Cinnamylindoline Derivatives: Synthesis and Factor Xa (FXa) Inhibitory Activities[1)]

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A series of cinnamylindoline derivatives were synthesized, and their factor Xa (FXa) inhibitory activities and selectivity over trypsin were evaluated. Among them, some novel derivatives showed potent FXa inhibitory activities and good selectivity over trypsin. Especially, (*E*)-2-{5-[1-(acetimidoyl)piperidin-4-yloxy]-2-[2-(5-amidino-2-hydroxyphenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetic acid (22f) having 2-hydroxycinnamyl moiety exhibited the most potent FXa inhibitory activity *in vitro*. Furthermore, 22f also exhibited potent anticoagulant activities *in vitro*.

Key words factor Xa inhibitory activity; cinnamylindoline derivative; anticoagulant

In recent days, factor Xa (FXa) inhibitor attracts much attention as a promising drug candidate for anticoagulation.[3)] FXa, a serine protease in the blood coagulation cascade,[4)] is essential for the formation of thrombin. It plays an important role in the coagulation cascade at the convergent point of the intrinsic and the extrinsic pathway. FXa inhibitor is expected to be a novel antithrombotic with potential for the treatment and prevention of thromboembolic diseases.[5,6)]

In previous papers,[7,8)] we reported the syntheses and FXa inhibitory activities of bisamidine compounds having indoline moiety in the center of the molecule. In these studies, we found that (*R*)-5-[1-(acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)-1-(ethanesulfonyl)indoline ((*R*)-**1**) and ({(*R*)-5-[1-(acetimidoyl)piperidin-4-yloxy]-2-(7-amidinonaphthalen-2-yl)indolin-1-yl}sulfonyl)acetic acid ((*R*)-**2**) exhibited potent FXa inhibitory activities (Fig. 1). However, these compounds also exhibited potent inhibitory activities against trypsin which belongs to a serine protease family. In general, compounds having selective inhibitory activity against target enzyme were favorable as drug candidates because of less possibility of unexpected adverse reaction. From this viewpoint, we searched for a potent and selective FXa inhibitor.

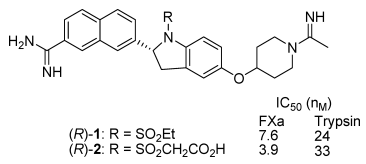


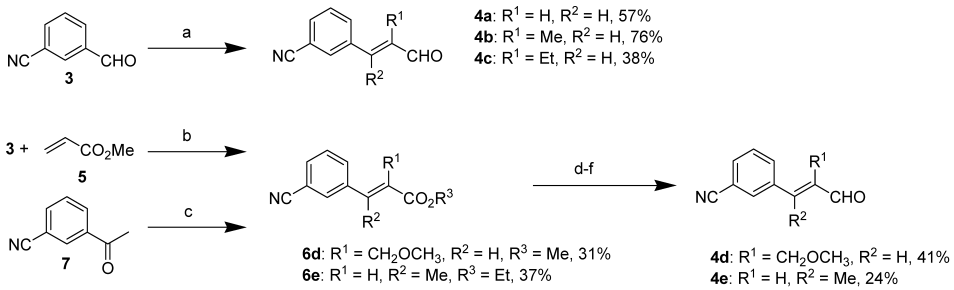
Fig. 1. Structures of Naphthylindoline Derivatives

Herein, we describe the synthesis and structure–activity relationships (SARs) and FXa selectivity of these compounds.

Chemistry

(*E*)-Substituted cinnamaldehyde intermediates **4a**—**e** were synthesized as shown in Chart 1. 3-Cyanobenzaldehyde (**3**) was reacted with ylides to give corresponding substituted cinnamaldehyde **4a**—**c**. Compound **3** and methyl acrylate (**5**) were coupled to give cinnamate **6d** having a methoxymethyl group on the α-position. 3-Cyanoacetophenone (**7**) was reacted with an ylide to give cinnamate **6e** having a methyl group on the β-position. Compounds **6d** and **6e** were converted to cinnamaldehydes **4d** and **4e** by 3 steps, respectively.

The syntheses of bisamidine derivatives (**13a**—**e**) are outlined in Chart 2. Cinnamaldehyde **4a**—**e** were coupled with compound **8a**[7)] by tetrabutylammonium fluoride (TBAF) to give the corresponding alcohols **9a**—**e**.[9)] Nitro groups of alcohols **9a**—**e** were converted to ethanesulfonylamino groups



[a] Reagents: a) $Ph_3P=C(R^1)CHO$ / $PhCH_3$; b) NaH, MeOH / THF; c) $Ph_3P=CHCO_2Et$ / xylene; d) DIBAL, *i*-Bu_3Al / hexane-CH_2Cl_2; e) $NH_2OH \cdot HCl$ / 1-methyl-2-pyrrolidinone; f) MnO_2 / hexane-CH_2Cl_2.

Chart 1

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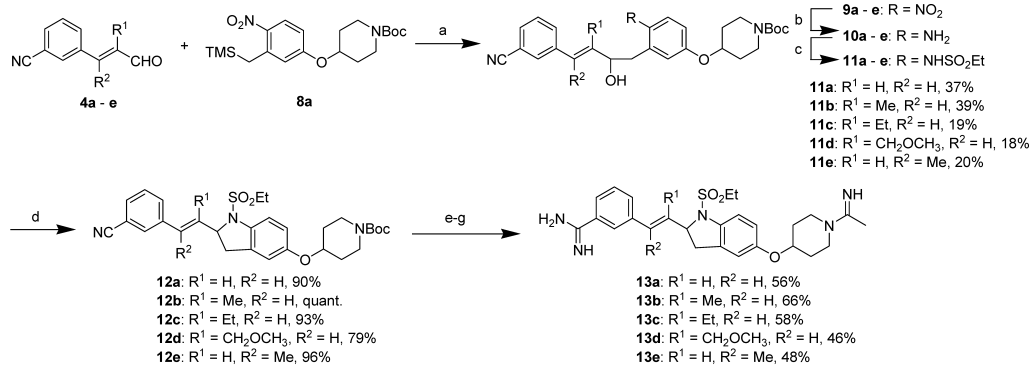
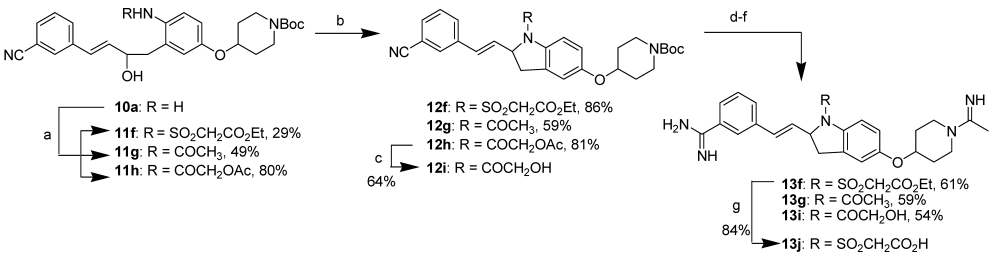


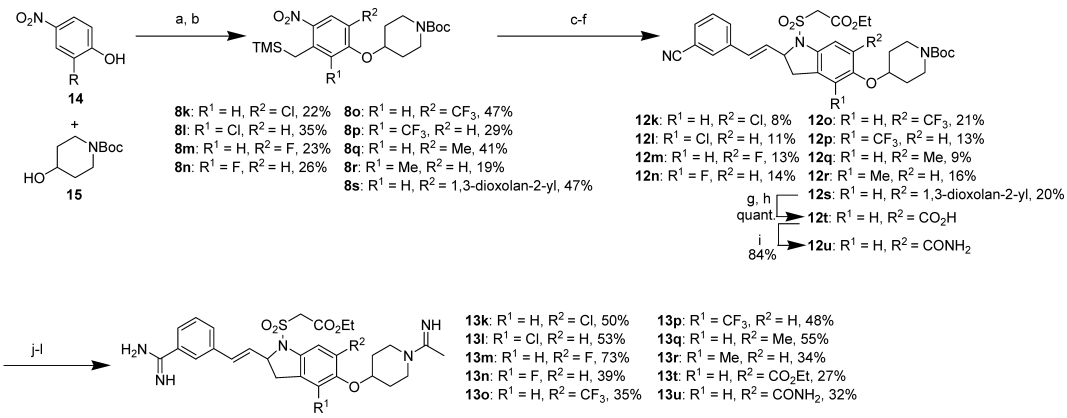
[a] Reagents : a) TBAF / THF; b) Zn / AcOH; c) $EtSO_2Cl$, Pyr. / CH_2Cl_2; d) *n*-Bu_3P, ADDP / THF; e) HCl g. / EtOH-CH_2Cl_2; f) NH_3 aq., NH_4Cl / EtOH-H_2O; g) Et_3N, ethyl acetimidate hydrochloride / EtOH.

Chart 2



[a] Reagents : a) RCl, Pyr. / CH_2Cl_2; b) *n*-Bu_3P, ADDP / THF; c) K_2CO_3 / MeOH; d) HCl g. / EtOH-CH_2Cl_2; e) NH_3 aq., NH_4Cl / EtOH-H_2O; f) Et_3N, ethyl acetimidate hydrochloride / EtOH; g) 4N HCl.

Chart 3



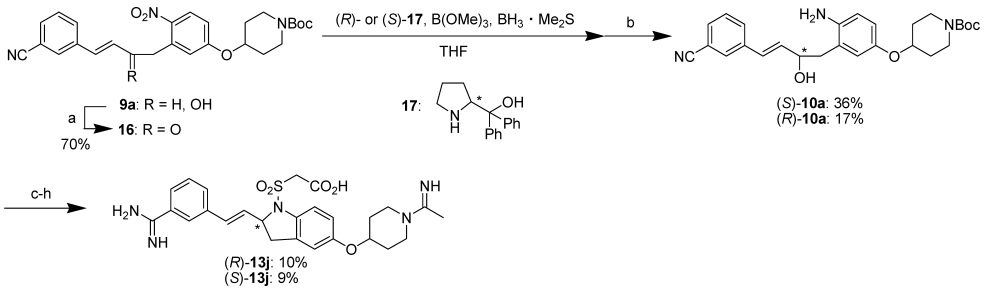
[a] Reagents : a) DEAD, PPh_3 / CH_2Cl_2 ; b) $TMSCH_2MgCl$, then DDQ / THF; c) **4a**, TBAF / THF; d) Zn or Sn / AcOH; e) $ClO_2SCH_2CO_2Et$, Pyr. / CH_2Cl_2; f) *n*-Bu_3P, ADDP / THF; g) *p*-TsOH・H_2O / acetone-H_2O; h) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4 / *t*-BuOH-H_2O; i) Et_3N, $ClCO_2i$-Pr, NH_3 aq. / CH_2Cl_2; j) HCl g. / EtOH-CH_2Cl_2; k) NH_3 aq., NH_4Cl / EtOH-H_2O; l) Et_3N, ethyl acetimidate hydrochloride / EtOH.

Chart 4

to give **11a**—**e**. Intramolecular Mitsunobu reaction[10] of **11a**—**e** with *n*-Bu_3P and 1,1′-(azodicarbonyl)dipiperidine (ADDP) afforded **12a**—**e** having indoline rings. **12a**—**e** were converted to desired bisamidine derivatives **13a**—**e** by 3 steps.

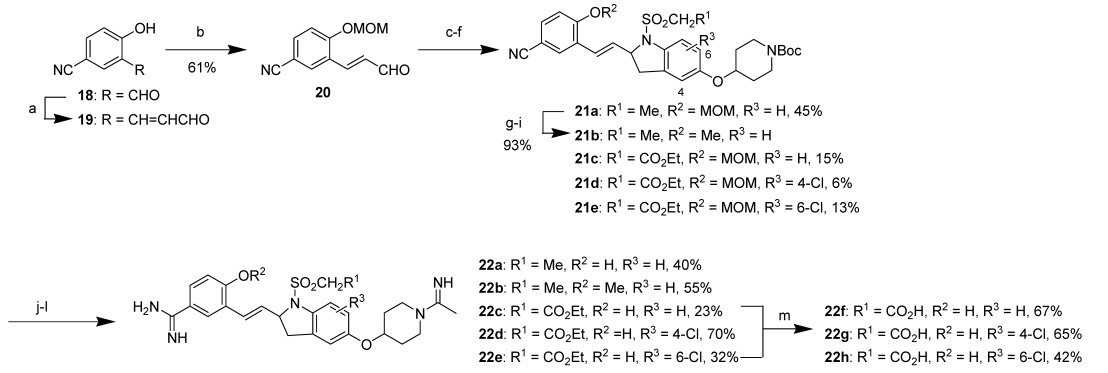
The syntheses of bisamidine derivatives (**13f**, **13g**, **13i**, **13j**) are outlined in Chart 3. After reaction of aniline **10a** with a sulfonyl chloride[11] or acyl chlorides, resulting sulfonamide **11f** or amides **11g** and **11h** were cyclized by the same process described above to give indoline **12f**—**h**. An acetoxy group of indoline **12h** was hydrolyzed to give alcohol **12i**. In a similar method described above, **12f**, **12g** and **12i** were converted to desired bisamidine derivatives **13f**, **13g** and **13i**, respectively. Carboxylic acid **13j** was synthesized from ester **13f** by acid hydrolysis.

The syntheses of bisamidine derivatives (**13k**—**r**, **13t**, **13u**) having substituents on aryl carbons of indoline are outlined in Chart 4. Substituted nitrophenols **14** were coupled with *N*-protected piperidinol **15**, followed by reaction with (trimethylsilylmethyl)magnesium chloride to give the corresponding 2-substituted-3-trimethylsilylmethyl derivatives (**8l**, **8n**, **8p**, **8r**) and/or 2-substituted-5-trimethylsilylmethyl derivatives (**8k**, **8m**, **8o**, **8q**, **8s**).[12] Compounds **8k**—**s** were converted to cyclized compounds **12k**—**s** by a similar method described in Chart 2. A 1,3-dioxolan-2-yl group of compound **12s** was converted to a carboxyl group (**12t**) by 2



[a] Reagents : a) PCC / CH_2Cl_2; b) Zn / AcOH; c) $ClO_2SCH_2CO_2Et$, Pyr. / CH_2Cl_2; d) *n*-Bu_3P, ADDP / THF; e) HCl g. / EtOH-CH_2Cl_2; f) NH_3 aq., NH_4Cl / EtOH-H_2O; g) Et_3N, ethyl acetimidate hydrochloride / EtOH; h) 1_N HCl.

Chart 5



[a] Reagents : a) Ph_3P=CHCHO / $PhCH_3$; b) MOMCl, Et_3N / DMA; c) **8a** or **8k** or **8l**, TBAF / THF; d) Zn / AcOH; e) $R^1CH_2SO_2Cl$, Pyr. / CH_2Cl_2; f) *n*-Bu_3P, ADDP / THF; g) HCl / AcOEt; h) Boc_2O, $NaHCO_3$ / acetone-H_2O; i) $TMSCHN_2$ / PhH-MeOH; j) HCl g. / EtOH-CH_2Cl_2; k) NH_3 aq., NH_4Cl / EtOH-H_2O; l) Et_3N, ethyl acetimidate hydrochloride / EtOH; m) 1_N HCl.

Chart 6

steps. Furthermore, **12t** was converted to amide **12u** in a standard manner. Cyclized compounds **12k**—**r**, **12t** and **12u** were converted to desired bisamidine compounds **13k**—**r**, **13t** and **13u** by a similar method described in Chart 2.

The syntheses of optically active (*R*)-**13j** and (*S*)-**13j** are outlined in Chart 5. After oxidation of racemic alcohol **9a**, ketone **16** was subjected to enantioselective reduction[13,14] by using chiral prolinol ligand (*R*)-**17** or (*S*)-**17**, followed by reduction of a nitro group to give optically pure aniline (*S*)-**10a** and (*R*)-**10a**, respectively. Optically pure and stereochemically inversed bisamidines (*R*)-**13j** and (*S*)-**13j** were synthesized from (*S*) and (*R*)-**10a** by the same method as their racemate, respectively.

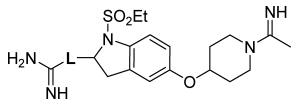
The syntheses of 5-amidino-2-hydroxycinnamyl derivatives (**22a**—**c**, **22f**—**h**) are outlined in Chart 6. After treatment of compound **18** with ylide, a hydroxyl group of resulting compound **19** was protected to give *O*-protected cinnamaldehyde **20**. Compound **20** was converted to cyclized compounds (**21a**, **21c**, **21d**, **21e**) by a similar method described in Chart 2. A methoxymethyl group of **21a** was converted to a methyl group by 3 steps to give compound **21b**. Cyclized compounds **21a**—**e** were converted to desired compounds **22a**—**e** by a similar method described in Chart 2. Furthermore, carboxylic acids **22f**—**h** were synthesized from the corresponding esters **22c**—**e** by acid hydrolysis.

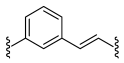
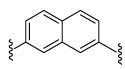
Results and Discussion

In vitro FXa and trypsin inhibitory activities of all compounds were evaluated and expressed as IC_{50} values.

As described above, we considered that it is important not only to enhance FXa inhibitory activity but to improve selectivity over trypsin. From this viewpoint, we reexamined various moieties of the indoline compound we have reported previously.[7,8]

Table 1. FXa and Trypsin Inhibitory Activities of Cinnamyl Compound **13a** and Naphthyl Compound **1**

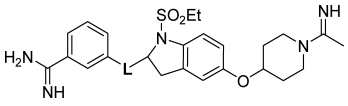


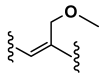
Compd.[a]	L	IC_{50} (nM)		Ratio[b]
		FXa	Trypsin	
13a		12	120	10
1		11	52	4.7

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

First, we focused on the naphthalene structure attached to an indoline ring (Table 1). We synthesized a cinnamyl compound **13a**, a ring-opening form of naphthalene, and tested its inhibitory activity against FXa and trypsin. Compound **13a** exhibited potent FXa inhibitory activity even equal to naphthyl compound **1**. Moreover, **13a** exhibited 10-fold enhanced selectivity for FXa over trypsin. This selectivity was superior to that of naphthyl compound **1**. According to this result, cinnamyl moiety seemed to be appropriate as an alter-

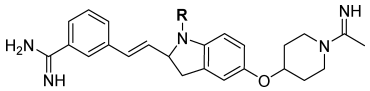
Table 2. FXa and Trypsin Inhibitory Activities of Compounds **13a**—**e**



Compd.[a]	L	IC_{50} (nM)		Ratio[b]
		FXa	Trypsin	
13a		12	120	10
13b		21	160	7.6
13c		24	140	5.8
13d		24	180	7.5
13e		49	130	2.7

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

Table 3. FXa and Trypsin Inhibitory Activities of Compounds **13a**, **13f**, **13g**, **13i** and **13j**



Compd.[a]	R	IC_{50} (nM)		Ratio[b]
		FXa	Trypsin	
13f	$SO_2CH_2CO_2Et$	11	110	10
13j	$SO_2CH_2CO_2H$	9.4	160	17
13g	$COCH_3$	17	190	11
13i	$COCH_2OH$	11	65	5.9
13a	SO_2Et	12	120	10

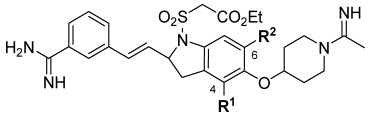
a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

native to naphthyl moiety.

To optimize this moiety, substituents were introduced on the double bond and their effects were evaluated (Table 2). An introduction of a methyl or an ethyl group on the β-position of the cinnamyl moiety (**13b**, **13c**) resulted in a decline of FXa inhibitory activity and selectivity compared to that of **13a**. To examine the effect of an introduction of a polar substituent at this position, methoxymethylene compound **13d** was synthesized and its inhibitory activity was evaluated. However, the activity was similar as those of **13b** and **13c**. On the other hand, compound **13e**, having a methyl group on the α-position, exhibited much less inhibitory activity and selectivity. According to these results, α,β-non-substituted cinnamyl moiety seems to be more suitable.

Next, the effect of the substitution of the nitrogen atom of the indoline ring was examined (Table 3). Conversion of ethanesulfonyl moiety of **13a** into sulfonylacetic acid (**13j**) and its ester form (**13f**) brought about similar FXa inhibitory activities as **13a**, but as for **13j**, selectivity over trypsin was

Table 4. FXa and Trypsin Inhibitory Activities of Compounds **13f**, **13k**—**r**, **13t** and **13u**



Compd.[a]	R^1	R^2	IC_{50} (nM)		Ratio[b]
			FXa	Trypsin	
13k	H	Cl	14	39	2.8
13m	H	F	11	160	15
13o	H	CF_3	6.2	20	3.2
13q	H	Me	13	84	6.5
13t	H	CO_2Et	14	64	4.6
13u	H	$CONH_2$	8.7	25	2.9
13l	Cl	H	9.5	200	21
13n	F	H	11	160	15
13p	CF_3	H	7.3	290	40
13r	Me	H	8.1	220	27
13f	H	H	11	110	10

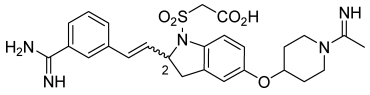
a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

improved. On the other hand, acetyl compound **13g** showed slightly less FXa inhibitory activity. An introduction of a hydroxyl group on the acetyl moiety (**13i**) resulted in similar FXa inhibitory activity as **13a**. However, **13i** also exhibited potent inhibitory activity against trypsin. These results were also confirmed for the naphthylindoline derivatives,[8] and suggest that sulfonylacetic acid type structures are favorable at this position.

Furthermore, the effects of the substituents on the indoline ring (4- *vs.* 6-position) were examined (Table 4). Compounds having a fluorine atom, a bioisoster of a hydrogen atom, on the 4- (**13n**) or 6-position (**13m**) resulted in the same result as non-substituted compound **13f**. Compounds having a more bulky group than a hydrogen atom (**13k**, **13o**, **13q**, **13t**, **13u**) at the 6-position exhibited potent inhibitory activities against both FXa and trypsin. On the other hand, compounds (**13l**, **13p**, **13r**) having a similar bulky group as above at the 4-position exhibited potent FXa inhibitory activity. Moreover, selectivity over trypsin was improved compared to that of **13f**. These results suggest that an introduction at the 4- or 6-position does not have an influence against FXa inhibitory activity, but they do have a significant influence against trypsin inhibitory activity. Furthermore, the bulkiness was important for these activities, whereas the electron property (electron withdrawing/donating group) was not so important. From these results, it seemed that the 4-substitution is preferable to 6-substitution.

All compounds discussed above are racemates having an asymmetric carbon atom at the 2-position of the indoline ring. We previously reported that the (*R*)-naphthylindoline derivative exhibited over 20 times higher FXa inhibitory activity than the corresponding (*S*)-isomer.[7] Based on this result, each of the enantiomers ((*R*)- and (*S*)-**13j**) of a cinnamylindoline derivative **13j** was prepared and their FXa and trypsin inhibitory activities were evaluated (Table 5). However, to our surprise, the FXa inhibitory activities of (*R*)- and (*S*)-**13j** were nearly equal. We thought that this result was caused by the structural flexibility of cinnnamyl moiety. The

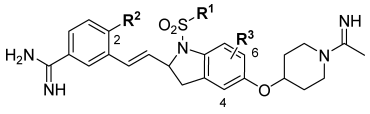
Table 5. FXa and Trypsin Inhibitory Activities of Compounds (*R*)-**13j**, (*S*)-**13j** and **13j**



Compd.[a]	2-position	IC_{50} (nM)		Ratio[b]
		FXa	Trypsin	
(*R*)-**13j**	*R*	11	130	12
(*S*)-**13j**	*S*	16	320	20
13j	*RS*	9.4	160	17

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

Table 6. FXa and Trypsin Inhibitory Activities of Compounds **22a**—**c**, **22f**—**h**, **13a** and **13j**



Compd.[a]	R^1	R^2	R^3	IC_{50} (nM)		Ratio[b]
				FXa	Trypsin	
22a	Et	OH	H	7.0	1300	190
22b	Et	OMe	H	280	2000	7.1
22c	CH_2CO_2Et	OH	H	6.8	1900	280
22f	CH_2CO_2H	OH	H	4.4	1500	340
22g	CH_2CO_2H	OH	4-Cl	20	2600	130
22h	CH_2CO_2H	OH	6-Cl	11	1200	110
13a	Et	H	H	12	120	10
13j	CH_2CO_2H	H	H	9.4	160	17

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Ratio: the IC_{50} values for Trypsin *vs.* FXa (Trypsin/FXa).

structure of the cinnamyl group was less rigid than that of the naphthyl group, so it seemed that the difference of FXa inhibitory activity between (*R*)- and (*S*)-cinnamylindoline derivative was not observed. Moreover, from the synthetic aspect, selective synthesis of the one enantiomer needs more effort compared to that of its racemate. According to this result, we considered that it is suitable to develop our cinnamylindoline derivatives as a racemate.

The effect of the substituents on the benzene ring of the cinnamyl moiety was examined (Table 6). Compound **22a**, having a hydroxyl group at the 2-position, exhibited more potent FXa inhibitory activity and much higher selectivity over trypsin than non-substituted compound **13a**. However, compound **22b**, having a methoxy group on the same position, showed much lower inhibitory activity. This result suggests that the hydroxyl group on this position is highly important for both FXa inhibitory activity and selectivity over trypsin. From the X-ray crystallographic analysis, FXa has an amino acid residue Ser 195 in its S1 pocket[7,15] and Ser 195 is located nearby the benzamidine moieties of FXa inhibitors. We speculate that the hydroxyl group at the 2-position of the benzene ring makes a hydrogen bond with Ser 195, whereas it makes a water-mediated hydrogen bond, a relatively indirect interaction, with Ser 195 in the S1 pocket of trypsin.[16—19] It seems that this difference leads to both potent FXa inhibitory activity and the enzyme selectivity. On the other hand, the methoxy group of **22b** makes it difficult to interact with the S1 pocket of both FXa and trypsin, so this caused a significant decline of inhibitory activity. Furthermore, the replacement of the ethanesulfonyl group by a carboxymethylsulfonyl group (and its ester form) gave the most potent FXa inhibitory activity (**22a** *vs.* **22f** and **22c**). Moreover, selectivity over trypsin of **22f** was over 20 times improved compared to that of **13j**. However, **22g** and **22h** with a chlorine atom at the 4- or 6-positon of the indoline ring exhibited, despite the result shown in Table 4, lower FXa inhibitory activities than that of non-substituted compound **22f**.

Table 7. FXa and Other Serine Protease Inhibitory Activities of Compound **22f**

Enzyme	IC_{50} (nM)
FXa	4.4
Trypsin	1500
FIIa	>100000
Plasmin	16000

Table 8. *In Vitro* Anticoagulant Activities of Compounds **22f** and (*R*)-**2**

Compd.	Human CT_2 (μM)[a]	
	PT	APTT
22f	0.39	0.34
(*R*)-**2**	0.48	1.2

a) The concentration required to double clotting time.

Compound **22f** also exhibited good enzyme selectivity over other serine proteases (Table 7). Therefore, compound **22f** had the best profile in both the FXa inhibitory activity and enzyme selectivity among all compounds we have synthesized and tested.

We evaluated the anticoagulant activity of **22f** on both prothrombin time (PT) and activated partial thromboplastin time (APTT) in human plasma (Table 8). CT_2 values, the concentration required to achieve 200% relative clotting time, of **22f** were 0.39 μM (PT) and 0.34 μM (APTT), whereas those of naphthyl compound (*R*)-**2** were 0.48 μM (PT) and 1.2 μM (APTT), respectively. These results indicate that compound **22f** has more potent *in vitro* anticoagulant activity than (*R*)-**2**.

In conclusion, we synthesized many cinnamylindoline derivatives to find compounds having potent FXa inhibitory activities and selectivity over trypsin. As a result, we found that some novel derivatives having 2-hydroxycinnnamyl moieties showed high FXa inhibitory activities and selectivity over trypsin. Among them, (*E*)-2-{5-[1-(acetimidoyl)piperidin-4-yloxy]-2-[2-(5-amidino-2-hydroxyphenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetic acid (**22f**) exhibited potent FXa inhibitory activity and good enzyme selectivity *in vitro*. Furthermore, compound **22f** exhibited potent *in vitro* anticoagulant activity in human plasma, although oral anticoagulant activity remains to be determined. Our further synthetic efforts are in progress and the results will be disclosed in the next report.

Table 9. Elemental Analysis Data for Cinnamylindoline Derivatives **13** and **22**

Compd.	Formula	Analysis (%) Calcd (Found)					
		C	H	N	Cl	S	F
13a	$C_{26}H_{33}N_5O_3S \cdot 2.0HCl \cdot 2.8H_2O$	50.45 (50.13)	6.61 (6.65)	11.31 (11.65)	11.45 (11.52)	5.18 (5.22)	—
13b	$C_{27}H_{35}N_5O_3S \cdot 2.4HCl \cdot 1.9H_2O$	51.36 (51.62)	6.58 (6.93)	11.09 (11.20)	13.48 (13.12)	5.08 (5.02)	—
13c	$C_{28}H_{37}N_5O_3S \cdot 2.1HCl \cdot 1.8H_2O$	53.16 (52.98)	6.80 (7.10)	11.07 (11.12)	11.77 (11.48)	5.07 (5.36)	—
13d	$C_{28}H_{37}N_5O_4S \cdot 2.0HCl \cdot 2.9H_2O$	50.58 (50.36)	6.79 (6.42)	10.53 (10.55)	10.66 (10.66)	4.82 (4.91)	—
13e	$C_{27}H_{35}N_5O_3S \cdot 2.0HCl \cdot 2.5H_2O$	51.67 (51.78)	6.75 (6.47)	11.16 (11.23)	11.30 (11.12)	5.11 (5.28)	—
13f	$C_{28}H_{35}N_5O_5S \cdot 2.0HCl \cdot 2.5H_2O$	50.07 (50.16)	6.30 (5.95)	10.43 (10.53)	10.56 (10.46)	4.77 (4.66)	—
13g	$C_{26}H_{31}N_5O_2 \cdot 2.1HCl \cdot 2.5H_2O$	55.06 (55.42)	6.77 (6.75)	12.35 (11.97)	13.13 (12.99)	—	—
13i	$C_{26}H_{31}N_5O_3 \cdot 2.0HCl \cdot 2.7H_2O$	53.55 (53.34)	6.64 (6.38)	12.01 (12.08)	12.16 (12.39)	—	—
13j	$C_{26}H_{31}N_5O_5S \cdot 2.4HCl \cdot 1.7H_2O$	48.51 (48.77)	5.76 (5.64)	10.88 (10.62)	13.22 (13.10)	4.98 (4.95)	—
13k	$C_{28}H_{34}ClN_5O_5S \cdot 1.9HCl \cdot 2.3H_2O$	48.12 (48.01)	5.84 (5.67)	10.02 (10.07)	14.71 (14.70)	4.59 (4.80)	—
13l	$C_{28}H_{34}ClN_5O_5S \cdot 2.1HCl \cdot 1.6H_2O$	48.49 (48.28)	5.71 (5.99)	10.10 (10.22)	15.85 (15.83)	4.62 (4.80)	—
13m	$C_{28}H_{34}FN_5O_5S \cdot 2.1HCl \cdot 1.4H_2O$	49.94 (49.91)	5.82 (5.95)	10.40 (10.52)	11.05 (11.16)	4.76 (4.66)	2.82 (2.67)
13n	$C_{28}H_{34}FN_5O_5S \cdot 1.7HCl \cdot 2.5H_2O$	49.55 (49.63)	6.04 (5.92)	10.32 (10.46)	8.88 (8.73)	4.72 (4.61)	2.80 (2.58)
13o	$C_{29}H_{34}F_3N_5O_5S \cdot 2.1HCl \cdot 2.2H_2O$	47.21 (47.32)	5.53 (5.28)	9.49 (9.61)	10.09 (10.01)	4.35 (4.19)	7.72 (7.76)
13p	$C_{29}H_{34}F_3N_5O_5S \cdot 2.3HCl \cdot 1.6H_2O$	47.43 (47.60)	5.42 (5.35)	9.54 (9.41)	11.10 (11.22)	4.37 (4.25)	7.76 (7.76)
13q	$C_{29}H_{37}N_5O_5S \cdot 2.1HCl \cdot 1.3H_2O$	52.17 (51.91)	6.30 (6.09)	10.49 (10.73)	11.15 (11.44)	4.80 (4.70)	—
13r	$C_{29}H_{37}N_5O_5S \cdot 2.1HCl \cdot 1.3H_2O$	52.17 (52.24)	6.30 (6.00)	10.49 (10.69)	11.15 (11.15)	4.80 (4.81)	—
13t	$C_{31}H_{39}N_5O_7S \cdot 2.0HCl \cdot 2.1H_2O$	50.56 (50.75)	6.19 (5.93)	9.51 (9.51)	9.63 (9.55)	4.35 (4.36)	—
13u	$C_{29}H_{36}N_6O_6S \cdot 2.4HCl \cdot 2.5H_2O$	47.76 (47.63)	6.00 (5.76)	11.52 (11.67)	11.67 (11.68)	4.40 (4.64)	—
22a	$C_{26}H_{33}N_5O_4S \cdot 2.0HCl \cdot 2.6H_2O$	49.46 (49.77)	6.42 (6.13)	11.09 (11.23)	11.23 (11.02)	5.08 (4.81)	—
22b	$C_{27}H_{35}N_5O_4S \cdot 2.1HCl \cdot 1.6H_2O$	51.39 (51.32)	6.44 (6.47)	11.10 (10.96)	11.80 (11.89)	5.08 (5.27)	—
22c	$C_{28}H_{35}N_5O_6S \cdot 2.0HCl \cdot 1.2H_2O$	50.79 (50.98)	5.69 (5.81)	10.58 (10.59)	10.71 (10.69)	4.84 (4.72)	—
22f	$C_{26}H_{31}N_5O_6S \cdot 2.5HCl \cdot 0.5H_2O$	48.66 (48.53)	5.42 (5.79)	10.91 (11.08)	13.81 (13.46)	5.00 (5.09)	—
22g	$C_{26}H_{30}ClN_5O_6S \cdot 1.9HCl \cdot 2.9H_2O$	44.77 (44.94)	5.45 (5.19)	10.04 (10.11)	14.74 (14.90)	4.60 (4.33)	—
22h	$C_{26}H_{30}ClN_5O_6S \cdot 2.0HCl \cdot 2.1H_2O$	45.47 (45.34)	5.31 (5.46)	10.20 (10.40)	15.49 (15.42)	4.67 (4.70)	—

Experimental

^{1}H-NMR spectra were obtained on a Varian Mercury 400 or Unity Inova 500 FT-NMR 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: bs=broad singlet, s=singlet, d=doublet, dd=double doublet, t=triplet, dt=double 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.

(*E*)-3-Cyanocinnamaldehyde (4a) To a solution of 3-cyanobenzaldehyde **3** (4.50 g, 34.3 mmol) in toluene (200 ml) was added (triphenylphosphoranylidene)acetaldehyde (13.6 g, 44.7 mmol) and the mixture was stirred at 70 °C for 4 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2) and then recrystallized (toluene/hexane) to give **4a** (3.09 g, 19.7 mmol, 57%) as pale yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 6.76 (1H, dd, J=7.4, 16.1 Hz), 7.46 (1H, d, J=16.1 Hz), 7.58 (1H, t, J=7.8 Hz), 7.73 (1H, d, J=7.8 Hz), 7.81 (1H, d, J=7.8 Hz), 7.84 (1H, s), 9.76 (1H, d, J=7.4 Hz).

Other derivatives (**4b**, **4c**) were similarly prepared.

4b: ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 7.25 (1H, s), 7.59 (1H, t, J=7.8 Hz), 7.69 (1H, d, J=7.8 Hz), 7.74 (1H, d, J=7.8 Hz), 7.79 (1H, s), 9.63 (1H, s).

4c: ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=7.5 Hz), 2.52 (2H, q, J=7.5 Hz), 7.19 (1H, s), 7.59 (1H, t, J=7.8 Hz), 7.68—7.73 (2H, m), 7.75 (1H, s), 9.59 (1H, s).

Methyl (*E*)-3-(3-Cyanophenyl)-2-(methoxymethyl)-2-propenoate (6d) To a suspension of NaH (680 mg, 15.6 mmol, as a 55% w/w dispersion in mineral oil) in THF (15 ml) was added MeOH (0.730 ml, 18.0 mmol) at 0 °C and the mixture was stirred at room temperature for 30 min. 3-Cyanobenzaldehyde **3** (1.31 g, 9.99 mmol) and methyl acrylate **5** (1.35 ml, 15.0 mmol) in THF (15 ml) was then added at 0 °C and the mixture was stirred at room temperature for 2 h. The mixture was concentrated and the resulting residue

Table 10. ^{1}H-NMR Data for Cinnamylindoline Derivatives **13** and **22**

Compd.	^{1}H-NMR δ (DMSO-d_6)
13a	1.17 (3H, t, *J*=7.4 Hz), 1.63—1.83 (2H, m), 1.95—2.12 (2H, m), 2.30 (3H, s), 2.90 (1H, dd, *J*=2.2, 16.7 Hz), 3.02—3.13 (1H, m), 3.19—3.31 (1H, m), 3.44—3.88 (4H, m), 3.66 (1H, dd, *J*=9.9, 16.7 Hz), 4.56—4.67 (1H, m), 5.11—5.21 (1H, m), 6.58 (1H, dd, *J*=6.2, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 6.87 (1H, dd, *J*=2.1, 8.8 Hz), 7.00 (1H, d, *J*=2.1 Hz), 7.24 (1H, d, *J*=8.8 Hz), 7.56 (1H, t, *J*=7.8 Hz), 7.70 (1H, d, *J*=7.8 Hz), 7.80 (1H, d, *J*=7.8 Hz), 7.93 (1H, s)
13b	1.19 (3H, t, *J*=7.4 Hz), 1.68—1.78 (2H, m), 1.84 (3H, s), 1.99—2.08 (2H, m), 2.31 (3H, s), 2.92 (1H, dd, *J*=3.4, 17.0 Hz), 3.05—3.29 (2H, m), 3.51—3.83 (4H, m), 3.67 (1H, dd, *J*=10.2, 17.0 Hz), 4.60—4.64 (1H, m), 5.06 (1H, dd, *J*=3.4, 10.2 Hz), 6.55 (1H, s), 6.86 (1H, dd, *J*=2.0, 8.8 Hz), 6.98 (1H, d, *J*=2.0 Hz), 7.24 (1H, d, *J*=8.8 Hz), 7.59—7.70 (4H, m)
13c	1.09 (3H, t, *J*=7.5 Hz), 1.18 (3H, t, *J*=7.4 Hz), 1.68—1.78 (2H, m), 2.00—2.08 (2H, m), 2.24 (1H, dt, *J*=7.5, 14.5 Hz), 2.29 (3H, s), 2.36 (1H, dt, *J*=7.5, 14.5 Hz), 2.89 (1H, dd, *J*=2.2, 16.8 Hz), 3.04—3.33 (2H, m), 3.47—3.58 (2H, m), 3.70—3.84 (3H, m), 4.58—4.64 (1H, m), 5.09 (1H, dd, *J*=2.2, 10.3 Hz), 6.48 (1H, s), 6.87 (1H, dd, *J*=2.2, 8.8 Hz), 6.98 (1H, d, *J*=2.2 Hz), 7.27 (1H, d, *J*=8.8 Hz), 7.59—7.68 (4H, m)
13d	1.18 (3H, t, *J*=7.3 Hz), 1.69—1.88 (2H, m), 1.98—2.06 (2H, m), 2.29 (3H, s), 3.03—3.82 (8H, m), 3.20 (3H, s), 4.05 (1H, d, *J*=11.5 Hz), 4.09 (1H. d, *J*=11.5 Hz), 4.58—4.64 (1H, m), 5.19 (1H, dd, *J*=2.2, 10.2 Hz), 6.74 (1H, s), 6.86 (1H, dd, *J*=2.4, 8.8 Hz), 6.98 (1H, d, *J*=2.4 Hz), 7.27 (1H, d, *J*=8.8 Hz), 7.60—7.73 (4H, m)
13e	1.19 (3H, t, *J*=7.3 Hz), 1.67—1.80 (2H, m), 1.99—2.05 (2H, m), 2.18 (3H, s), 2.29 (3H, s), 2.79 (1H, dd, *J*=3.0, 16.8 Hz), 3.03—3.31 (2H, m), 3.49—3.59 (2H, m), 3.65—3.81 (3H, m), 4.59—4.63 (1H, m), 5.40 (1H, dt, *J*=3.0, 9.0 Hz), 6.08 (1H, d, *J*=9.0 Hz), 6.86 (1H, d, *J*=8.7 Hz), 6.99 (1H, s), 7.19 (1H, d, *J*=8.7 Hz), 7.57 (1H, t, *J*=7.8 Hz), 7.70 (1H, d, *J*=7.8 Hz), 7.79 (1H, d, *J*=7.8 Hz), 7.84 (1H, s)
13f	1.11 (3H, t, *J*=7.1 Hz), 1.64—1.83 (2H, m), 1.97—2.09 (2H, m), 2.29 (3H, s), 2.90 (1H, d, *J*=16.8 Hz), 3.45—3.62 (2H, m), 3.65—3.85 (2H, m), 3.67 (1H, dd, *J*=10.3, 16.8 Hz), 3.88—4.06 (2H, m), 4.28 (1H, d, *J*=14.0 Hz), 4.43 (1H, d, *J*=14.0 Hz), 4.58—4.67 (1H, m), 5.20—5.28 (1H, m), 6.58 (1H, dd, *J*=6.6, 15.9 Hz), 6.67 (1H, d, *J*=15.9 Hz), 6.89 (1H, dd, *J*=1.3, 8.9 Hz), 7.02 (1H, d, *J*=1.3 Hz), 7.24 (1H, d, *J*=8.9 Hz), 7.56 (1H, t, *J*=7.5 Hz), 7.69 (1H, d, *J*=7.5 Hz), 7.80 (1H, d, *J*=7.5 Hz), 7.91 (1H. s)
13g	1.65—1.82 (2H, m), 1.96—2.10 (2H, m), 2.16 (3H, s), 2.30 (3H, s), 2.88 (1H, d, *J*=16.5 Hz), 3.46—3.64 (3H, m), 3.68—3.87 (2H, m), 4.58—4.66 (1H, m), 5.23—5.31 (1H, m), 6.57 (2H, s), 6 84 (1H, d, *J*=9.2 Hz), 6.96 (1H, s), 7.55 (1H, t, *J*=7.8 Hz), 7.70 (1H, d, *J*=7.8 Hz), 7.79 (1H, d, *J*=7.8 Hz), 7.94 (1H, s), 7.99 (1H, d, *J*=9.2 Hz)
13i	1.65—1.82 (2H, m), 1.96—2.11 (2H, m), 2.30 (3H, s), 2.88 (1H, d, *J*=16.2 Hz), 3.45—3.63 (3H, m), 3.67—3.87 (2H, m), 3.96—4.11 (1H, m), 4.32—4.44 (1H, m), 4.58—4.67 (1H, m), 5.18—5.32 (1H, m), 6.50—6.62 (2H, m), 6.87 (1H, dd, *J*=2.1, 8.8 Hz), 6.98 (1H, d, *J*=2.1 Hz), 7.56 (1H, t, *J*=7.9 Hz), 7.70 (1H, d, *J*=7.9 Hz), 7.79 (1H, d, *J*=7.9 Hz), 7.92 (1H, s), 7.98—8.07 (1H, m)
13j	1.65—1.82 (2H, m), 1.97—2.01 (2H, m), 2.30 (3H, s), 2.88 (1H, d, *J*=16.0 Hz), 3.46—3.61 (2H, m), 3.65—3.86 (2H, m), 3.67 (1H, dd, *J*=10.1, 16.0 Hz), 4.01 (1H, d, *J*=14.2 Hz), 4.30 (1H, d, *J*=14.2 Hz), 4.58—4.67 (1H, m), 5.19—5.27 (1H, m), 6.59 (1H, dd, *J*=6.0, 15.8 Hz), 6.67 (1H, d, *J*=15.8 Hz), 6.89 (1H, dd, *J*=2.4, 8.8 Hz), 7.01 (1H, d, *J*=2.4 Hz), 7.24 (1H, d, *J*=8.8 Hz), 7.56 (1H, t, *J*=8.0 Hz), 7.69 (1H, d, *J*=8.0 Hz), 7.80 (1H, d, *J*=8.0 Hz), 7.92 (1H, s)
13k	1.11 (3H, t, *J*=7.1 Hz), 1.72—1.89 (2H, m), 1.96—2.11 (2H, m), 2.30 (3H, s), 2.92 (1H, dd, *J*=2.1, 16.9 Hz), 3.51—3.80 (4H, m), 3.67 (1H, dd, *J*=9.9, 16.9 Hz), 3.90—4.07 (2H, m), 4.44 (1H, d, *J*=14.3 Hz), 4.54 (1H, d, *J*=14.3 Hz), 4.68—4.77 (1H, m), 5.24—5.33 (1H, m), 6.59 (1H, dd, *J*=6.2, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 7.33 (1H, s), 7.34 (1H, s), 7.57 (1H, t, *J*=7.9 Hz), 7.70 (1H, d, *J*=7.9 Hz), 7.81 (1H, d, *J*=7.9 Hz), 7.92 (1H, s)
13l	1.10 (3H, t, *J*=7.1 Hz), 1.71—1.90 (2H, m), 1.96—2.14 (2H, m), 2.30 (3H, s), 2.95 (1H, dd, *J*=2.6, 16.8 Hz), 3.51—3.82 (4H, m), 3.69 (1H, dd, *J*=10.0, 16.8 Hz), 3.85—3.95 (1H, m), 3.98—4.08 (1H, m), 4.41 (1H, d, *J*=14.3 Hz), 4.50 (1H, d, *J*=14.3 Hz), 4.69—4.77 (1H, m), 5.27—5.35 (1H, m), 6.62 (1H, dd, *J*=5.9, 15.8 Hz), 6.69 (1H, d, *J*=15.8 Hz), 7.19 (1H, d, *J*=8.9 Hz), 7.23 (1H, d, *J*=8.9 Hz), 7.57 (1H, t, *J*=8.0 Hz), 7.71 (1H, d, *J*=8.0 Hz), 7.81 (1H, d, *J*=8.0 Hz), 7.95 (1H, s)
13m	1.11 (3H, t, *J*=7.3 Hz), 1.66—1.85 (2H, m), 1.98—2.01 (2H, m), 2.30 (3H, s), 3.00 (1H, d, *J*=16.5 Hz), 3.47—3.61 (2H, m), 3.63—3.85 (3H, m), 3.89—4.08 (2H, m), 4.40 (1H, d, *J*=14.3 Hz), 4.50 (1H, d, *J*=14.3 Hz), 4.57—4.65 (1H, m), 5.29—5.36 (1H, m), 6.60 (1H, dd, *J*=6.3, 15.8 Hz), 6.70 (1H, d, *J*=15.8 Hz), 7.07 (1H, d, *J*=8.7 Hz), 7.19 (1H, t, *J*=8.7 Hz), 7.57 (1H, t, *J*=7.9 Hz), 7.70 (1H, d, *J*=7.9 Hz), 7.81 (1H, d, *J*=7.9 Hz), 7.93 (1H, s)
13n	1.12 (3H, t, *J*=7.1 Hz), 1.69—1.85 (2H, m), 1.97—2.10 (2H, m), 2.30 (3H, s), 2.90 (1H, d, *J*=15.3 Hz), 3.46—3.86 (5H, m), 3.90—4.08 (2H, m), 4.43 (1H, d, *J*=14.4 Hz), 4.54 (1H, d, *J*=14.4 Hz), 4.57—4.65 (1H, m), 5.24—5.32 (1H, m), 6.60 (1H, dd, *J*=6.2, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 7.14 (1H, d, *J*=11.6 Hz), 7.32 (1H, d, *J*=8.3 Hz), 7.57 (1H, t, *J*=7.8 Hz), 7.71 (1H, d, *J*=7.8 Hz), 7.80 (1H. d, *J*=7.8 Hz), 7.95 (1H, s)
13o	1.10 (3H, t, *J*=7.1 Hz), 1.74—1.86 (2H, m), 2.02—2.11 (2H, m), 2.31 (3H, s), 3.00 (1H, d, *J*=16.9 Hz), 3.56—3.70 (4H, m), 3.77 (1H, dd, *J*=9.4, 16.9 Hz), 3.89—4.03 (2H, m), 4.49 (1H, d, *J*=13.0 Hz), 4.57 (1H, d, *J*=13.0 Hz), 4.88—4.90 (1H, m), 5.33 (1H, t, *J*=7.1 Hz), 6.61 (1H, dd, *J*=6.1, 15.8 Hz), 6.69 (1H, d, *J*=15.8 Hz), 7.47 (1H, s), 7.50 (1H, s), 7.57 (1H, t, *J*=7.8 Hz), 7.72 (1H, d, *J*=7.8 Hz), 7.81 (1H, d, *J*=7.8 Hz), 7.96 (1H, s)
13p	1.09 (3H, t, *J*=7.1 Hz), 1.75—1.85 (2H, m), 2.01—2.12 (2H, m), 2.30 (3H, s), 3.10 (1H, d, *J*=18.1 Hz), 3.56—3.71 (4H, m), 3.80—4.06 (3H, m), 4.44 (1H, d, *J*=14.4 Hz), 4.53 (1H, d, *J*=14.4 Hz), 4.86—4.88 (1H, m), 5.26—5.34 (1H, m), 6.62 (1H, dd, *J*=6.1, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 7.29 (1H, d, *J*=9.2 Hz), 7.54 (1H, d, *J*=9.2 Hz), 7.57 (1H, t, *J*=7.8 Hz), 7.69 (1H, d, *J*=7.8 Hz), 7.81 (1H, d, *J*=7.8 Hz), 7.92 (1H, s)
13q	1.12 (3H, t, *J*=7.1 Hz), 1.70—1.85 (2H, m), 1.96—2.10 (2H, m), 2.17 (3H, s), 2.31 (3H, s), 2.87 (1H, d, *J*=15.6 Hz), 3.52—3.84 (5H, m), 3.90—4.08 (2H, m), 4.24 (1H, d, *J*=14.2 Hz), 4.43 (1H, d, *J*=14.2 Hz), 4.60—4.69 (1H, m), 5.18—5.26 (1H, m), 6.55 (1H, dd, *J*=6.2, 15.8 Hz), 6.66 (1H, d, *J*=15.8 Hz), 7.06 (1H, s), 7.16 (1H, s), 7.60 (1H, t, *J*=7.8 Hz), 7.68 (1H, d, *J*=7.8 Hz), 7.80 (1H. d, *J*=7.8 Hz), 7.87 (1H, s)
13r	1.11 (3H, t, *J*=7.1 Hz), 1.68—1.85 (2H, m), 1.93—2.13 (2H, m), 2.10 (3H, s), 2.32 (3H, s), 2.89 (1H, d, *J*=16.0 Hz), 3.46—3.84 (5H, m), 3.88—4.09 (2H, m), 4.24 (1H, d, *J*=14.7 Hz), 4.42 (1H, d, *J*=14.7 Hz), 4.58—4.69 (1H, m), 5.20—5.30 (1H, m), 6.60 (1H, dd, *J*=6.1, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 6.95 (1H, d, *J*=8.8 Hz), 7.11 (1H, d, *J*=8.8 Hz), 7.56 (1H, t, *J*=7.8 Hz), 7.73 (1H, d, *J*=7.8 Hz), 7.80 (1H, d, *J*=7.8 Hz), 7.96 (1H, s)
13t	1.11 (3H, t, *J*=7.2 Hz), 1.28 (3H, t, *J*=7.1 Hz), 1.81—1.86 (2H, m), 1.96—2.02 (2H, m), 2.30 (3H, s), 2.96 (1H, dd, *J*=1.8, 14.3 Hz), 3.62—3.77 (5H, m), 3.96—4.00 (2H, m), 4.27 (2H, q, *J*=7.2 Hz), 4.41 (1H. d, *J*=14.3 Hz), 4.51 (1H, d, *J*=14.3 Hz), 4.80—4.81 (1H, m), 5.29—5.30 (1H, m), 6.58 (1H, dd, *J*=6.0, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 7.32 (1H, s), 7.57 (1H, t, *J*=7.7 Hz), 7.61 (1H, s), 7.69 (1H, d, *J*=7.7 Hz), 7.81 (1H, d, *J*=7.7 Hz), 7.91 (1H, s)
13u	1.12 (3H, t, *J*=7.1 Hz), 1.78—1.92 (2H, m), 2.00—2.10 (2H, m), 2.30 (3H, s), 2.95 (1H, d, *J*=17.0 Hz), 3.47—3.59 (2H, m), 3.69—3.75 (2H, m), 3.82—3.87 (1H, m), 3.96—4.05 (2H, m), 4.34 (1H, d, *J*=15.0 Hz), 4.48 (1H, d, *J*=15.0 Hz), 4.78—4.81 (1H, m), 5.26 (1H, t, *J*=6.9 Hz), 6.59 (1H, dd, *J*=6.0, 15.8 Hz), 6.68 (1H, d, *J*=15.8 Hz), 7.29 (1H, s), 7.57 (1H, t, *J*=7.9 Hz), 7.69 (1H, d, *J*=7.9 Hz), 7.71 (1H, s), 7.81 (1H, d, *J*=7.9 Hz), 7.92 (1H, s)

Table 10. (Continued)

Compd.	^{1}H-NMR δ (DMSO-d_6)
22a	1.17 (3H, t, J=7.4 Hz), 1.65—1.83 (2H, m), 1.96—2.11 (2H, m), 2.30 (3H, s), 2.86 (1H, dd, J=2.4, 17.0 Hz), 3.00—3.12 (1H, m), 3.19—3.30 (1H, m), 3.46—3.61 (2H, m), 3.65 (1H, dd, J=9.9, 17.0 Hz), 3.67—3.86 (2H, m), 4.57—4.66 (1H, m), 5.09—5.18 (1H, m), 6.52 (1H, dd, J=6.9, 16.0 Hz), 6 82 (1H, d, J=16.0 Hz), 6.86 (1H, dd, J=2.4, 8.8 Hz), 7.01 (1H, d, J=2.4 Hz), 7.06 (1H, d, J=8.6 Hz), 7.23 (1H, d, J=8.8 Hz), 7.62 (1H, dd, J=2.4, 8.6 Hz), 7.97 (1H, d, J=2.4 Hz)
22b	1.17 (3H, t, J=7.4 Hz), 1.64—1.82 (2H, m), 1.95—2.11 (2H, m), 2.30 (3H, s), 2.87 (1H, dd, J=2.4, 16.8 Hz), 3.00—3.12 (1H, m), 3.18—3.30 (1H, m), 3.44—3.87 (4H, m), 3.66 (1H, dd, J=10.0, 16.8 Hz), 3.92 (3H, s), 4.56—4.67 (1H, m), 5.11—5.20 (1H, m), 6.56 (1H, dd, J=7.0, 16.1 Hz), 6.85 (1H, d, J=16.1 Hz), 6.86 (1H, dd, J=2.3, 8.9 Hz), 7.00 (1H, d, J=2.3 Hz), 7.23 (1H, d, J=8.8 Hz), 7.24 (1H, d, J=8.9 Hz), 7.82 (1H, dd, J=2.4, 8.8 Hz), 8.05 (1H, d, J=2.4 Hz)
22c	1.10 (3H, t, J=7.1 Hz), 1.65—1.82 (2H, m), 1.96—2.10 (2H, m), 2.30 (3H, s), 2.87 (1H, d, J=16.4 Hz), 3.46—3.62 (2H, m), 3.67 (1H, dd, J=9.6, 16.4 Hz), 3.68—3.85 (2H, m), 3.87—4.06 (2H, m), 4.26 (1H, d, J=14.1 Hz), 4.42 (1H, d, J=14.1 Hz), 4.60—4.67 (1H, m), 5.18—5.27 (1H, m), 6.53 (1H, dd, J=6.9, 15.8 Hz), 6.82 (1H, d, J=15.8 Hz), 6.89 (1H, dd, J=2.3, 8.8 Hz), 7.02 (1H, s), 7.08 (1H, d, J=8.6 Hz), 7.23 (1H, d, J=8.8 Hz), 7.64 (1H, d, J=8.6 Hz), 7.98 (1H, s)
22f	1.65—1.82 (2H, m), 1.96—2.10 (2H, m), 2.30 (3H, s), 2.85 (1H, d, J=15.8 Hz), 3.44—3.61 (2H, m), 3.66 (1H, dd, J=10.1, 15.8 Hz), 3.68—3.87 (2H, m), 4.02 (1H, d, J=14.2 Hz), 4.31 (1H, d, J=14.2 Hz), 4.58—4.67 (1H, m), 5.15—5.25 (1H, m), 6.53 (1H, dd, J=6.8, 15.9 Hz), 6.82 (1H, d, J=15.9 Hz), 6.88 (1H, dd, J=2.4, 8.8 Hz), 7.01 (1H, d, J=2.4 Hz), 7.08 (1H, d, J=8.6 Hz), 7.24 (1H, d, J=8.8 Hz), 7.63 (1H, dd, J=2.2, 8.6 Hz), 7.98 (1H, d, J=2.2 Hz)
22g	1.72—1.90 (2H, m), 1.96—2.13 (2H, m), 2.30 (3H, s), 2.87 (1H, d, J=16.4 Hz), 3.51—3.80 (4H, m), 3.68 (1H, dd, J=9.6, 16.4 Hz), 4.10 (1H, d, J=14.0 Hz), 4.32 (1H, d, J=14.0 Hz), 4.67—4.77 (1H, m), 5.25—5.33 (1H, m), 6.54 (1H, dd, J=6.9, 15.9 Hz), 6.84 (1H, d, J=15.9 Hz), 7.06 (1H, d, J=8.7 Hz), 7.17 (1H, d, J=8.8 Hz), 7.23 (1H, d, J=8.8 Hz), 7.62 (1H, dd, J=2.2, 8.7 Hz), 7.99 (1H, d, J=2.2 Hz)
22h	1.73—1.88 (2H, m), 1.97—2.11 (2H, m), 2.30 (3H, s), 2.87 (1H, dd, J=1.2, 16.7 Hz), 3.49—3.80 (5H, m), 4.14 (1H, d, J=14.2 Hz), 4.38 (1H, d, J=14.2 Hz), 4.68—4.76 (1H, m), 5.22—5.28 (1H, m), 6.53 (1H, dd, J=6.9, 15.7 Hz), 6.82 (1H, d, J=15.7 Hz), 7.05 (1H, d, J=8.7 Hz), 7.32 (2H, s), 7.62 (1H, dd, J=2.3, 8.7 Hz), 7.97 (1H, d, J=2.3 Hz)

was diluted 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 (toluene/EtOAc=20/1) to give **6d** (0.720 g, 3.11 mmol, 31%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 3.46 (3H, s), 3.88 (3H, s), 4.19 (2H, s), 7.55 (1H, t, J=7.8 Hz), 7.68 (1H, d, J=7.8 Hz), 7.75 (1H, d, J=7.8 Hz), 7.84 (1H, s), 7.87 (1H, s).

Ethyl (*E*)-3-(3-Cyanophenyl)-3-methylacrylate (6e) A solution of 3-cyanoacetophenone **7** (2.90 g, 20.0 mmol) and (carbethoxymethylene)triphenylphosphorane (17.4 g, 49.9 mmol) in xylene (150 ml) was refluxed for 4 h with stirring and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give **6e** (1.61 g, 7.48 mmol, 37%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.1 Hz), 2.56 (3H, s), 4.23 (2H, q, J=7.1 Hz), 6.13 (1H, s), 7.50 (1H, t, J=8.0 Hz), 7.64 (1H, d, J=8.0 Hz), 7.70 (1H, d, J=8.0 Hz), 7.75 (1H, s).

(*E*)-3-(3-Cyanophenyl)-2-(methoxymethyl)-2-propenal (4d) To a solution of methyl (*E*)-3-(3-cyanophenyl)-2-(methoxymethyl)-2-propenoate **6d** (2.01 g, 8.69 mmol) in CH_2Cl_2 (20 ml) and hexane (50 ml) was added diisobutylaluminum hydride (DIBAL) (1.5 M in toluene, 6.70 ml, 10.1 mmol) and *i*-Bu_3Al (1.0 M in hexane, 10.0 ml, 10.0 mmol) at −78 °C and the mixture was stirred for 30 min. After adding DIBAL (1.5 M in toluene, 6.70 ml, 10.1 mmol) and *i*-Bu_3Al (1.0 M in hexane, 10.0 ml, 10.0 mmol) at −78 °C and the mixture was stirred for 30 min. MeOH was added, and the mixture was diluted with EtOAc and washed with 1 N HCl, H_2O, $NaHCO_3$ solution, 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 a mixture of (*E*)- and (*Z*)-3-(3-formylphenyl)-2-(methoxymethyl)-2-propen-1-ol. The mixture was dissolved in 1-methyl-2-pyrrolidinone (30 ml) and the solution was added hydroxylamine hydrochloride (700 mg, 10.1 mmol). The mixture was stirred at 120 °C for 4 h. After cooling, the mixture was diluted with EtOAc and washed with H_2O, brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give (*Z*)-3-(3-cyanophenyl)-2-(methoxymethyl)-2-propen-1-ol (850 mg, 4.18 mmol) as a yellow solid. To a solution of (*Z*)-3-(3-cyanophenyl)-2-(methoxymethyl)-2-propen-1-ol (850 mg, 4.18 mmol) in CH_2Cl_2 (10 ml) and hexane (10 ml) was added MnO_2 (5.00 g, 63.3 mmol) and the mixture was stirred at room temperature for 4 h. After adding MnO_2 (5.00 g, 63.3 mmol) and the mixture was stirred at room temperature for 1 h. MnO_2 was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **4d** (0.71 g, 3.53 mmol, 41%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (3H, s), 4.22 (2H, s), 7.47 (1H, s), 7.60 (1H, t, J=7.8 Hz), 7.74 (1H, d, J=7.8 Hz), 7.90 (1H, d, J=7.8 Hz), 7.99 (1H, s), 9.67 (1H, s).

Another derivative (**4e**) was similarly prepared.

4e: ^{1}H-NMR ($CDCl_3$) δ: 2.63 (3H, s), 6.41 (1H, d, J=7.5 Hz), 7.60 (1H, t, J=7.8 Hz), 7.76 (1H, d, J=7.8 Hz), 7.81 (1H, d, J=7.8 Hz), 7.86 (1H, s), 10.24 (1H, d, J=7.5 Hz).

***t*-Butyl (*E*)-4-{3-[4-(3-Cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate (9a)** To a solution of (*E*)-3-cyanocinnamaldehyde **4a** (1.00 g, 6.36 mmol) and *t*-butyl 4-[4-nitro-3-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxlate **8a** (2.86 g, 7.00 mmol) in THF (50 ml) was added a solution of TBAF monohydrate (0.180 g, 0.644 mmol) in THF (10 ml) at −10 °C and the mixture was stirred at −10 °C for 1 h. TBAF (75% in H_2O, 1.19 g, 6.07 mmol) in THF (10 ml) was then added and the mixture was stirred at −10 °C for 1 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **9a** (2.59 g, 5.25 mmol, 82%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.71—1.82 (2H, m), 1.85—1.98 (2H, m), 3.08 (1H, dd, J=8.5, 13.4 Hz), 3.29—3.42 (2H, m), 3.43 (1H, dd, J=4.0, 13.4 Hz), 3.60—3.70 (2H, m), 4.54—4.62 (1H, m), 4.65—4.73 (1H, m), 6.41 (1H, dd, J=5.8, 16.4 Hz), 6.63 (1H, d, J=16.4 Hz), 6.84—6.90 (2H, m), 7.44 (1H, t, J=7.8 Hz), 7.53 (1H, d, J=7.8 Hz), 7.60 (1H, d, J=7.8 Hz), 7.65 (1H, s), 8.08 (1H, d, J=9.6 Hz).

***t*-Butyl (*E*)-4-{4-Amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate (10a)** To a solution of *t*-butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate **9a** (2.49 g, 5.05 mmol) in AcOH (25 ml) was added zinc powder (1.98 g, 30.3 mmol) and the mixture was stirred at room temperature for 1 h. The 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=1/3) to give **10a** (1.39 g, 3.00 mmol, 59%) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.62—1.74 (2H, m), 1.80—1.92 (2H, m), 2.82—2.87 (2H, m), 3.21—3.32 (2H, m), 3.62—3.73 (2H, m), 4.23—4.30 (1H, m), 4.58—4.65 (1H, m), 6.37 (1H, dd, J=5.9, 15.7 Hz), 6.62 (1H, d, J=15.7 Hz), 6.67—6.71 (3H, m), 7.42 (1H, t, J=7.8 Hz), 7.52 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.64 (1H, s).

***t*-Butyl (*E*)-4-{3-[4-(3-Cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-[(ethanesulfonyl)amino]phenoxy}piperidine-1-carboxylate (11a)** To a solution of *t*-butyl (*E*)-4-{4-amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate **10a** (1.38 g, 2.98 mmol) in CH_2Cl_2 (15 ml) was added $EtSO_2Cl$ (0.340 ml, 3.59 mmol) and pyridine (0.290 ml, 3.59 mmol) and the mixture was stirred at room temperature for 4 h. H_2O was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **11a** (1.26 g, 2.27 mmol, 76%) as a yellow oil. ^{1}H-NMR

($CDCl_3$) δ: 1.42 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.64—1.77 (2H, m), 1.81—1.94 (2H, m), 2.98 (2H, d, J=6.3 Hz), 3.12 (2H, q, J=7.4 Hz), 3.24—3.36 (2H, m), 3.58—3.70 (2H, m), 4.35—4.44 (1H, m), 4.59—4.67 (1H, m), 6.34 (1H, dd, J=6.4, 16.0 Hz), 6.62 (1H, d, J=16.0 Hz), 6.75 (1H, d, J=2.9 Hz), 6.81 (1H, dd, J=2.9, 8.8 Hz), 7.40 (1H, d, J=8.8 Hz), 7.44 (1H, t, J=7.8 Hz), 7.55 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.63 (1H, s).

(*E*)-5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)-ethen-1-yl]-1-(ethanesulfonyl)indoline (12a) To a solution of *t*-butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-[(ethanesulfonyl)-amino]phenoxy}piperidine-1-carboxylate **11a** (1.20 g, 2.16 mmol) in THF (30 ml) was added n-Bu_3P (0.770 ml, 3.09 mmol) and ADDP (0.710 g, 2.81 mmol) in THF (10 ml) and the mixture was stirred at room temperature for 3 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=11/9) to give **12a** (1.05 g, 1.95 mmol, 90%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.67—1.78 (2H, m), 1.84—1.96 (2H, m), 2.89 (1H, dd, J=2.8, 16.5 Hz), 2.98—3.13 (2H, m), 3.27—3.36 (2H, m), 3.58 (1H, dd, J=9.8, 16.5 Hz), 3.64—3.74 (2H, m), 4.34—4.42 (1H, m), 5.05—5.12 (1H, m), 6.30 (1H, dd, J=6.9, 15.6 Hz), 6.69 (1H, d, J=15.6 Hz), 6.75—6.82 (2H, m), 7.33 (1H, d, J=8.6 Hz), 7.40 (1H, t, J=7.8 Hz), 7.51 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.64 (1H, s).

(*E*)-5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)-ethen-1-yl]-1-(ethanesulfonyl)indoline Dihydrochloride (13a) HCl gas was bubbled through a solution of (*E*)-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]-1-(ethanesulfonyl)indoline **12a** (970 mg, 1.80 mmol) in CH_2Cl_2 (12 ml) and EtOH (12 ml) at 0 °C. Then the mixture was stirred at room temperature for 7 h and concentrated. The resulting residue was dissolved in EtOH (21 ml) and the solution was treated with NH_4Cl (174 mg, 3.25 mmol) and NH_3 solution (0.360 ml, 5.92 mmol). The mixture was allowed to stand overnight at room temperature and concentrated. The resulting residue was purified by reverse-phase HPLC (YMC-pack ODS, YMC, H_2O/MeCN=17/3) to give (*E*)-2-[2-(3-amidinophenyl)-ethen-1-yl]-1-(ethanesulfonyl)-5-(piperidin-4-yloxy)indoline (684 mg, 1.50 mmol, 83%) as an amorphous solid. This solid (481 mg, 1.06 mmol) was dissolved in EtOH (12 ml) and treated with ethyl acetimidate hydrochloride (288 mg, 2.33 mmol) and Et_3N (0.490 ml, 3.53 mmol). The mixture was stirred overnight at room temperature. Ethyl acetimidate hydrochloride (65 mg, 0.53 mmol) and Et_3N (0.074 ml, 0.53 mmol) was added, and the mixture was stirred for 3 h. The mixture was concentrated and the resulting residue was purified by reverse-phase HPLC (YMC-pack ODS, YMC, H_2O/MeCN=4/1) to give the free base of **13a** (430 mg, 0.867 mmol) as an amorphous solid. This solid was dissolved in MeOH (8 ml) and treated with 4 N HCl in dioxane (0.640 ml, 2.56 mmol). The mixture was concentrated and the resulting residue was lyophilized to give **13a** (411 mg, 0.723 mmol, 68%) as a colorless amorphous solid.

Other derivatives (**13b**—**e**) were similarly prepared.

***t*-Butyl (*E*)-4-{3-[4-(3-Cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-[(ethoxycarbonylmethlysulfonyl)amino]phenoxy}piperidine-1-carboxylate (11f)** To a solution of *t*-butyl (*E*)-4-{4-amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate **10a** (1.50 g, 3.24 mmol) in CH_2Cl_2 (25 ml) was added ethoxycarbonylmethylsulfonyl chloride (664 mg, 3.56 mmol) in CH_2Cl_2 (10 ml) at −10 °C and the mixture was stirred for 1 h. Pyridine (0.290 ml, 3.59 mmol) was added, and the mixture was stirred for 1.5 h. Ethoxycarbonylmethylsulfonyl chloride (664 mg, 3.56 mmol) in CH_2Cl_2 (2 ml) was added, and the mixture was stirred for 0.5 h. $NaHCO_3$ solution was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **11f** (576 mg, 0.938 mmol, 29%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz), 1.47 (9H, s), 1.65—1.77 (2H, m), 1.81—1.95 (2H, m), 3.02—3.14 (2H, m), 3.25—3.36 (2H, m), 3.59—3.72 (2H, m), 4.01 (1H, d, J=14.7 Hz), 4.05 (1H, d, J=14.7 Hz), 4.26 (2H, q, J=7.1 Hz), 4.38—4.46 (1H, m), 4.61—4.68 (1H, m), 6.36 (1H, dd, J=6.4, 15.9 Hz), 6.63 (1H, d, J=15.9 Hz), 6.78 (1H, d, J=2.8 Hz), 6.81 (1H, dd, J=2.8, 8.7 Hz), 7.44 (1H, t, J=7.8 Hz), 7.48 (1H, d, J=8.7 Hz), 7.54 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.63 (1H, s).

Ethyl (*E*)-2-{5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate (12f) *t*-Butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-[(ethoxycarbonylmethlysulfonyl)amino]phenoxy}piperidine-1-carboxylate **11f** was converted into **12f** by the same procedure as that for **12a**. **12f** was obtained (86%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 1.47 (9H, s), 1.67—1.80 (2H, m), 1.84—1.96 (2H, m), 2.86 (1H, dd, J=2.0, 16.1 Hz), 3.27—3.37 (2H, m), 3.63—3.78 (3H, m), 3.99 (1H, d, J=14.2 Hz), 4.03 (1H, d, J=14.2 Hz), 4.10—4.22 (2H, m), 4.35—4.43 (1H, m), 5.18—5.25 (1H, m), 6.31 (1H, dd, J=6.8, 15.7 Hz), 6.67 (1H, d, J=15.7 Hz), 6.77 (1H, dd, J=2.5, 8.7 Hz), 6.81 (1H, d, J=2.5 Hz), 7.35 (1H, d, J=8.7 Hz), 7.40 (1H, t, J=7.8 Hz), 7.51 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.64 (1H, s).

Other derivatives (**12g**, **12h**) were similarly prepared.

12g: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.68—1.79 (2H, m), 1.83—1.96 (2H, m), 2.24 (3H, s), 2.88 (1H, d, J=16.5 Hz), 3.27—3.37 (2H, m), 3.56—3.74 (3H, m), 4.35—4.43 (1H, m), 4.96—5.05 (1H, m), 6.28 (1H, dd, J=6.2, 15.9 Hz), 6.47 (1H, d, J=15.9 Hz), 6.76 (1H, s), 6.79 (1H, d, J=8.7 Hz), 7.41 (1H, t, J=7.7 Hz), 7.53 (2H, t, J=7.7 Hz), 7.62 (1H, s), 8.14 (1H, d, J=8.7 Hz).

12h: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.66—1.79 (2H, m), 1.83—1.97 (2H, m), 2.20 (3H, s), 2.92 (1H, d, J=16.1 Hz), 3.25—3.38 (2H, m), 3.54—3.75 (3H, m), 4.36—4.45 (1H, m), 4.69 (1H, d, J=14.6 Hz), 4.90 (1H, d, J=14.6 Hz), 4.98—5.11 (1H, m), 6.28 (1H, dd, J=5.6, 15.8 Hz), 6.55 (1H, d, J=15.8 Hz), 6.75—6.82 (2H, m), 7.41 (1H, t, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.56 (1H, d, J=7.7 Hz), 7.63 (1H, s), 8.08—8.17 (1H, m).

(*E*)-5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)-ethen-1-yl]-1-(hydroxyacetyl)indoline (12i) To a solution of (*E*)-1-(acetoxyacetyl)-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]indoline **12h** (813 mg, 1.49 mmol) in MeOH (12 ml) was added K_2CO_3 (51 mg, 0.37 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was concentrated and the resulting residue was diluted with EtOAc. The organic layer was washed with H_2O, brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=2/3) to give **12i** (478 mg, 0.949 mmol, 64%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.68—1.80 (2H, m), 1.86—1.97 (2H, m), 2.92 (1H, d, J=15.8 Hz), 3.28—3.38 (2H, m), 3.55—3.75 (3H, m), 4.20—4.27 (1H, m), 4.30—4.46 (2H, m), 4.84—4.92 (1H, m), 6.24 (1H, dd, J=7.1, 15.9 Hz), 6.48 (1H, d, J=15.9 Hz), 6.77—6.88 (2H, m), 7.42 (1H, t, J=8.0 Hz), 7.54 (2H, d, J=8.0 Hz), 7.61 (1H, s), 8.13 (1H, d, J=8.5 Hz).

Ethyl (*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate Dihydrochloride (13f) Ethyl (*E*)-2-{5-[1-(*t*-buthoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate **12f** was converted into **13f** by the similar procedure as that for **13a**. **13f** was obtained (61%, 3 steps) as a colorless amorphous solid.

Other derivatives (**13g**, **13i**) were similarly prepared.

(*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)-ethen-1-yl]indolin-1-ylsulfonyl}acetic Acid Dihydrochloride (13j) A solution of ethyl (*E*)-2-{5-[1-(acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate dihydrochloride **13f** (248 mg, 0.448 mmol) in 4 N HCl (12 ml) was stirred at 80 °C for 1.5 h. The mixture was concentrated and the resulting residue was purified by reverse-phase HPLC (YMC-pack ODS, YMC, H_2O/MeCN=87/13) to give the free base of **13j** as an amorphous solid. This solid was dissolved in 1 N HCl (7 ml) and the mixture was concentrated. The resulting residue was lyophilized to give **13j** (226 mg, 0.378 mmol, 84%) as a colorless amorphous solid.

***t*-Butyl 4-[2-Chloro-4-nitro-5-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxylate (8k) and *t*-Butyl 4-[2-Chloro-4-nitro-3-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxylate (8l)** To a solution of 2-chloro-4-nitrophenol **14** (R^4=Cl) (2.36 g, 13.6 mmol), *t*-butyl 4-hydroxypiperidine-1-carboxylate **15** (3.32 g, 16.5 mmol) and PPh_3 (5.11 g, 19.5 mmol) in CH_2Cl_2 (60 ml) was added DEAD (3.10 ml, 19.7 mmol) at 0 °C and the mixture was stirred at room temperature for 18 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=5/2) to give *t*-butyl 4-(2-chloro-4-nitro)phenoxypiperidine-1-carboxylate (3.90 g, 10.9 mmol) as a pale yellow solid. This solid (12.90 g, 36.2 mmol) was dissolved in THF (200 ml) and treated with (trimethylsilylmethyl)magnesium chloride (1.0 M in Et_2O, 40.0 ml, 40.0 mmol) slowly at −25 °C and the mixture was stirred at −10 °C for 1 h. DDQ (10.21 g, 45.0 mmol) in THF (30 ml) was added slowly, and the mixture was stirred at −10 °C for 2 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=4/1) to give **8k** (4.40 g, 9.93 mmol, 22%) as a yellow oil and **8l** (7.04 g, 15.9 mmol, 35%) as a yellow oil.

8k: ^{1}H-NMR ($CDCl_3$) δ: 0.02 (9H, s), 1.48 (9H, s), 1.79—1.98 (4H, m), 2.64 (2H, s), 3.43—3.65 (4H, m), 4.60—4.68 (1H, m), 6.56 (1H, s), 8.16 (1H, s).

8l: ^{1}H-NMR ($CDCl_3$) δ: 0.06 (9H, s), 1.48 (9H, s), 1.82—1.98 (4H, m), 2.84 (2H, s), 3.48—3.66 (4H, m), 4.64—4.75 (1H, m), 6.76 (1H, d, J=9.2 Hz), 7.91 (1H, d, J=9.2 Hz).

Ethyl (*E*)-2-{5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-6-chloro-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate (12k) *t*-Butyl 4-[2-chloro-4-nitro-5-(trimethylsilylmethyl)phenoxy]piperidine-1-carboxylate **8k** was converted into **12k** by the same procedure as that for **12a**. **12k** was obtained (8%, 4 steps) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.76—1.95 (4H, m), 2.85 (1H, dd, J=1.8, 16.2 Hz), 3.36—3.47 (2H, m), 3.63—3.77 (3H, m), 4.05 (2H, s), 4.10—4.22 (2H, m), 4.39—4.48 (1H, m), 5.19—5.27 (1H, m), 6.30 (1H, dd, J=6.8, 15.4 Hz), 6.67 (1H, d, J=15.4 Hz), 6.87 (1H, s), 7.41 (1H, t, J=7.8 Hz), 7.49 (1H, s), 7.52 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.65 (1H, s).

Other derivatives (**12l**—**s**) were similarly prepared.

Ethyl (*E*)-2-{5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-6-carboxy-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate (12t) To a solution of ethyl (*E*)-2-{5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]-6-(1,3-dioxolan-2-yl)indolin-1-ylsulfonyl}acetate **12s** (850 mg, 1.27 mmol) in acetone (40 ml) and H_2O (10 ml) was added *p*-TsOH monohydrate (80 mg, 0.42 mmol) and the mixture was stirred at room temperature for 30 min. $NaHCO_3$ solution was added, and the mixture was concentrated. The resulting residue was extracted with EtOAc and the organic layer was washed with brine. The organic layer was dried and concentrated to give Ethyl (*E*)-2-{5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-[2-(3-cyanophenyl)ethen-1-yl]-6-formylindolin-1-ylsulfonyl}acetate (780 mg) as a yellow amorphous solid. This solid (770 mg, 1.23 mmol) and 2-methyl-2-butene (8.00 ml, 75.5 mmol) was dissolved in *t*-BuOH (80 ml) and treated with $NaClO_2$ (1.03 g, 11.4 mmol) and NaH_2PO_4 (1.37 g, 11.4 mmol) in H_2O (12 ml) slowly. The mixture was stirred at room temperature for 0.5 h and concentrated. The resulting residue was extracted with EtOAc. The organic layer was washed with $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to give **12t** (920 mg, quant.) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.81—1.86 (2H, m), 2.04—2.11 (2H, m), 2.94 (1H, dd, J=2.3, 17.0 Hz), 3.26 (2H, t, J=10.3 Hz), 3.79—3.86 (3H, m), 4.07 (2H, s), 4.11—4.24 (2H, m), 4.66—4.68 (1H, m), 5.28 (1H, t, J=6.8 Hz), 6.30 (1H, dd, J=6.8, 15.7 Hz), 6.68 (1H, d, J=15.7 Hz), 6.99 (1H, s), 7.41 (1H, t, J=7.7 Hz), 7.52 (1H, d, J=7.7 Hz), 7.58 (1H, d, J=7.7 Hz), 7.65 (1H, s), 8.13 (1H, s).

Ethyl (*E*)-2-{5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-6-carbamoyl-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate (12u) To a solution of ethyl (*E*)-2-{5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-6-carboxy-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate **12t** (460 mg, 0.719 mmol) in CH_2Cl_2 (10 ml) was added Et_3N (0.120 ml, 0.866 mmol) and $ClCO_2i$-Pr (0.110 ml, 0.966 mmol) and the mixture was stirred at room temperature for 30 min. NH_3 solution (0.090 ml, 1.5 mmol) was added, and the mixture was stirred at room temperature for 30 min. The mixture was extracted with EtOAc and 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 (EtOAc) to give **12u** (380 mg, 0.595 mmol, 83%) as a brown amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.2 Hz), 1.47 (9H, s), 1.73—1.83 (2H, m), 1.99—2.08 (2H, m), 2.90 (1H, dd, J=2.4, 16.8 Hz), 3.25 (2H, t, J=10.5 Hz), 3.77—3.84 (3H, m), 4.05 (1H, d, J=14.4 Hz), 4.08 (1H, d, J=14.4 Hz), 4.10—4.24 (2H, m), 4.55—4.59 (1H, m), 5.27 (1H, t, J=7.0 Hz), 6.29 (1H, dd, J=6.6, 15.7 Hz), 6.67 (1H, d, J=15.7 Hz), 6.92 (1H, s), 7.40 (1H, t, J=7.8 Hz), 7.51 (1H, d, J=7.8 Hz), 7.57 (1H, d, J=7.8 Hz), 7.65 (1H, s), 8.18 (1H, s).

Ethyl (*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)ethen-1-yl]-6-chloroindolin-1-ylsulfonyl}acetate Dihydrochloride (13k) Ethyl (*E*)-2-{5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-6-chloro-2-[2-(3-cyanophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate **12k** was converted into **13k** by the same procedure as that for **13a**. **13k** was obtained (50%, 3 steps) as a colorless amorphous solid.

Other derivatives (**13l**—**r**, **13t**, **13u**) were similarly prepared.

***t*-Butyl (*E*)-4-{3-[4-(3-Cyanophenyl)-2-oxo-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate (16)** To a solution of *t*-butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate **9a** (2.55 g, 5.17 mmol) in CH_2Cl_2 (50 ml) was added pyridinium chlorochromate (PCC) (1.45 g, 6.73 mmol) at 0 °C and the mixture was stirred overnight at room temperature. The mixture was filtered, and the filtrate was washed with H_2O and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=4/1) to give **16** (1.79 g, 3.64 mmol, 70%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.73—1.86 (2H, m), 1.90—2.02 (2H, m), 3.30—3.44 (2H, m), 3.61—3.75 (2H, m), 4.35 (2H, s), 4.57—4.64 (1H, m), 6.80 (1H, d, J=2.7 Hz), 6.92 (1H, dd, J=2.7, 9.2 Hz), 6.94 (1H, d, J=16.1 Hz), 7.54 (1H, t, J=7.9 Hz), 7.63 (1H, d, J=16.1 Hz), 7.69 (1H, d, J=7.9 Hz), 7.80 (1H, d, J=7.9 Hz), 7.86 (1H, s), 8.22 (1H, d, J=9.2 Hz).

***t*-Butyl (*S*)-(*E*)-4-{4-Amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate ((*S*)-10a)** To a solution of (*R*)-α,α-diphenyl-2-pyrrolidinemethanol (*R*)-**17** (665 mg, 2.62 mmol) in THF (30 ml) was added trimethoxyborane (409 mg, 3.94 mmol) in THF (5 ml) and the mixture was stirred at room temperature for 1 h. Borane-dimethylsulfide complex (2.0 M in THF, 2.62 ml, 5.24 mmol) and *t*-butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-oxo-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate **16** (1.29 g, 2.62 mmol) in THF (25 ml) was added, and the mixture was stirred at room temperature for 1.5 h. NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give *t*-butyl (*S*)-(*E*)-4-{3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate (963 mg, 1.95 mmol, 74%) as a colorless amorphous solid. To a solution of this solid in AcOH (15 ml) was added zinc powder (762 mg, 11.7 mmol) and the mixture was stirred at room temperature for 1 h. Zinc powder (762 mg, 11.7 mmol) was added, and the mixture was stirred at room temperature for 1 h. The 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=1/3) and then purified by chiral HPLC (Daicel Chiralcel OD, Daicel Chemical Industries Ltd., hexane/*i*-PrOH=7/3) to give (*S*)-**10a** (432 mg, 0.932 mmol, 48%, >99% ee) as a yellow oil. $[\alpha]_D$ +46.1° (c=0.43, MeOH).

(*R*)-(*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetic Acid Dihydrochloride ((*R*)-13j) *t*-Butyl (*S*)-(*E*)-4-{4-amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate (*S*)-**10a** was converted into (*R*)-**13j** by the same procedure as that for racemate **13j**. (*R*)-**13j** was obtained (10%, 6 steps) as a colorless amorphous solid. $[\alpha]_D$ −13.6° (c=0.29, MeOH).

***t*-Butyl (*R*)-(*E*)-4-{4-Amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate ((*R*)-10a)** *t*-Butyl (*E*)-4-{3-[4-(3-cyanophenyl)-2-oxo-3-buten-1-yl]-4-nitrophenoxy}piperidine-1-carboxylate **16** was converted into (*R*)-**10a** by the same procedure as that for (*S*)-**10a**. (*S*)-α,α-Diphenyl-2-pyrrolidinemethanol (*S*)-**17** was used instead of (*R*)-**17**. (*R*)-**10a** was obtained (17%, 2 steps, >99% ee) as a brown amorphous solid. $[\alpha]_D$ −43.6° (c=1.02, MeOH).

(*S*)-(*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(3-amidinophenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetic Acid Dihydrochloride ((*S*)-13j) *t*-Butyl (*R*)-(*E*)-4-{4-amino-3-[4-(3-cyanophenyl)-2-hydroxy-3-buten-1-yl]phenoxy}piperidine-1-carboxylate (*R*)-**10a** was converted into (*S*)-**13j** by the same procedure as that for racemate **13j**. (*S*)-**13j** was obtained (9%, 6 steps) as a yellow amorphous solid. $[\alpha]_D$ +16.1° (c=0.99, MeOH).

5-Cyano-2-(methoxymethoxy)cinnamaldehyde (20) To a solution of 5-cyano-2-hydroxybenzaldehyde **18** (2.08 g, 14.1 mmol) in toluene (60 ml) was added (triphenylphosphoranylidene)acetaldehyde (4.52 g, 14.9 mmol) and the mixture was stirred at 70 °C for 1.5 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give 5-cyano-2-hydroxycinnamaldehyde **19** (1.65 g, 9.53 mmol) as a colorless solid. To a solution of this solid (1.63 g, 9.41 mmol) in DMA (30 ml) was added methoxymethylchloride (0.850 ml, 11.2 mmol) and Et_3N (1.57 ml, 11.3 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. Methoxymethylchloride (0.210 mmol, 2.76 mmol) and Et_3N (0.390 ml, 2.81 mmol) were added, and the mixture was stirred for 2 h. Brine was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=17/3) to give **20** (1.86 g, 8.56 mmol, 61%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (3H, s), 5.36 (2H, s), 6.80 (1H, dd, J=7.6, 16.2 Hz), 7.30 (1H, d, J=8.7 Hz), 7.66 (1H, dd, J=2.1, 8.7 Hz), 7.75 (1H, d, J=16.2 Hz), 7.84 (1H, d, J=2.1 Hz), 9.74 (1H, d, J=7.6 Hz).

Ethyl (*E*)-2-(5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-{2-[5-cyano-2-(methoxymethoxy)phenyl]ethen-1-yl}indolin-1-ylsulfonyl)acetate (21c) 5-Cyano-2-(methoxymethoxy)cinnamaldehyde **20** was converted into **21c** by the similar procedure as that for **12a**. **21c** was obtained (15%, 4 steps) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 1.47 (9H, s), 1.68—1.79 (2H, m), 1.85—1.95 (2H, m), 2.87 (1H, dd, J=2.1, 16.3 Hz), 3.28—3.38 (2H, m), 3.47 (3H, s), 3.64—3.77 (3H, m), 3.98 (1H, d, J=14.1 Hz), 4.03 (1H, d, J=14.1 Hz), 4.09—4.20 (2H, m), 4.34—4.42

(1H, m), 5.17—5.24 (1H, m), 5.25 (2H, s), 6.29 (1H, dd, J=7.4, 15.9 Hz), 6.77 (1H, dd, J=2.5, 8.7 Hz), 6.81 (1H, d, J=2.5 Hz), 6.96 (1H, d, J=15.9 Hz), 7.14 (1H, d, J=8.6 Hz), 7.34 (1H, d, J=8.7 Hz), 7.47 (1H, dd, J=2.1, 8.6 Hz), 7.69 (1H, d, J=2.1 Hz).

Other derivatives (**21a**, **21d**, **21e**) were similarly prepared.

(*E*)-5-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-2-[2-(5-cyano-2-methoxyphenyl)ethen-1-yl]-1-(ethanesulfonyl)indoline (21b) To a solution of (*E*)-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-{2-[5-cyano-2-(methoxymethoxy)phenyl]ethen-1-yl}-1-(ethanesulfonyl)indoline **21a** (530 mg, 0.887 mmol) in EtOAc (5 ml) was added 4 N HCl in EtOAc (5 ml) at 0 °C and the mixture was stirred at room temperature for 4 h. The mixture was concentrated to give monohydrochloride of (*E*)-2-[2-(5-cyano-2-hydroxyphenyl)ethen-1-yl]-1-(ethanesulfonyl)-5-(piperidin-4-yloxy)indoline (514 mg) as a pale brown oil. To a solution of this oil (514 mg) in acetone (10 ml) and H_2O (10 ml) was added Boc_2O (203 mg, 0.930 mmol) and $NaHCO_3$ (82.0 mg, 0.976 mmol) at 0 °C and the mixture was stirred at room temperature for 5 h. The mixture was concentrated and the resulting residue was extracted with EtOAc. The organic layer was washed with NH_4Cl solution 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 (*E*)-5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-[2-(5-cyano-2-hydroxyphenyl)ethen-1-yl]-1-(ethanesulfonyl)indoline (472 mg, 0.852 mmol) as a colorless oil. To a solution of this oil (452 mg, 0.816 mmol) in benzene (16 ml) and MeOH (4 ml) was added (trimethylsilyl)diazomethane (2.0 M in hexane, 1.22 ml, 2.44 mmol) and the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **21b** (448 mg, 0.789 mmol, 93%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.4 Hz), 1.47 (9H, s), 1.67—1.79 (2H, m), 1.83—1.96 (2H, m), 2.89 (1H, dd, J=2.7, 16.4 Hz), 2.98—3.14 (2H, m), 3.26—3.39 (2H, m), 3.57 (1H, dd, J=9.7, 16.4 Hz), 3.63—3.75 (2H, m), 3.89 (3H, s), 4.33—4.42 (1H, m), 5.04—5.12 (1H, m), 6.30 (1H, dd, J=7.5, 16.0 Hz), 6.76 (1H, dd, J=2.4, 8.7 Hz), 6.79 (1H, d, J=2.4 Hz), 6.90 (1H, d, J=8.6 Hz), 6.93 (1H, d, J=16.0 Hz), 7.31 (1H, d, J=8.7 Hz), 7.51 (1H, dd, J=2.0, 8.6 Hz), 7.65 (1H, d, J=2.0 Hz).

Ethyl (*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(5-amidino-2-hydroxyphenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate Dihydrochloride (22c) Ethyl (*E*)-2-(5-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-2-{2-[5-cyano-2-(methoxymethoxy)phenyl]ethen-1-yl}indolin-1-ylsulfonyl)acetate **21c** was converted into **22c** by the similar procedure as that for **13a**. **22c** was obtained (23%, 3 steps) as a pink amorphous solid.

Other derivatives (**22a**, **22b**, **22d**, **22e**) were similarly prepared.

(*E*)-2-{5-[1-(Acetimidoyl)piperidin-4-yloxy]-2-[2-(5-amidino-2-hydroxyphenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetic Acid Dihydrochloride (22f) A solution of dihydrochloride of ethyl (*E*)-2-{5-[1-(acetimidoyl)piperidin-4-yloxy]-2-[2-(5-amidino-2-hydroxyphenyl)ethen-1-yl]indolin-1-ylsulfonyl}acetate **22c** (223 mg, 0.347 mmol) in 1 N HCl (10 ml) was stirred at 80 °C for 7.5 h. The mixture was concentrated and the resulting residue was purified by reverse-phase HPLC (YMC-pack ODS, YMC, H_2O/MeCN=9/1) to give the free base of **22f** as an amorphous solid. This solid was dissolved in 1 N HCl (10 ml) and the mixture was concentrated to give **22f** (143 mg, 0.247 mmol, 67%) as a pale brown amorphous solid.

Other derivatives (**22g**, **22h**) were similarly prepared.

Biology. Anti-FXa, Trypsin, FIIa and Plasmin Assay The hydrolysis of 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 enzyme and compounds in reaction buffer (50 mM Tris–HCl–150 mM NaCl, pH 8.4, as for plasmin: pH 7.4). Reactions were initiated by the addition of 10 μl of substrate and monitored for 5 min. The concentration required to inhibit enzyme activity by 50% (IC_{50}) was estimated from dose–response curves. Enzyme and substrate were used as follows: human FXa (0.5 IU, Enzyme Research Laboratories, Inc., IN, U.S.A.) and S-2222 (4 mM, Daiichi Pure Chemical, Japan); human trypsin (750 μU, Athens Research & Tech., Inc., GA, U.S.A.) and S-2222 (4 mM, Daiichi Pure Chemical, Japan); human alpha thrombin (1.25NIH u, Enzyme Research Laboratories, Inc., IN, U.S.A.) and S-2238 (4 mM, Daiichi Pure Chemical, Japan); human plasmin (8 μg, Enzyme Research Laboratories, Inc., IN, U.S.A.) and S-2251 (4 mM, Daiichi Pure Chemical, Japan).

Coagulation Assay Citrated blood samples were collected from healthy male volunteers (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) and activated partial thromboplastin time (APTT) were measured using Simplastin Excel (Organon Teknika, NC, U.S.A.) and Platelin LS (Organon Teknika, NC, U.S.A.), respectively. Coagulation times for each compound were compared with coagulation times measured using a distilled water 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.

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