy)indoline Dihydrochloride (9g: R^1=Ac) (Method B) To a solution of 1-acetyl-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)indoline **8g** (1.14 g, 2.23 mmol) in MeOH (20 ml) were added hydroxylamine hydrochloride (510 mg, 7.34 mmol) and Na_2CO_3 (350 mg, 3.30 mmol), and the resulting mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated and to the residue was added H_2O. The resulting precipitate was filtered to give a colorless solid. This solid was dissolved in AcOH (20 ml) and treated with Ac_2O (0.30 ml, 3.17 mmol). After stirring at room temperature for 20 min, the mixture was hydrogenated over 10% Pd–C (150 mg) at room temperature for 10 h while stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (Chromatorex™ 'NH', Fuji Chemical Ltd., CH_2Cl_2/MeOH=9/1) to give the free base of **9g** (843 mg, 1.97 mmol) as an amorphous solid. This amorphous solid was dissolved in EtOAc (25 ml) and treated with a 4 N solution of hydrogen chloride in EtOAc (10.6 ml, 42.4 mmol). The mixture was stirred at room temperature for 3 h and the resulting precipitate was filtered to give **9g** (817 mg, 1.63 mmol, 73%) as an amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.72—2.16 (4H, m), 1.95 (3H, s), 2.84—3.28 (5H, m), 3.87 (1H, dd, J=10.0, 16.5 Hz), 4.47—4.63 (1H, m), 5.86—5.96 (1H, m), 6.85—6.97 (2H, m), 7.55—7.64 (1H, m), 7.75 (1H, br s), 7.83 (1H, d, J=8.5 Hz), 8.03—8.21 (3H, m), 8.46 (1H, br s).

Similarly, compound **9i** was prepared.

9i: ^{1}H-NMR (DMSO-d_6) δ: 1.03 (3H, t, J=7.0 Hz), 1.77—1.89 (2H, m), 2.02—2.18 (2H, m), 2.92 (1H, d, J=16.5 Hz), 2.97—3.08 (2H, m), 3.10 (1H, d, J=16.0 Hz), 3.15—3.27 (2H, m), 3.71 (1H, d, J=16.0 Hz), 3.74—4.00 (3H, m), 4.49—4.65 (1H, m), 5.94 (1H, d, J=9.0 Hz), 6.88—6.99 (2H, m), 7.57 (1H, d, J=8.5 Hz), 7.77 (1H, s), 7.84 (1H, d, J=8.5 Hz), 8.05—8.22 (3H, m), 8.46 (1H, s).

Ethyl ({5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetate Dihydrochloride (10d: R^1=$SO_2CH_2CO_2Et$) To a solution of ethyl {[2-(7-amidinonaphthalen-2-yl)-5-(piperidin-4-yloxy)indolin-1-yl]sulfonyl}acetate dihydrochloride **9d** (460 mg, 0.755 mmol) in EtOH (12 ml) were added ethyl acetimidate hydrochloride (233 mg, 1.89 mmol) and Et_3N (0.390 ml, 2.81 mmol). The resulting mixture was stirred at room temperature for 4 h and allowed to stand overnight. Ethyl acetimidate hydrochloride (106 mg, 0.858 mmol) and Et_3N (0.24 ml, 1.73 mmol) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the resulting residue was purified by preparative HPLC (TSK gel ODS-80Ts, Tosoh Corp., H_2O/MeCN=9/1) to give the free base of **10d** (325 mg, 0.563 mmol) as an amorphous solid. This amorphous solid (55 mg) was dissolved in EtOH (4 ml) and treated with a 4 N solution of hydrogen chloride in dioxane (0.071 ml, 0.284 mmol). The mixture was stored at room temperature for 5 min and concentrated. The resulting residue was dried overnight at 70 °C to give **10d** (60 mg, 0.092 mmol, 72%) as an amorphous solid.

Similarly, other bisamidine derivatives **10a**—**c**, **10g** were prepared.

({5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-indolin-1-yl}sulfonyl)acetic acid Dihydrochloride (11a: R^1=$SO_2CH_2CO_2H$) Ethyl (5-{[1-(acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetate dihydrochloride **10d** (261 mg, 0.452 mmol) was dissolved in a solution of 1 N hydrogen chloride (10 ml) and stirred at 80 °C for 7 h. The reaction mixture was concentrated and the resulting residue was purified by preparative HPLC (TSK gel ODS-80Ts, Tosoh Corp., H_2O/MeCN=9/1) to give the free base of **11d** as an amorphous solid. This amorphous solid was dissolved in a solution of 1 N hydrogen chloride (10 ml) and the mixture was stored at room temperature for 10 min. The mixture was concentrated to give **11d** (228 mg, 0.366 mmol, 81%) as an

amorphous solid.

Similarly, other bisamidine derivatives **11e**, **11f** and **11i** were prepared.

***t*-Butyl 4-(3-Nitrophenoxy)piperidine-1-carboxylate (13)** Diisopropyl azodicarboxylate (DIAD) (8.50 ml, 43.2 mmol) was added to a solution of 3-nitrophenol **12** (5.00 g, 35.9 mmol), 1-(*t*-butoxycarbonyl)-4-hydroxypiperidine **7** (8.68 g, 43.1 mmol) and PPh_3 (11.30 g, 43.1 mmol) in CH_2Cl_2 (100 ml), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=17/3) to give **13** (9.72 g, 30.1 mmol, 84%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.71—1.85 (2H, m), 1.89—2.03 (2H, m), 3.32—3.44 (2H, m), 3.65—3.76 (2H, m), 4.53—4.62 (1H, m), 7.23 (1H, dd, J=2.5, 8.0 Hz), 7.43 (1H, t, J=8.0 Hz), 7.74 (1H, t, J=2.5 Hz), 7.83 (1H, dd, J=2.5, 8.0 Hz).

***t*-Butyl 4-[3-Nitro-2-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxylate (14) and *t*-Butyl 4-[3-Nitro-4-(trimethylsilylmethyl)phenoxy]-piperidine-1-carboxylate (15)** To a solution of *t*-butyl 4-(3-nitrophenoxy)piperidine-1-carboxylate **13** (8.42 g, 26.1 mmol) in THF (40 ml) was slowly added (trimethylsilylmethyl)magnesium chloride (1.0 M in Et_2O, 30.0 ml, 30.0 mmol) and the mixture was stirred at −30 °C for 0.5 h. Then a solution of DDQ (6.20 g, 27.3 mmol) in THF (80 ml) was added slowly and the mixture was stirred at −30 °C for 2 h. The reaction mixture was concentrated and the resulting residue was suspended in EtOAc. The mixture was filtrated through a silica gel column and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=19/1—17/3) to give **14** (1.81 g, 4.43 mmol, 17%) as a yellow oil and **15** (1.93 g, 4.72 mmol, 18%) as a yellow oil, respectively.

14: ^{1}H-NMR ($CDCl_3$) δ: 0.00 (9H, s), 1.48 (9H, s), 1.71—1.82 (2H, m), 1.93—2.02 (2H, m), 2.48 (2H, s), 3.25—3.35 (2H, m), 3.70—3.81 (2H, m), 4.48—4.57 (1H, m), 7.00 (1H, d, J=8.0 Hz), 7.12 (1H, t, J=8.0 Hz), 7.43 (1H, d, J=8.0 Hz).

15: ^{1}H-NMR ($CDCl_3$) δ: 0.00 (9H, s), 1.47 (9H, s), 1.68—1.82 (2H, m), 1.88—1.98 (2H, m), 2.49 (2H, s), 3.30—3.39 (2H, m), 3.65—3.76 (2H, m), 4.42—4.51 (1H, m), 7.01—7.06 (2H, m), 7.48 (1H, d, J=2.5 Hz).

***t*-Butyl 4-{3-Amino-2-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-phenoxy}piperidine-1-carboxylate (17)** To a solution of *t*-butyl 4-[3-nitro-2-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxylate **14** (1.81 g, 4.43 mmol) and 7-formylnaphthalene-2-carbonitrile **16** (1.04 g, 5.74 mmol) in THF (25 ml) was slowly added a solution of TBAF monohydrate (116 mg, 0.444 mmol) in THF (3 ml) and the mixture was stirred at −10 °C for 0.5 h. TBAF (75% in H_2O, 772 mg, 2.21 mmol) 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 resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1—1/1) to give *t*-butyl 4-{2-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]-3-nitrophenoxy}piperidine-1-carboxylate (1.29 g, 2.49 mmol, 56%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.72—1.87 (2H, m), 1.96—2.09 (2H, m), 3.30—3.44 (4H, m), 3.70—3.84 (2H, m), 4.58—4.67 (1H, m), 5.26 (1H, t, J=6.0 Hz), 7.16 (1H, d, J=8.5 Hz), 7.38 (1H, t, J=8.5 Hz), 7.47 (1H, d, J=8.5 Hz), 7.61 (1H, dd, J=1.5, 8.0 Hz), 7.72 (1H, dd, J=1.5, 8.0 Hz), 7.90—7.95 (3H, m), 8.24 (1H, br s). To a solution of this amorphous solid (1.29 g, 2.49 mmol) in AcOH (15 ml) was added Sn powder (1.77 g, 14.9 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with EtOAc and washed with $NaHCO_3$ solution and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1—1/1) to give **17** (936 mg, 1.92 mmol, 77%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.62—2.05 (4H, m), 2.94 (1H, dd, J=9.5, 14.0 Hz), 3.21 (1H, dd, J=2.5, 14.0 Hz), 3.28—3.45 (2H, m), 3.60—3.77 (2H, m), 4.45—4.55 (1H, m), 5.17 (1H, dd, J=2.5, 9.5 Hz), 6.35—6.42 (2H, m), 7.03 (1H, t, J=8.0 Hz), 7.61 (1H, dd, J=1.5, 8.5 Hz), 7.69 (1H, dd, J=1.5, 8.5 Hz), 7.88—7.94 (3H, m), 8.22 (1H, br s).

4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (19) *t*-Butyl 4-{3-amino-2-[2-(7-cyanonaphthalen-2-yl)-2-hydroxyethyl]phenoxy}piperidine-1-carboxylate **17** was converted to **19** by the same procedure as that for **8d**. Compound **19** was obtained (79%, 2 steps) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.0 Hz), 1.45 (9H, s), 1.64—1.81 (2H, m), 1.82—1.98 (2H, m), 2.92—3.13 (3H, m), 3.27—3.43 (2H, m), 3.51—3.67 (2H, m), 3.76 (1H, dd, J=11.0, 17.0 Hz), 4.47—4.57 (1H, m), 5.66 (1H, dd, J=3.5, 11.0 Hz), 6.62 (1H, d, J=8.0 Hz), 7.12 (1H, d, J=8.0 Hz), 7.23 (1H, t, J=8.0 Hz), 7.56—7.63 (2H, m), 7.84—7.92 (3H, m), 8.22 (1H, br s).

4-[1-(Acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline Dihydrochloride (21) 4-[1-(*t*-Butoxycarbonyl)-piperidin-4-yloxy]-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **19** was converted to **21** by the same procedure as that for **10d**. Compound **21** was obtained (51%, 3 steps) as a pale yellow amorphous solid.

Similarly, the 6-substituted indoline derivative **22** was prepared.

2-(7-Cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-{(trifluoromethanesulfonyl)oxy}indoline (24) To a solution of 2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-hydroxyindoline **23** (1.00 g, 2.64 mmol) in pyridine (10 ml) was added trifluoromethanesulfonic anhydride (0.490 ml, 2.91 mmol), and the mixture was stirred at 0 °C for 5 min and room temperature for 1 h. The resulting mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with H_2O, 1 N HCl and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1—1/1) to give **24** (1.27 g, 2.49 mmol, 94%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.5 Hz), 2.88—3.00 (2H, m), 3.11 (1H, dd, J=3.5, 17.0 Hz), 3.91 (1H, dd, J=11.0, 17.0 Hz), 5.71 (1H, dd, J=3.5, 11.0 Hz), 7.13—7.21 (2H, m), 7.51—7.65 (3H, m), 7.84—7.93 (3H, m), 8.23 (1H, br s).

5-{[1-(*t*-Butoxycarbonyl)piperidin-4-yl]methyl}-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (26) To a solution of 9-borabicyclo[3.3.1]nonane (BBN) (0.4 M in THF, 5.4 ml, 2.2 mmol) was added 1-(*t*-butoxycarbonyl)-4-methylenepiperidine **25** (400 mg, 2.03 mmol) and the mixture was refluxed for 7 h. The resulting mixture was allowed to stand at room temperature overnight and 2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)-5-{(trifluoromethanesulfonyl)oxy}indoline (739 mg, 1.45 mmol) in DMF (6 ml), $PdCl_2(dppf)\cdot CH_2Cl_2$ (118 mg, 0.144 mmol) and K_2CO_3 (301 mg, 2.18 mmol) in H_2O (10 ml) were added. The mixture was stirred at 80 °C for 5 h and the resulting mixture was poured into 1 N NaOH and extracted with EtOAc. The organic layer was 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=9/1—1/1) to give **26** (283 mg, 0.506 mmol, 35%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.75 (5H, m), 1.32 (3H, t, J=7.5 Hz), 1.45 (9H, s), 2.47—3.18 (9H, m), 3.88 (1H, dd, J=10.5, 16.0 Hz), 5.64 (1H, dd, J=3.5, 10.5 Hz), 6.96—7.06 (2H, m), 7.41 (1H, d, J=8.0 Hz), 7.56—7.62 (2H, m), 7.84—7.90 (3H, m), 8.20 (1H, br s).

5-{[1-(Acetimidoyl)piperidin-4-yl]methyl}-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline Dihydrochloride (27) 5-{[1-(*t*-Butoxycarbonyl)piperidin-4-yl]methyl}-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **26** was converted to **27** by the same procedure as for **10d**. Compound **27** was obtained (27%, 3 steps) as a pale brown amorphous solid.

***t*-Butyl 4-(4-Nitroanilyl)piperidine-1-carboxylate (30)** A solution of *t*-butyl 4-aminopiperidine-1-carboxylate **29** (10.0 g, 49.9 mmol) in DMA (100 ml) was treated with NaH (2.18 g, 50.0 mmol, as a 55% w/w dispersion in mineral oil) under cooling conditions and the mixture was stirred at 0 °C for 15 min. Then a solution of 4-fluoro-1-nitrobenzene **28** (7.04 g, 49.9 mmol) in DMA (30 ml) was added and 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=9/1—3/2) to give **30** (7.86 g, 26.7 mmol, 95%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.33—1.60 (2H, m), 1.47 (9H, s), 1.99—2.10 (2H, m), 2.88—3.02 (2H, m), 3.46—3.60 (1H, m), 4.01—4.18 (2H, m), 6.53 (2H, d, J=9.0 Hz), 8.09 (2H, d, J=9.0 Hz).

***t*-Butyl 4-(*N*-Methyl-4-nitroanilyl)piperidine-1-carboxylate (31)** A solution of *t*-butyl 4-(4-nitroanilyl)piperidine-1-carboxylate **30** (100 mg, 0.311 mmol) in DMF (3 ml) was treated with NaH (15.0 mg, 0.344 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 MeI (0.020 ml, 0.32 mmol) was 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 H_2O and brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=9/1—7/3) to give **31** (96.6 mg, 0.288 mmol, 93%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.67—1.80 (4H, m), 2.76—2.89 (2H, m), 2.91 (3H, s), 3.83—3.93 (1H, m), 4.21—4.37 (2H, m), 6.70 (2H, d, J=9.5 Hz), 8.13 (2H, d, J=9.5 Hz).

5-{*N*-[1-(*t*-Butoxycarbonyl)piperidin-4-yl]-*N*-methylamino}-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline (32) *t*-Butyl 4-(*N*-methyl-4-nitroanilyl)piperidine-1-carboxylate **31** was converted to **32** by the same procedure as that for **19**. Compound **32** was obtained (8%, 5 steps) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.5 Hz), 1.47 (9H, s), 1.55—1.75 (4H, m), 2.70—3.21 (5H, m), 2.74 (3H, s), 3.56—3.64

(1H, m), 3.86 (1H, dd, J=10.0, 16.5 Hz), 4.18—4.26 (2H, m), 5.60 (1H, dd, J=2.5, 10.0 Hz), 6.65—6.75 (2H, m), 7.40 (1H, d, J=9.0 Hz), 7.56—7.62 (2H, m), 7.82—7.89 (3H, m), 8.20 (1H, br s).

5-{*N*-[1-(Acetimidoyl)piperidin-4-yl]-*N*-methylamino}-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline Trihydrochloride (33) 5-{*N*-[1-(*t*-Butoxycarbonyl)piperidin-4-yl]-*N*-methylamino}-2-(7-cyanonaphthalen-2-yl)-1-(ethanesulfonyl)indoline **32** was converted to **33** by the same procedure as that for **10d**. Compound **33** was obtained (12%, 3 steps) as a pale brown amorphous solid.

(*S*)-7-{1-[(*S*)-α-(Acetoxyphenyl)acetoxy]-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile ((*S*)-34) To a solution of 7-{1-hydroxy-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile **2** (22.00 g, 58.14 mmol) in CH_2Cl_2 (250 ml) were added (*S*)-acetylmandel chloride (14.8 g, 69.6 mmol) in CH_2Cl_2 (20 ml) and pyridine (9.19 g, 116 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, and the resulting residue was dissolved in EtOAc. The resulting mixture was washed with H_2O and brine, dried and concentrated. The resulting residue was crystallized from EtOAc and Et_2O (1/20) to give (*S*)-**32** (10.46 g, 18.86 mmol, 32%) as colorless crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 3.32 (1H, dd, J=9.5, 14.0 Hz), 3.49 (3H, m), 3.61 (1H, dd, J=3.0, 14.0 Hz), 5.26 (2H, s), 5.98 (1H, s), 6.22 (1H, dd, J=3.0, 9.5 Hz), 6.99—7.09 (2H, m), 7.17 (1H, br s), 7.36—7.60 (7H, m), 7.75 (1H, d, J=8.5 Hz), 7.80—7.88 (2H, m), 8.09 (1H, d, J=9.0 Hz). $[\alpha]_D$ +73.6° (c=1.00, $CHCl_3$).

Additional Synthesis of (*S*)-7-{1-[(*S*)-α-(Acetoxyphenyl)acetoxy]-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile ((*S*)-32) The filtrate obtained above was concentrated and the resulting residue was dissolved in MeOH (200 ml). To the solution was added K_2CO_3 (1.30 g, 9.41 mmol), and the resulting mixture was stirred at 80 °C for 15 min. The mixture was concentrated and the resulting residue was dissolved in EtOAc. The resulting mixture was washed with H_2O and brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give a mixture of (*S*)-**2** and (*R*)-**2** ((*R*)-**2**>(*S*)-**2**, 13.12 g) as a colorless solid. To a solution of this solid (13.12 g, 34.67 mmol), (*S*)-acetylmandelic acid (10.10 g, 52.10 mmol) and PPh_3 (13.60 g, 51.85 mmol) in CH_2Cl_2 (200 ml) was added DEAD (40% in toluene, 22.65 g, 52.02 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 0.5 h and at room temperature for 3 h. The reaction mixture was concentrated, and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give a diastereomixture of mandelate **32** (22.58 g) as an amorphous solid. The amorphous solid (22.58 g) was crystallized from Et_2O to give (*S*)-**32** (10.11 g, 18.23 mmol, 45%) as crystals. $[\alpha]_D$ +74.6° (c=1.00, $CHCl_3$).

(*S*)-7-{2-[2-Amino-5-(methoxymethoxy)phenyl]-1-hydroxyethyl}naphthalene-2-carbonitrile ((*S*)-3) To a suspension of (*S*)-7-{1-[(*S*)-α-(acetoxyphenyl)acetoxy]-2-[5-(methoxymethoxy)-2-nitrophenyl]ethyl}naphthalene-2-carbonitrile (*S*)-**32** (23.00 g, 41.48 mmol) in MeOH (200 ml) was added K_2CO_3 (2.00 g, 14.5 mmol), and the resulting mixture was stirred at 60 °C for 20 min. The mixture was diluted with EtOAc and the resulting mixture was washed with H_2O, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give (*S*)-**2** (15.62 g, 41.28 mmol) as a colorless solid. A solution of (*S*)-**2** (15.00 g, 39.64 mmol) in THF (30 ml) and EtOH (200 ml) was hydrogenated over 10% Pd–C (2.00 g) at room temperature for 6 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 (*S*)-**3** (10.01 g, 28.73 mmol, 72%) as an oil. $[\alpha]_D$ −11.3° (c=1.00, $CHCl_3$).

Optically active bisamidine derivatives ((*R*)-**10d** and (*R*)-**11d**) were prepared in a manner similar to their racemates from (*S*)-**2**.

(*R*)-**10d**: $[\alpha]_D$ −47° (c=0.35, MeOH), >99% ee.

(*R*)-**11d**: $[\alpha]_D$ −52° (c=0.37, MeOH), >99% ee.

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 Device, CA, U.S.A.). Reaction mixtures (90 μl) were prepared in 96-well plates containing human FXa (0.5IU, Enzyme Research Laboratories, 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 the concentration-response curves.

Coagulation Assay. *In Vitro* Studies: Citrated blood samples were collected from healthy male volunteers or male hamsters (Japan SLC). Plasma was prepared by centrifugation at 2000×***g*** for 10 min and stored at −20 °C until use. Plasma clotting times were measured by an automated blood coagulation analyzer, COAGMASTER II (Sankyo, Japan), using PT reagent, SIMPLASTIN EXCEL (Organon Teknika, NC, U.S.A.). Coagulation times for each compound were compared with the control. In the control group, distilled water instead of the test compound solution was added to plasma. 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 of the predicted 2-fold PT.

Ex Vivo Studies: Compounds were dissolved in distilled water and orally administered to hamsters (Japan SLC), marmosets (CLEA Japan) and cynomolgus monkeys (CLEA Japan) in a volume of 1 ml/kg. One to six hours after the administration, blood was collected into a plastic syringe containing 3.8% sodium citrate. Plasma was prepared and coagulation times were measured using a coagulometer, KC-10A micro (Heinrich Amelung GmbH), using PT reagent, Thromboplastin C plus (Dade Behring Marburg GmbH). The CT_2 values were estimated as described above.

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References and Notes

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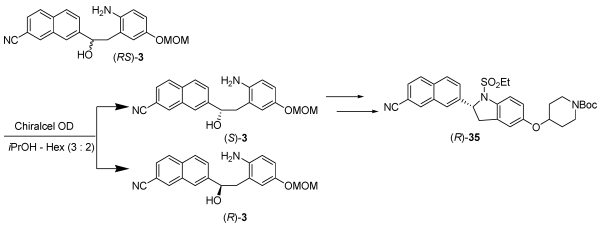

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