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

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To develop a potent and oral anticoagulant, a series of compounds with cinnamyl moiety was synthesized and their factor Xa (FXa) inhibitory activities were examined. As a result, some cinnamyl derivatives showed potent FXa inhibitory activities *in vitro*. Among them, compounds with substituent at the 3-position on the central benzene ring represented by (*N*-{4-[1-(acetimidoyl)piperidin-4-yloxy]-3-chlorophenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetic acid dihydrochloride (45b) and (*N*-{4-[1-(acetimidoyl)piperidin-4-yloxy]-3-carbamoylphenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetic acid dihydrochloride (45j) exhibited potent FXa inhibitory activities with IC_{50} values of less than 10 nM *in vitro*. These compounds also showed potent anticoagulant activities both *in vitro* and *ex vivo*. Furthermore, these compounds exhibited no lethal toxicity (30 mg/kg, i.v.).

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

Thrombotic diseases, such as deep vein thrombosis and stroke, are major causes of mortality in developed countries. Current oral anticoagulant therapy for the prevention and treatment of thromboembolic disorders has many drawbacks: vitamin K antagonists interact with food and drugs and require frequent laboratory monitoring. Moreover, despite monitoring, many patients remain outside the therapeutic range for a considerable period, and still more patients are not treated due to these issues. Thus, effective oral anticoagulants for the prevention and treatment of thrombotic diseases have been highly desired. Recent research has focused on the development of small-molecule inhibitor of factor Xa (FXa), the protease at the pivotal point of the coagulation cascade with good oral bioavailability[3,4)] because it is thought that FXa inhibitor is more useful than warfarin.[5,6)]

We have researched for novel and orally active FXa inhibitors.[7—9)] In the previous research, we found optically active naphthylindoline derivative **1** and cinnamylindoline derivative **2**, having potent FXa inhibitory activities and anticoagulant activities *in vitro* (Fig. 1). However, compound **1** has less selectivity and compound **2** has less oral anticoagulant activity. In the synthetic aspects, compound **2** has some structural drawbacks, *i.e.* compound **2** needs multistep reactions for its preparation and it is a racemate with an asymmetric carbon at the 2-position on the indoline ring. Moreover, compound **2** has 4-hydroxybenzamidine moiety which is difficult to synthesize.[10)] In order to explore a potent and selective FXa inhibitor with oral activity and safety, we started further synthetic research. As a result, we found a series of cinnamyl derivatives with favorable characteristics. We describe the syntheses and structure-activity relationships (SARs) of cinnamyl derivatives.

Chemistry Bisamidine derivatives **17**—**21** with various linker chains between benzamidine moiety and ethanesulfonamide moiety were synthesized as shown in Chart 1. After reduction of a nitro group of compound **3**[7)] by catalytic hydrogenation, aniline **4** was reacted with ethanesulfonyl chloride under basic condition to give ethanesulfonamide **5**. Reduction of a carbonyl group of 3-cyanocinnamaldehyde (**6**)[9)] resulted in (*E*)-allyl alcohol **7**, which was reacted with $ClCO_2Et$ to give carbonate **8**. This carbonate **8** was subjected to Pd-catalyzed coupling reaction with ethanesulfonamide **5** to give compound **9**.[11)] 3-Cyanobenzaldehyde (**10**) was subjected to Wittig reaction,[12)] followed by deprotection of a tetrahydropyranyl group (THP) to give (*Z*)-allyl alcohol **11**. This allyl alcohol **11** and known alcohol[13)] **12** were subjected to Mitsunobu reaction[14)] with ethanesulfonamide **5** to give compounds **13** and **14**, respectively. 3-Cyanobenzyl bromide (**15**) was coupled with ethanesulfonamide **5** to give compound **16** under basic condition. These benzonitrile compounds **9**, **13**, **14** and **16** were converted to corresponding amidine compounds by bubbling HCl gas into an EtOH solution of benzonitriles, followed by amination of the resulting imidates (method A), or by treatment with hydroxylamine, followed by acetylation and hydrogenation of the resulting amidoximes (method B).[15)] The treatment of these amidine

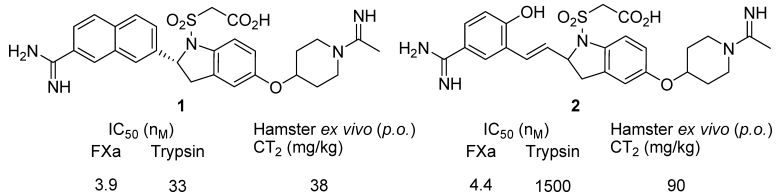

Fig. 1

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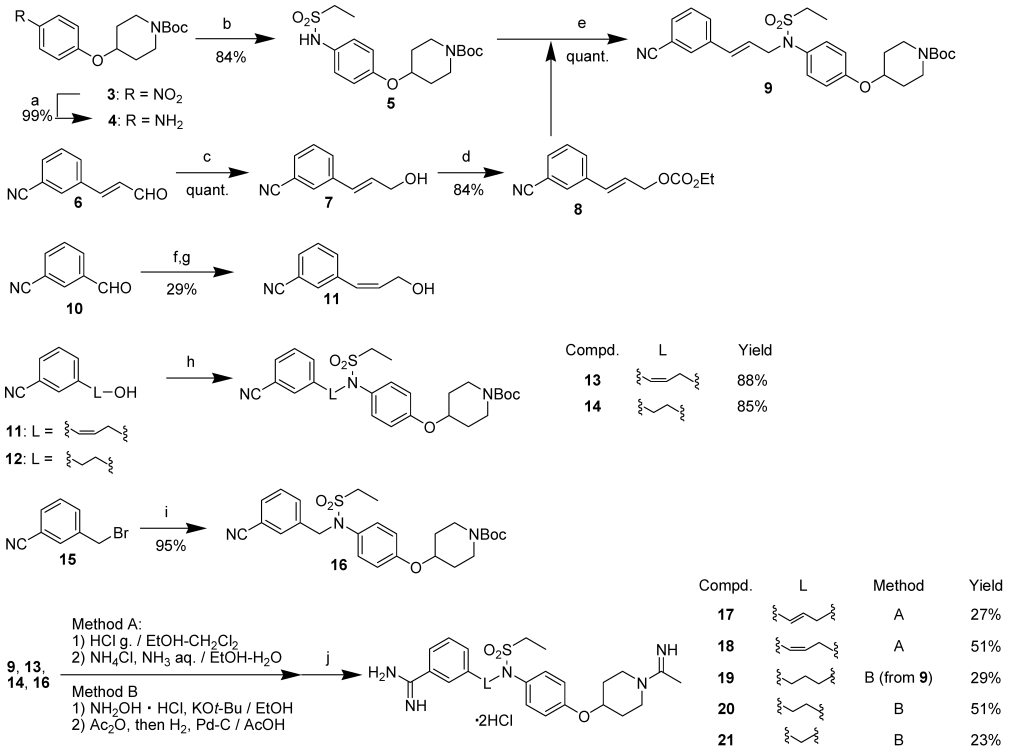
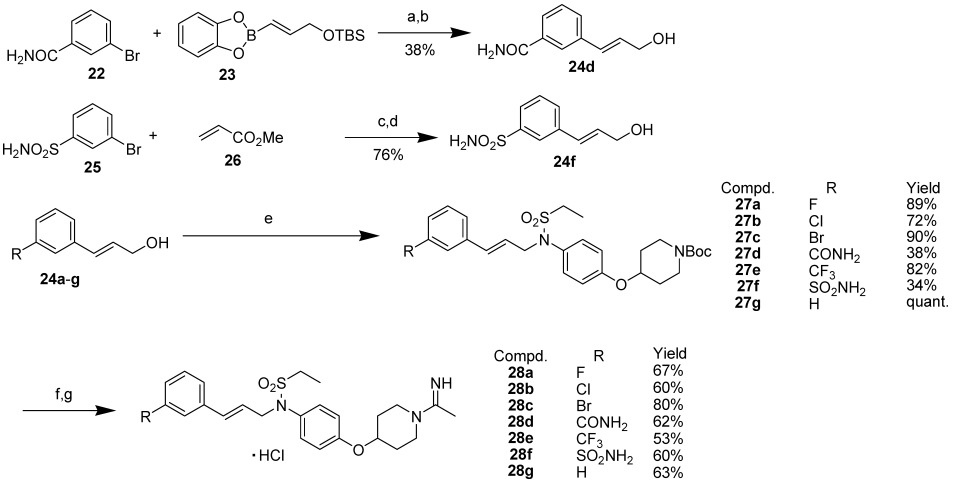


Reagents : a) H_2, Pd-C / MeOH; b) $EtSO_2Cl$, Pyr. / CH_2Cl_2; c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$ / CH_2Cl_2-EtOH; d) $ClCO_2Et$, Pyr. / CH_2Cl_2; e) $Pd_2(dba)_3 \cdot CHCl_3$, PPh_3 / THF; f) $BrPh_3P(CH_2)_2OTHP$, KHMDS / THF; g) *p*-TsOH・H_2O / MeOH; h) **5**, DEAD, PPh_3 / CH_2Cl_2; i) 5, KO*t*-Bu / THF-DMF; j) ethyl acetimidate・HCl, Et_3N / EtOH.

Chart 1



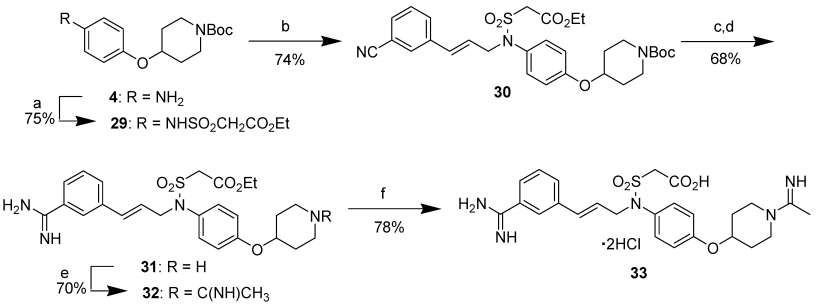
Reagents : a) $Pd(PPh_3)_4$, NaOEt / $PhCH_3$-EtOH; b) TBAF / THF; c) $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N / MeCN; d) DIBAL / CH_2Cl_2; e) **5**, DEAD, PPh_3 / CH_2Cl_2; f) HCl / dioxane-MeOH; g) ethyl acetimidate・HCl, Et_3N / EtOH.

Chart 2

compounds having the non-substituted amine moieties with ethyl acetimidate under basic conditions afforded bisamidine derivatives **17**—**21**, respectively. Regarding the derivative **19**, this derivative was synthesized from compound **9** *via* method B. Under this method, a double bond of the cinnamyl moiety was reduced.

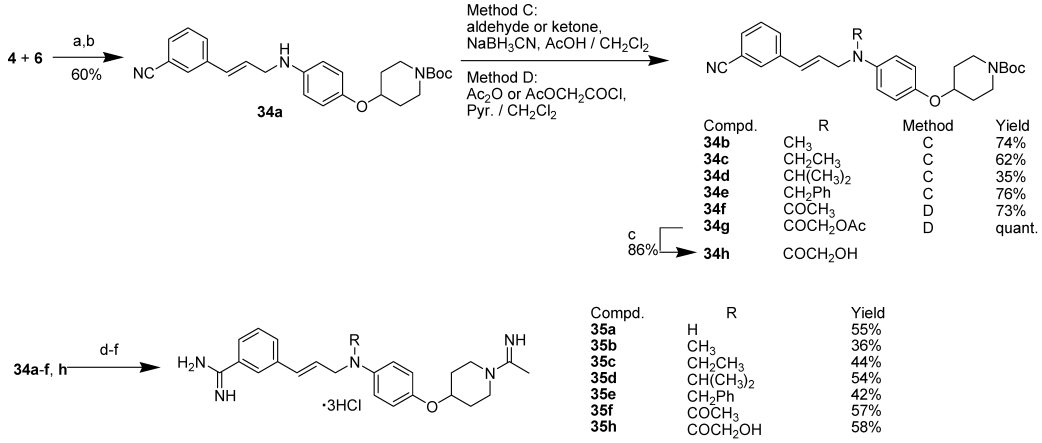
Compounds with various substituents instead of amidino group (**28a**—**g**) were synthesized as shown in Chart 2. Benzamide **22** was reacted with borate **23** by Suzuki–Miyaura cross coupling reaction to give allyl alcohol **24d**.[16] Benzenesulfonamide **25** was converted to allyl alcohol **24f** by Heck reaction,[17] followed by treatment with diisobutylaluminum hydride (DIBAL). These allyl alcohols **24d**, **24f** and known alcohols **24a**—**c**, **24e** and **24g**[18—20] were coupled with ethanesulfonamide **5** to give corresponding compounds **27a**—**g** by means of Mitsunobu reaction. *t*-Butoxycarbonyl (Boc) groups of compounds **27a**—**g** were converted to acetimidoyl groups to give compounds **28a**—**g** by 2 steps, respectively.

Cinnamyl derivative **33** with carboxymethylsulfonyl group on the central aniline moiety was synthesized as shown in Chart 3. The treatment of aniline **4** with ethoxycarbonyl-



Reagents : a) $EtO_2CCH_2SO_2Cl$, Pyr. / CH_2Cl_2; b) **7**, DEAD, PPh_3 / CH_2Cl_2; c) HCl g. / CH_2Cl_2-EtOH; d) NH_4Cl, NH_3 aq. / EtOH-H_2O; e) ethyl acetimidate・HCl, Et_3N / EtOH; f) 3_N HCl.

Chart 3



Reagents : a) MS 5A / $PhCH_3$; b) $NaBH_4$, $CeCl_3$・$7H_2O$ / EtOH; c) K_2CO_3 / MeOH; d) HCl g. / CH_2Cl_2-EtOH; e) NH_4Cl, NH_3 aq. / EtOH-H_2O; f) ethyl acetimidate・HCl, Et_3N / EtOH.

Chart 4

methylsulfonyl chloride[21] under basic condition afforded sulfonamide **29**. This sulfonamide **29** was coupled with allyl alcohol **7** by means of Mitsunobu reaction to give compound **30**. Compound **30** was converted to ethyl ester **32** by the same method described in Chart 1. The ester moiety of **32** was hydrolyzed under acidic condition to give corresponding carboxylic acid **33**.

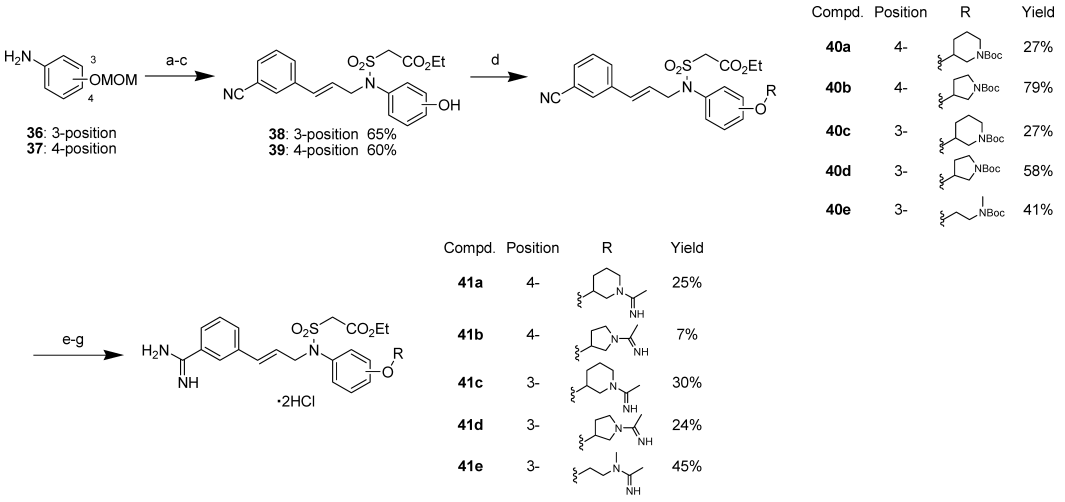
Cinnamyl derivatives with alkyl and acyl substituents on the central aniline moieties (**35a**—**f**, **h**) were synthesized as shown in Chart 4. Condensation of cinnamaldehyde **6** and aniline **4**, followed by reduction of resulting imine afforded compound **34a**. Various alkyl and acyl substituents were introduced on the nitrogen atom of compound **34a** to give corresponding compounds **34b**—**g** by reductive amination with aldehydes and ketones (method C), or reaction with corresponding acyl reagents under basic condition (method D). *N*-Alkyl or acyl compounds **34b**—**f**, **h** and *N*-H compound **34a** were subjected to the same reactions as cinnamyl derivative **32** to give compounds **35a**—**f** and **h**.

Cinnamyl derivatives with aminoalkyloxy moieties at the 3- or 4-position on the central benzene rings (**41a**—**e**) were synthesized as shown in Chart 5. 3- and 4-methoxymethoxyaniline (**36**, **37**)[22,23] were converted to phenols **38** and **39** by 3 steps. These phenols were coupled with alcohols by means of Mitsunobu reaction to give corresponding compounds **40a**—**e**. These compounds were subjected to the same reactions as shown in Chart 1 to give cinnamyl derivatives **41a**—**e**.

Cinnamyl derivatives with substituents on the central benzene ring were synthesized as shown in Chart 6. Mono- or disubstituted nitrophenols **42a**—**i** were coupled with *N*-Boc-4-hydroxypiperidine by means of Mitsunobu reaction to give corresponding compounds **43a**—**i**. Ethoxycarbonyl group of compound **43f** was converted to carbamoyl group (**43j**) by 2 steps. Nitro groups of these compounds were reduced to give corresponding anilines **44a**—**e** and **44g**—**j** by catalytic hydrogenation (method E), or treatment with zinc powder and acetic acid (method F). Anilines **44a**—**e** and **44g**—**j** were converted to cinnamyl derivatives **45a**—**e** and **45g**—**j** by the same method described in Chart 3, respectively.

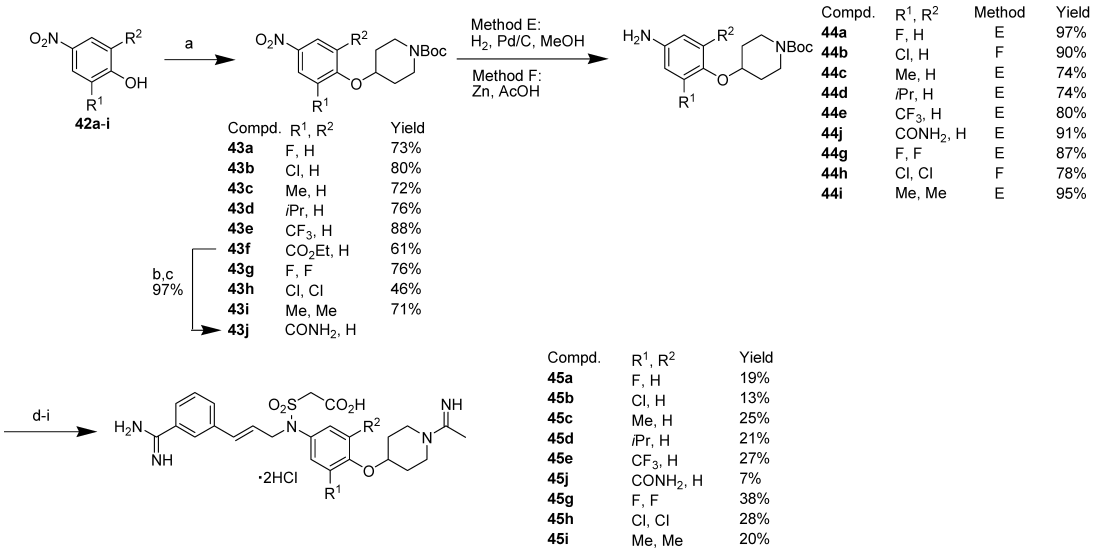
Results and Discussion

In vitro FXa and trypsin inhibitory activities of all compounds were evaluated and expressed as IC_{50} values. In the previous papers,[7—9] we intended to introduce an indoline ring in the center of the molecule to increase the molecular rigidity and enhance affinity towards FXa. As a result, we found that naphthylindoline derivatives and cinnamylindoline derivatives exhibited potent FXa inhibitory activities *in vitro*. However, the naphthylindoline derivative **1** also exhibited potent trypsin inhibitory activity and the cinnamylindoline derivative **2** exhibited low oral anticoagulant activity. Moreover,



Reagents : a) $EtO_2CCH_2SO_2Cl$, Pyr. / CH_2Cl_2; b) **7**, DEAD, PPh_3 / CH_2Cl_2; c) HCl /AcOEt; d) R-OH, DEAD, PPh_3 / CH_2Cl_2 or THF; e) HCl g. / CH_2Cl_2-EtOH; f) NH_4Cl, NH_3 aq. / EtOH-H_2O; g) ethyl acetimidate・HCl, Et_3N / EtOH.

Chart 5



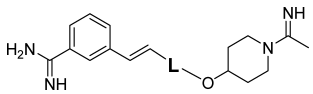
Reagents : a) 1-Boc-4-hydroxypiperidine, PPh_3, DEAD / CH_2Cl_2; b) KOH / EtOH; c) $ClCO_2Et$, Et_3N, NH_3 aq. / CH_2Cl_2; d) $ClO_2SCH_2CO_2Et$, Pyr. / CH_2Cl_2; e) **7**, DEAD, PPh_3 / CH_2Cl_2; f) HCl g. / CH_2Cl_2-EtOH; g) NH_4Cl, NH_3 aq. / EtOH-H_2O; h) ethyl acetimidate・HCl, Et_3N / EtOH; i) 3_N HCl.

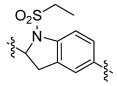
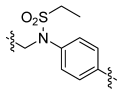
Chart 6

these derivatives have asymmetric carbons in their indoline structures. To assess the necessity of the indoline ring, we synthesized non-indoline compound **17** and compared its FXa inhibitory activity to previously tested indoline compound **46**[7] (Table 1). Non-indoline compound **17** showed potent FXa inhibitory activity comparable to **46** and, in addition, more improved selectivity over trypsin than that of **46**. This result suggests that indoline ring is not necessary for FXa inhibitory activity and the selectivity. Non-indoline derivative also has an advantage to have no asymmetric carbon in the structure. This result suggests that non-indoline structure had a potential to be a new lead framework for our research.

We introduced some chain structures as 'backbones' in the non-indoline compound **17** and their effects were examined (Table 2). An introduction of a *Z*-propenyl chain instead of the *E*-propenyl chain decreased the FXa inhibitory activity

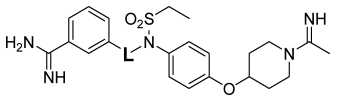
Table 1. FXa and Trypsin Inhibitory Activities of Compounds **46** and **17**



Compd.[a]	L	IC_{50} (nM)	
		FXa	Trypsin
46		12	120
17		14	780

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

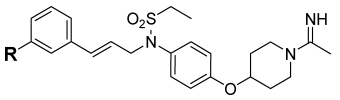
Table 2. FXa and Trypsin Inhibitory Activities of Compounds **17**—**21**



Compd.[a]	L	IC_{50} (nM)	
		FXa	Trypsin
17		14	780
18		88	7900
19		160	5800
20		1100	16000
21		430	3600

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

Table 3. FXa and Trypsin Inhibitory Activities of Compounds **17** and **28a**—**g**



Compd.[a]	R	IC_{50} (nM)	
		FXa	Trypsin
17	$C(NH)NH_2$	14	780
28a	F	9100	NA[b]
28b	Cl	210	NA[b]
28c	Br	1300	NA[b]
28d	$CONH_2$	61000	NA[b]
28e	CF_3	8800	NA[b]
28f	SO_2NH_2	20000	NA[b]
28g	H	5000	NA[b]

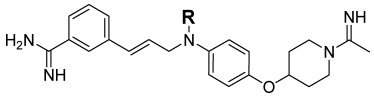
a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) Not active (>100000).

(**17** *vs.* **18**). Reduction of this double bond also decreased the activity (**17** *vs.* **19**). Regarding the length of the chain, shortening of this carbon chain did not improve the activity (**17** *vs.* **20** and **21**). From these results, we thought that *E*-propenyl, *i.e.* cinnamyl structure was suitable as a new lead framework.

Next, we attempted to optimize each moiety of this cinnamyl compound **17**. At the beginning, the effects of the substitutents on the ω-phenyl ring were examined (Table 3). Introduction of halogen atoms instead of an amidino group at the 3-position on the ω-phenyl ring decreased FXa inhibitory activity (**17** *vs.* **28a**, **28b** and **28c**). Introduction of a carbamoyl group at the same position resulted in minimal inhibitory activity (**17** *vs.* **28d**). Compounds having a trifluoromethyl group (**28e**) and a sulfonamide group (**28f**) also exhibited significantly lower inhibitory activity. In addition, non-substituted phenyl derivative **28g** also exhibited weak inhibitory activity. These results suggest that an amidino group is the suitable substituent at this position.

Next, the effects of the substituents on the central nitrogen atom were examined (Table 4). Compound **33** with a carboxymethylsulfonyl group and its ester form **32** exhibited *ca.* 2-fold higher FXa inhibitory activities than that of compound **17** with an ethanesulfonyl group. An introduction of a carboxyl group on the sulfonyl side chain enhanced the inhibitory activity. On the other hand, compound **35f** with an acetyl group and compound **35h** with a hydroxyacetyl group exhibited lower inhibitory activities. It seemed that FXa inhibitory activities of sulfonamide derivatives were superior to those of carboxamide derivatives. These tendencies were observed in the series of indoline derivatives.[8] In the present study, we introduced alkyl chain groups on the same position and their inhibitory activities were evaluated. Although non-substituted derivative **35a** exhibited lower FXa inhibitory activity, some alkyl derivatives, especially isopropyl derivative **35d**, exhibited potent FXa inhibitory activity. However, in acute toxicity tests in mice, all the mice died immediately after administration of compound **35d** (10 mg/kg, i.v.), while all the mice survived with no adverse reactions after administration of compound **33** (30 mg/kg, i.v.). From these results, we thought that a carboxymethylsulfonyl group was the most appropriate as the substituent of this part.

Table 4. FXa and Trypsin Inhibitory Activities of Compounds **17**, **32**, **33**, **35a**—**f** and **h**



Compd.[a]	R	IC_{50} (nM)	
		FXa	Trypsin
17	SO_2Et	14	780
32	$SO_2CH_2CO_2Et$	8.6	590
33	$SO_2CH_2CO_2H$	6.4	520
35f	$COCH_3$	53	2800
35h	$COCH_2OH$	40	1600
35a	H	28	960
35b	Me	14	640
35c	Et	13	760
35d	*i*-Pr	8.3	440
35e	CH_2Ph	13	490

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

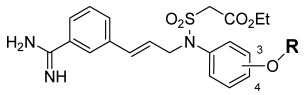
Table 5 shows the effect of acetimidoylpiperidine moiety attached to the central benzene ring. An introduction of a 3-piperidyl group (**40a**) instead of a 4-piperidyl group (**32**) exhibited 10-fold lower FXa inhibitory activity. Regarding the ring size, a translation from 6-membered ring (**32**) to 5-membered one (**40b**) significantly decreased the inhibitory activity. Regarding the substitution position connected to the central benzene ring, a translation from 4-position to 3-position exhibited much lower FXa inhibitory activities (**40a** *vs.* **40c**, **40b** *vs.* **40d**). An opening of the piperidine ring (**40e**) also exhibited no improvement about FXa inhibitory activity. From these results, it seemed that 4-(1-acetimidoyl-4-piperidyloxy)phenyl moiety is the most favorable as this part, and these tendencies were similar to those of indoline derivatives.[7]

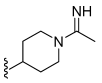
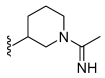
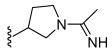
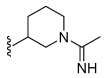
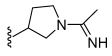
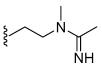
Table 6 shows the effects of the substituents at the 3- or/and 5-position on the central benzene ring against FXa and trypsin inhibitory activities. *In vitro* anticoagulant activities in human plasma and *ex vivo* effects on prothrombin time (PT) in hamster (*p.o.*) were also evaluated. All compounds synthesized with a substituent on the 3-position (**45a**—**e**, **j**) exhibited potent FXa inhibitory activities with

IC_{50} values of less than 10 nM and potent *in vitro* anticoagulant activities. Moreover, compounds **45a**—**c**, **e** and **j** also exhibited potent *ex vivo* anticoagulant activities comparable to that of nonsubstituted derivative **33** (*p.o.*). CT_2 values, the doses required to double clotting time, of these compounds were similar or superior to those of naphthylindoline derivative **1** (38 mg/kg) and cinnamylinndoline derivative **2** (90 mg/kg). Among them, 3-chloro derivative **45b** and 3-carbamoyl derivative **45j** exhibited superior anticoagulant effects. Regarding 3,5-disubstituted derivatives (**45g**, **45h** and **45i**), they all exhibited potent FXa inhibitory activity and relatively good selectivity over trypsin *in vitro*. These compounds also exhibited potent *in vitro* anticoagulant activities similar to non- and 3-substituted derivatives. Among them, difluoro derivative **45g** exhibited highly potent FXa inhibitory activity (3.7 nM). However, all of disubstituted derivatives including **45g** exhibited significantly lower *ex vivo* anticoagulant activities than those of 3-substituted derivatives (**45a** *vs.* **45g**, **45b** *vs.* **45h**, **45c** *vs.* **45i**). From these results, we found that non- and 3-substituted derivatives exhibited the potent *in vitro* and *ex vivo* anticoagulant activities. As a further evaluation, we examined acute toxicity tests in mice against our representative cinnamyl derivatives (**45b**, **45j**). These derivatives exhibited no lethal toxicity (30 mg/kg, i.v.).

In conclusion, we synthesized many amidine derivatives with the cinnamyl moiety and evaluated their FXa inhibitory activities and anticoagulant activities. Among them, a series of cimmanyl derivatives with substituent at the 3-position on the central benzene ring represented by **45b** and **45j** exhibited potent *in vitro* FXa inhibitory activities. Moreover, these compounds exhibited potent *in vitro* and *ex vivo* anticoagulant activities and some compounds also exhibited no lethal toxicity. These compounds are currently under further evaluation and we are continuing synthetic efforts to explore novel compounds having both more potent FXa inhibitory activities and favorable profiles.

Table 5. FXa and Trypsin Inhibitory Activities of Compounds **32** and **40a**—**e**



Compd.[a]	Position	R	IC_{50} (nM)	
			FXa	Trypsin
32	4-		8.6	590
40a[b]	4-		94	2900
40b[b]	4-		68	3300
40c[b]	3-		110	2400
40d[b]	3-		130	3000
40e	3-		250	3700

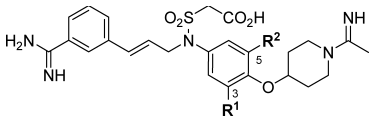
a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) A racemate.

Experimental

Mass spectra were obtained on a JEOL LCmate spectrometer. ^{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: br s=broad singlet, s=singlet, d=doublet, dd=double doublet, t=triplet, dt=double triplet, q=quartet and m=multiplet. IR spectra were obtained on a Jasco FT/IR-6100 spectrometer in KBr pellets. Merck Silica gel 60 (230—400 mesh) was used in the column chromatography. Tetrahydrofuran, *N*,*N*-dimethylformamide, and dimethylsulfoxide are abbreviated as THF, DMF and DMSO, respectively.

4-[(1-*t*-Butoxycarbonylpiperidin)-4-yloxy]aniline (4) A solution of 4-[(1-*t*-butoxycarbonylpiperidin)-4-yloxy]nitrobenzene **3** (11.9 g, 36.9 mmol) in MeOH (100 ml) was hydrogenated over 10% Pd–C (1.85 g) at room temperature for 4 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **4** (10.7 g, 36.6 mmol, 99%) as a pale red solid. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.65—1.76 (2H, m), 1.83—

Table 6. Enzyme Inhibitory Activities and *Ex Vivo* Anticoagulant Activities of Compounds **33**, **45a**—**e**, **45g**—**j**, **1** and **2**



Compd.[a]	R^1	R^2	IC_{50} (nM)		Human *in vitro* CT_2 (μM)[b]	Hamster *ex vivo* (*p.o.*, 1 h) CT_2 (mg/kg)[b]
			FXa	Trypsin		
33	H	H	6.4	520	0.39	34
45a	F	H	8.1	840	0.30	28
45b	Cl	H	7.4	520	0.24	14
45c	Me	H	5.0	850	0.17	34
45d	*i*-Pr	H	10	720	0.33	66
45e	CF_3	H	4.6	760	0.20	32
45j	$CONH_2$	H	7.1	320	0.37	16
45g	F	F	3.7	920	0.34	109
45h	Cl	Cl	9.8	2000	0.29	2.1 fold @ 100 mg
45i	Me	Me	12	7600	0.36	2.2 fold @ 100 mg
1			3.9	33	0.48	38
2			4.4	1500	0.39	90

a) All compounds were synthesized and evaluated as their hydrochlorides. *b*) The concentration required to double clotting time.

1.92 (2H, m), 3.22—3.32 (2H, m), 3.45 (2H, br s), 3.66—3.77 (2H, m), 4.23—4.30 (1H, m), 6.63 (2H, d, J=8.5 Hz), 6.76 (2H, d, J=8.5 Hz).

***N*-{4-[(1-*t*-Butoxycarbonylpiperidin)-4-yloxy]phenyl}ethanesulfonamide (5)** To a solution of 4-[(1-*t*-butoxycarbonylpiperidin)-4-yloxy]aniline **4** (10.6 g, 36.3 mmol) and pyridine (8.00 ml, 98.9 mmol) in CH_2Cl_2 (75 ml) was added $EtSO_2Cl$ (4.10 ml, 43.3 mmol), and the mixture was stirred at room temperature for 5 h. MeOH (1 ml) was added, and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **5** (11.7 g, 30.4 mmol, 84%) as a pale pink solid. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=8.0 Hz), 1.47 (9H, s), 1.70—1.80 (2H, m), 1.85—1.94 (2H, m), 3.07 (2H, q, J=8.0 Hz), 3.29—3.40 (2H, m), 3.64—3.74 (2H, m), 4.38—4.45 (1H, m), 6.40 (1H, br s), 6.88 (2H, d, J=9.0 Hz), 7.17 (2H, d, J=9.0 Hz).

(*E*)-3-(3-Cyanophenyl)-2-propen-1-ol (7) To a solution of 3-cyanocinnamaldehyde **6** (3.00 g, 19.1 mmol) in CH_2Cl_2 (30 ml) and EtOH (70 ml) were added $NaBH_4$ (1.32 g, 34.9 mmol) and $CeCl_3 \cdot 7H_2O$ (2.49 g, 6.68 mmol), and the mixture was stirred at 0 °C for 1.5 h. NH_4Cl solution 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=3/2) to give **7** (3.27 g, quant.) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 4.33—4.40 (2H, m), 6.43 (1H, dt, J=16.0, 5.0 Hz), 6.62 (1H, d, J=16.0 Hz), 7.43 (1H, t, J=8.0 Hz), 7.52 (1H, d, J=8.0 Hz), 7.60 (1H, d, J=8.0 Hz), 7.65 (1H, s).

Ethyl (*E*)-3-(3-Cyanophenyl)-2-propenyl Carbonate (8) To a solution of (*E*)-3-(3-cyanophenyl)-2-propen-1-ol **7** (403 mg, 2.53 mmol) and pyridine (1.00 ml, 12.4 mmol) in CH_2Cl_2 (6 ml) was added $ClCO_2Et$ (0.382 ml, 4.02 mmol), and the mixture was stirred at 0 °C for 2 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=4/1) to give **8** (492 mg, 2.13 mmol, 84%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.0 Hz), 4.24 (2H, q, J=7.0 Hz), 4.80 (2H, d, J=5.5 Hz), 6.36 (1H, dt, J=16.0, 5.5 Hz), 6.67 (1H, d, J=16.0 Hz), 7.44 (1H, t, J=8.0 Hz), 7.55 (1H, d, J=8.0 Hz), 7.61 (1H, d, J=8.0 Hz), 7.66 (1H, s).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]ethanesulfonamide (9)** To a suspension of ethyl (*E*)-3-(3-cyanophenyl)-2-propenyl carbonate **8** (1.04 g, 4.50 mmol) and *N*-{4-[(1-*t*-butoxycarbonylpiperidin)-4-yloxy]phenyl}ethanesulfonamide **5** (1.15 g, 2.99 mmol) in THF (6 ml) were added $Pd_2(dba)_3 \cdot CHCl_3$ (77 mg, 0.074 mmol) and PPh_3 (39 mg, 0.15 mmol), and the mixture was stirred at room temperature for 3 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=8/1) to give **9** (1.57 g, quant.) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 1.47 (9H, s), 1.69—1.80 (2H, m), 1.85—1.95 (2H, m), 3.06 (2H, q, J=7.0 Hz), 3.29—3.38 (2H, m), 3.63—3.73 (2H, m), 4.42 (2H, d, J=7.0 Hz), 4.42—4.48 (1H, m), 6.28 (1H, dt, J=15.5, 7.0 Hz), 6.42 (1H, d, J=15.5 Hz), 6.89 (2H, d, J=9.0 Hz), 7.26 (2H, d, J=9.0 Hz), 7.40 (1H, t, J=7.5 Hz), 7.49—7.55 (2H, m), 7.56 (1H, s).

(*Z*)-3-(3-Cyanophenyl)-2-propen-1-ol (11) To a suspension of triphenyl[(2-tetrahydropyranyl)oxyethyl]phosphonium bromide (4.72 g, 10.0 mmol) in THF (60 ml) was added potassium bis(trimethylsilyl)amide (KHMDS) (0.5 M in toluene, 20 ml, 10 mmol) at −78 °C, and the mixture was stirred at −78 °C for 3 h. 3-Cyanobenzaldehyde **10** (1.05 g, 8.01 mmol) in THF (20 ml) was added, and the mixture was stirred at −20 °C for 2 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=2/1) to give (*Z*)-3-(3-cyanophenyl)-1-(tetrahydropyran-2-yloxy)-2-propene (598 mg, 2.46 mmol, 31%) as an oil. This oil (555 mg, 2.28 mmol) was dissolved in MeOH (20 ml) and treated with *p*-TsOH·H_2O (97 mg, 0.51 mmol). The solution was stirred at room temperature for 1 h and the solution was added $NaHCO_3$ solution. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **11** (342 mg, 2.15 mmol, 94%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 4.36—4.44 (2H, m), 6.02 (1H, dt, J=11.5, 6.0 Hz), 6.55 (1H, d, J=11.5 Hz), 7.45—7.57 (4H, m).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*Z*)-3-(3-cyanophenyl)-2-propenyl]ethanesulfonamide (13)** Diethyl azodicarboxylate (DEAD) (0.438 ml, 2.78 mmol) was added to a solution of *N*-{4-[(1-*t*-butoxycarbonylpiperidin)-4-yloxy]phenyl}ethanesulfonamide **5** (823 mg, 2.14 mmol), (*Z*)-3-(3-cyanophenyl)-2-propen-1-ol **11** (340 mg, 2.14 mmol) and PPh_3 (730 mg, 2.79 mmol) in CH_2Cl_2 (20 ml), and the resulting mixture was stirred at 0 °C for 3 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=10/1) to give **13** (1.28 g, 2.44 mmol, 88%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.5 Hz), 1.47 (9H, s), 1.71—1.82 (2H, m), 1.86—1.96 (2H, m), 3.03 (2H, q, J=7.5 Hz), 3.29—3.38 (2H, m), 3.65—3.75 (2H, m), 4.41 (2H, d, J=6.5 Hz), 4.44—4.51 (1H, m), 5.87 (1H, dt, J=12.0, 6.5 Hz), 6.50 (1H, d, J=12.0 Hz), 6.88 (2H, d, J=9.0 Hz), 7.11 (1H, s), 7.18 (2H, d, J=9.0 Hz), 7.25 (1H, d, J=8.0 Hz), 7.39 (1H, t, J=8.0 Hz), 7.51 (1H, d, J=8.0 Hz).

Similarly, compound **14** was prepared.

14: MS m/z: 514 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=8.0 Hz), 1.48 (9H, s), 1.71—1.82 (2H, m), 1.88—1.99 (2H, m), 2.84—2.90 (2H, m), 2.97 (2H, q, J=8.0 Hz), 3.33—3.40 (2H, m), 3.66—3.75 (2H, m), 3.88—3.94 (2H, m), 4.45—4.51 (1H, m), 6.91 (2H, d, J=9.0 Hz), 7.21 (2H, d, J=9.0 Hz), 7.37—7.45 (3H, m), 7.51 (1H, d, J=8.0 Hz).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-(3-cyanobenzyl)ethanesulfonamide (16)** To a solution of *N*-{4-[(1-*t*-butoxycarbonylpiperidin)-4-yloxy]phenyl}ethanesulfonamide **5** (1.15 g, 3.00 mmol) in THF (25 ml) was added KO*t*-Bu (336 mg, 3.00 mmol), and the mixture was stirred at room temperature for 15 min. 3-Cyanobenzyl bromide **15** (588 mg, 3.00 mmol) in DMF (7 ml) was added, and the resulting mixture was stirred at room temperature for 30 min. H_2O was added, and the mixture was extracted with EtOAc–Et_2O (1/1). The organic layer was washed with H_2O and brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=12/1) to give **16** (1.42 g, 2.84 mmol, 95%) as a colorless amorphous solid. MS m/z: 500 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=8.0 Hz), 1.46 (9H, s), 1.66—1.77 (2H, m), 1.84—1.95 (2H, m), 3.09 (2H, q, J=8.0 Hz), 3.28—3.37 (2H, m), 3.63—3.72 (2H, m), 4.38—4.45 (1H, m), 4.84 (2H, s), 6.83 (2H, d, J=9.0 Hz), 7.12 (2H, d, J=9.0 Hz), 7.42 (1H, t, J=8.0 Hz), 7.48 (1H, s), 7.53—7.61 (2H, m).

***N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]ethanesulfonamide Dihydrochloride (17) (Method A)** Into a solution of *N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]ethanesulfonamide **9** (955 mg, 1.82 mmol) in CH_2Cl_2 (40 ml) and EtOH (20 ml) was bubbled hydrogen chloride under ice-cooling, and the resulting mixture was stirred at room temperature under tightly sealed condition for 9 h. The mixture was concentrated and the resulting residue was dissolved in EtOH (30 ml) and H_2O (10 ml). The solution was treated with NH_4Cl (193 mg, 3.61 mmol) and NH_3 solution (0.375 ml, 6.17 mmol) and the mixture was allowed to stand overnight at room temperature. The mixture was concentrated and the resulting residue was dissolved in MeOH (20 ml) and a 4 N solution of hydrogen chloride in dioxane (2 ml). The solution was concentrated and the resulting residue was purified by a preparative HPLC (YMC-Pack ODS, YMC Corp., H_2O/MeCN=17/3) to give an amorphous solid. This amorphous solid was dissolved in MeOH (10 ml) and a 4 N solution of hydrogen chloride in dioxane (1 ml), and the mixture was concentrated. The resulting residue was lyophilized to give *N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[4-(piperidin-4-yloxy)phenyl]ethanesulfonamide dihydrochloride (354 mg, 0.687 mmol, 44%) as a colorless amorphous solid. This amorphous solid (311 mg, 0.603 mmol) was dissolved in EtOH (10 ml) and treated with ethyl acetimidate hydrochloride (260 mg, 2.10 mmol) and Et_3N (0.500 ml, 3.61 mmol). The mixture was stirred at room temperature for 12 h, and added a 4 N solution of hydrogen chloride in dioxane (1 ml). The mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=4/1) to give an amorphous solid. This amorphous solid was dissolved in MeOH (10 ml) and a 4 N solution of hydrogen chloride in dioxane (0.50 ml), and the mixture was concentrated. The resulting residue was lyophilized to give **17** (243 mg, 0.437 mmol, 72%) as a colorless amorphous solid. MS m/z: 484 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.0 Hz), 1.65—1.78 (2H, m), 1.98—2.10 (2H, m), 2.30 (3H, s), 3.18 (2H, q, J=7.0 Hz), 3.50—3.59 (2H, m), 3.69—3.75 (1H, m), 3.80—3.88 (1H, m), 4.45 (2H, d, J=6.0 Hz), 4.66—4.74 (1H, m), 6.46 (1H, dt, J=15.5, 6.0 Hz), 6.55 (1H, d, J=15.5 Hz), 7.01 (2H, d, J=9.0 Hz), 7.37 (2H, d, J=9.0 Hz), 7.54 (1H, t, J=8.0 Hz), 7.67—7.75 (2H, m), 7.91 (1H, s). IR (KBr) cm^{-1}: 1674, 1625. *Anal.* Calcd for $C_{25}H_{33}N_5O_3S \cdot 2HCl \cdot 1.1H_2O$: C, 52.10; H, 6.51; N, 12.15; Cl, 12.30; S, 5.56. Found: C, 51.85; H, 6.40; N, 12.00; Cl, 12.64; S, 5.66.

Similarly, compound **18** was prepared.

18: MS m/z: 484 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz), 1.67—1.79 (2H, m), 1.99—2.11 (2H, m), 2.31 (3H, s), 3.18 (2H, q, J=7.0 Hz), 3.49—3.61 (2H, m), 3.69—3.75 (1H, m), 3.80—3.88 (1H, m), 4.61 (2H, d, J=5.5 Hz), 4.67—4.75 (1H, m), 5.79 (1H, dt, J=11.5, 5.5 Hz), 6.54 (1H, d, J=11.5 Hz), 6.98 (2H, d, J=9.0 Hz), 7.30 (2H, d, J=9.0 Hz), 7.52 (1H, d, J=7.5 Hz), 7.55—7.61 (2H, m), 7.73 (1H, d, J=7.5 Hz). IR

(KBr) cm^{-1}: 1674, 1626. *Anal.* Calcd for $C_{25}H_{33}N_5O_3S \cdot 2.0HCl \cdot 1.5H_2O$: C, 51.45; H, 6.56; N, 12.00; Cl, 12.15; S, 5.49. Found: C, 51.29; H, 6.46; N, 11.99; Cl, 12.11; S, 5.28.

***N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[3-(3-amidinophenyl)propyl]ethanesulfonamide Dihydrochloride (19) (Method B)** To a solution of *N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]ethanesulfonamide **9** (611 mg, 1.16 mmol) in MeOH (20 ml) were added hydroxylamine hydrochloride (84.6 mg, 1.22 mmol) and KO*t*-Bu (130 mg, 1.16 mmol), and the mixture was refluxed for 3 h. Hydroxylamine hydrochloride (84.0 mg, 1.21 mmol) and KO*t*-Bu (130 mg, 1.16 mmol) were added, and the mixture was refluxed for 5 h. Hydroxylamine hydrochloride (84.0 mg, 1.21 mmol) and KO*t*-Bu (130 mg, 1.16 mmol) were added, and the mixture was refluxed for 8 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=20/1) to give a pale green amorphous solid. This amorphous solid was dissolved in AcOH (8 ml) and treated with Ac_2O (0.142 ml, 1.51 mmol). After stirring at room temperature for 15 min, the mixture was hydrogenated over 10% Pd–C (60 mg) at room temperature for 5 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was dissolved in MeOH (20 ml) and treated with a 4 N solution of hydrogen chloride in dioxane (5.0 ml). The mixture was stirred at room temperature for 10 min. The mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC, H_2O/MeCN=17/3) to give *N*-[3-(3-amidinophenyl)propyl]-*N*-[4-(piperidin-4-yloxy)phenyl]ethanesulfonamide dihydrochloide (282 mg, 0.634 mmol, 55%) as a colorless amorphous solid. This amorphous solid (253 mg, 0.569 mmol) was dissolved in EtOH (10 ml) and treated with ethyl acetimidate hydrochloride (211 mg, 1.71 mmol) and Et_3N (0.396 ml, 2.85 mmol). The mixture was stirred at room temperature for 13 h, and then added a 4 N solution of hydrogen chloride in dioxane (2 ml). The mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=4/1) to give an amorphous solid. This amorphous solid was dissolved in MeOH (10 ml) and a 4 N solution of hydrogen chloride in dioxane (0.500 ml), and the mixture was concentrated. The resulting residue was lyophilized to give **19** (164 mg, 0.294 mmol, 52%) as a colorless amorphous solid. MS *m/z*: 486 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, *J*=7.5 Hz), 1.64—1.82 (4H, m), 2.01—2.11 (2H, m), 2.31 (3H, s), 2.68 (2H, t, *J*=7.5 Hz), 3.09 (2H, q, *J*=7.5 Hz), 3.50—3.88 (6H, m), 4.69—4.75 (1H, m), 7.04 (2H, d, *J*=9.0 Hz), 7.34 (2H, d, *J*=9.0 Hz), 7.47—7.66 (4H, m). IR (KBr) cm^{-1}: 1674, 1624, 1330, 1143. *Anal.* Calcd for $C_{25}H_{35}N_5O_3S \cdot 2.0HCl \cdot 1.3H_2O$: C, 51.59; H, 6.86; N, 12.03; Cl, 12.18; S, 5.51. Found: C, 51.64; H, 6.80; N, 12.12; Cl, 12.23; S, 5.56.

Similarly, compounds **20** and **21** were prepared.

20: MS *m/z*: 472 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, *J*=7.5 Hz), 1.68—1.82 (2H, m), 2.02—2.12 (2H, m), 2.34 (3H, s), 2.78 (2H, t, *J*=8.0 Hz), 3.09 (2H, q, *J*=7.5 Hz), 3.52—3.97 (6H, m), 4.70—4.77 (1H, m), 7.04 (2H, d, *J*=9.0 Hz), 7.32 (2H, d, *J*=9.0 Hz), 7.49—7.54 (2H, m), 7.69—7.75 (2H, m). IR (KBr) cm^{-1}: 1672, 1626, 1330, 1143. *Anal.* Calcd for $C_{24}H_{33}N_5O_3S \cdot 2.2HCl \cdot 1.9H_2O$: C, 49.19; H, 6.71; N, 11.95; Cl, 13.31; S, 5.47. Found: C, 49.37; H, 6.42; N, 11.87; Cl, 13.44; S, 5.42.

21: MS *m/z*: 458 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.30 (3H, t, *J*=7.5 Hz), 1.62—1.76 (2H, m), 1.96—2.06 (2H, m), 2.29 (3H, s), 3.24 (2H, q, *J*=7.5 Hz), 3.46—3.84 (4H, m), 4.63—4.69 (1H, m), 4.93 (2H, s), 6.94 (2H, d, *J*=8.5 Hz), 7.33 (2H, d, *J*=8.5 Hz), 7.51—7.71 (4H, m). IR (KBr) cm^{-1}: 1672, 1625, 1332, 1146. *Anal.* Calcd for $C_{23}H_{31}N_5O_3S \cdot 2.0HCl \cdot 1.7H_2O$: C, 49.23; H, 6.54; N, 12.48; Cl, 12.64; S, 5.71. Found: C, 49.12; H, 6.80; N, 12.53; Cl, 12.73; S, 5.55.

(*E*)-3-(3-Carbamoylphenyl)-2-propen-1-ol (24d) A mixture of 1-(*t*-butyldimethylsilyloxy)-2-propyne (1.70 g, 10.0 mmol) and catecholborane (1.07 ml, 10.0 mmol) was stirred at 60 °C for 3 h and added toluene (20 ml) at room temperature. To the solution were added 3-bromobenzamide **22** (1.40 g, 7.00 mmol), $Pd(PPh_3)_4$ (405 mg, 0.350 mmol) and NaOEt (2.9 M in EtOH, 3.4 ml, 10.0 mmol), and the mixture was refluxed for 5 h. The reaction mixture was poured into a 1 N solution of NaOH (40 ml) 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=5/4) to give (*E*)-1-(*t*-butyldimethylsilyloxy)-3-(3-carbamoylphenyl)-2-propene (1.17 g, 4.01 mmol, 57%) as a colorless solid. This solid (1.17 g, 4.01 mmol) was dissolved in THF (20 ml) and treated with TBAF (1.0 M in THF, 4.8 ml, 4.8 mmol). The solution was stirred at room temperature for 1 h and then added brine. The mixture was extracted with EtOAc and CH_2Cl_2, and these organic layers were combined. The combined organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeCN=1/1) to give **24d** (470 mg, 2.65 mmol, 66%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 4.12—4.18 (2H, m), 6.48 (1H, dt, *J*=16.5, 5.0 Hz), 6.60 (1H, d, *J*=16.5 Hz), 7.39 (1H, t, *J*=8.0 Hz), 7.55 (1H, d, *J*=8.0 Hz), 7.72 (1H, d, *J*=8.0 Hz), 7.93 (1H, s).

(*E*)-3-(3-Sulfamoylphenyl)-2-propen-1-ol (24f) To a solution of 3-bromobenzenesulfonamide **25** (2.13 g, 9.00 mmol) and methyl acrylate **26** (0.973 ml, 10.8 mmol) in MeCN (9.5 ml) were added $Pd(OAc)_2$ (101 mg, 0.450 mmol), P(*o*-tol)$_3$ (274 mg, 0.900 mmol) and Et_3N (1.81 ml, 13.0 mmol), and the mixture was stirred at 100 °C in a sealed tube for 3 h. The reaction mixture was filtered through a pad of SiO_2, and the resulting solution was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=1/1) to give ethyl 3-sulfamoylcinnamate (1.86 g, 7.70 mmol, 86%) as a pale yellow solid. This solid (1.62 g, 6.71 mmol) was suspended in CH_2Cl_2 (70 ml) and treated with DIBAL (1.5 M in toluene, 22.0 ml, 33.6 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h and added additional DIBAL (1.5 M in toluene, 6.70 ml, 10.1 mmol). The mixture was allowed to become warm to room temperature for 2 h. To the reaction mixture were added a 1 N solution of hydrogen chloride and brine, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=1/1) to give **24f** (1.26 g, 5.90 mmol, 88%) as pale yellow crystals. MS *m/z*: 214 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 4.10—4.18 (2H, m), 6.48 (1H, dt, *J*=16.0, 5.0 Hz), 6.62 (1H, d, *J*=16.0 Hz), 7.50 (1H, t, *J*=7.5 Hz), 7.61—7.67 (2H, m), 7.85 (1H, s).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-fluorophenyl)-2-propenyl]ethanesulfonamide (27a)** (*E*)-3-(3-Fluorophenyl)-2-propen-1-ol **24a** was converted to **27a** by the same procedure as that for **13**. Compound **27a** was obtained (89%) as a colorless amorphous solid. MS *m/z*: 519 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=8.0 Hz), 1.47 (9H, s), 1.68—1.78 (2H, m), 1.85—1.95 (2H, m), 3.06 (2H, q, *J*=8.0 Hz), 3.28—3.38 (2H, m), 3.62—3.78 (2H, m), 4.37—4.47 (3H, m), 6.20 (1H, dt, *J*=15.5, 7.0 Hz), 6.39 (1H, d, *J*=15.5 Hz), 6.86—7.08 (5H, m), 7.22—7.28 (3H, m).

Similarly, compounds **27b**—**g** were prepared.

27b: MS *m/z*: 535 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=7.5 Hz), 1.47 (9H, s), 1.69—1.79 (2H, m), 1.86—1.95 (2H, m), 3.06 (2H, q, *J*=7.5 Hz), 3.29—3.38 (2H, m), 3.63—3.73 (2H, m), 4.37—4.49 (3H, m), 6.21 (1H, dt, *J*=16.0, 6.5 Hz), 6.36 (1H, d, *J*=16.0 Hz), 6.88 (2H, d, *J*=9.0 Hz), 7.16—7.30 (6H, m).

27c: MS *m/z*: 579 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=8.0 Hz), 1.47 (9H, s), 1.69—1.78 (2H, m), 1.86—1.95 (2H, m), 3.06 (2H, q, *J*=8.0 Hz), 3.29—3.37 (2H, m), 3.64—3.73 (2H, m), 4.37—4.47 (3H, m), 6.19 (1H, dt, *J*=15.5, 7.0 Hz), 6.35 (1H, d, *J*=15.5 Hz), 6.88 (2H, d, *J*=9.0 Hz), 7.14—7.28 (4H, m), 7.36 (1H, d, *J*=8.0 Hz), 7.44 (1H, s).

27d: MS *m/z*: 544 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=8.0 Hz), 1.46 (9H, s), 1.69—1.78 (2H, m), 1.85—1.95 (2H, m), 3.07 (2H, q, *J*=8.0 Hz), 3.29—3.38 (2H, m), 3.62—3.72 (2H, m), 4.38—4.48 (3H, m), 6.28 (1H, dt, *J*=15.5, 6.0 Hz), 6.46 (1H, d, *J*=15.5 Hz), 6.88 (2H, d, *J*=9.0 Hz), 7.26 (2H, d, *J*=9.0 Hz), 7.38 (1H, t, *J*=8.0 Hz), 7.47 (1H, d, *J*=8.0 Hz), 7.63 (1H, d, *J*=8.0 Hz), 7.77 (1H, s).

27e: MS *m/z*: 569 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, *J*=7.5 Hz), 1.46 (9H, s), 1.67—1.79 (2H, m), 1.84—1.96 (2H, m), 3.07 (2H, q, *J*=7.5 Hz), 3.28—3.38 (2H, m), 3.63—3.72 (2H, m), 4.39—4.48 (3H, m), 6.28 (1H, dt, *J*=15.5, 6.5 Hz), 6.45 (1H, d, *J*=15.5 Hz), 6.89 (2H, d, *J*=9.0 Hz), 7.25—7.54 (6H, m).

27f: MS *m/z*: 580 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=7.5 Hz), 1.46 (9H, s), 1.67—1.77 (2H, m), 1.83—1.94 (2H, m), 3.07 (2H, q, *J*=7.5 Hz), 3.27—3.37 (2H, m), 3.61—3.71 (2H, m), 4.38—4.48 (3H, m), 6.30 (1H, dt, *J*=16.0, 6.0 Hz), 6.44 (1H, d, *J*=16.0 Hz), 6.88 (2H, d, *J*=9.0 Hz), 7.26 (2H, d, *J*=9.0 Hz), 7.39—7.51 (2H, m), 7.77 (1H, d, *J*=7.5 Hz), 7.85 (1H, s).

27g: MS *m/z*: 501 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, *J*=7.5 Hz), 1.46 (9H, s), 1.65—1.97 (4H, m), 3.06 (2H, q, *J*=7.5 Hz), 3.26—3.40 (2H, m), 3.58—3.75 (2H, m), 4.35—4.48 (3H, m), 6.20 (1H, dt, *J*=16.0, 6.5 Hz), 6.42 (1H, d, *J*=16.0 Hz), 6.87 (2H, d, *J*=9.0 Hz), 7.22—7.33 (7H, m).

***N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-fluorophenyl)-2-propenyl]ethanesulfonamide Hydrochloride (28a)** To a solution of *N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-fluorophenyl)-2-propenyl]ethanesulfonamide **27a** (1.07 g, 2.06 mmol) in MeOH (20 ml) was added a 4 N solution of hydrogen chloride in dioxane (5 ml), and the mixture was stirred overnight at room temperature. The mixture was concentrated and the resulting residue was recrystallized from MeOH to give *N*-[(*E*)-3-(3-fluorophenyl)-2-propenyl]-*N*-[4-(piperidin-4-

yloxy)phenyl]ethanesulfonamide monohydrochloride (765 mg, 1.68 mmol, 82%) as colorless crystals. The crystals (300 mg, 0.659 mmol) were dissolved in MeOH (20 ml) and treated with ethyl acetimidate hydrochloride (244 mg, 1.97 mmol) and Et_3N (0.37 ml, 2.67 mmol). The mixture was stirred overnight at room temperature, and then added a 4 N solution of hydrogen chloride in dioxane (0.5 ml). The mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=11/9) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride (0.300 ml), and the mixture was concentrated. The resulting residue was lyophilized to give **28a** (268 mg, 0.540 mmol, 82%) as a colorless amorphous solid. MS *m/z*: 460 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.5 Hz), 1.65—1.79 (2H, m), 1.99—2.10 (2H, m), 2.28 (3H, s), 3.17 (2H, q, J=7.5 Hz), 3.45—3.57 (2H, m), 3.66—3.81 (2H, m), 4.40 (2H, d, J=6.0 Hz), 4.64—4.71 (1H, m), 6.29 (1H, dt, J=16.0, 6.0 Hz), 6.46 (1H, d, J=16.0 Hz), 6.98—7.08 (3H, m), 7.20 (1H, d, J=8.0 Hz), 7.23—7.38 (4H, m). IR (KBr) cm^{-1}: 1673, 1624, 1334, 1145. *Anal.* Calcd for $C_{24}H_{30}FN_3O_3S \cdot 1.1HCl \cdot 1.7H_2O$: C, 54.36; H, 6.56; N, 7.92; Cl, 7.35; F, 3.58; S, 6.05. Found: C, 54.50; H, 6.32; N, 8.06; Cl, 7.28; F, 3.69; S, 6.23.

Similarly, compounds **28b**—**g** were prepared.

28b: MS *m/z*: 476 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.5 Hz), 1.66—1.79 (2H, m), 1.99—2.09 (2H, m), 2.30 (3H, s), 3.18 (2H, q, J=7.5 Hz), 3.44—3.88 (4H, m), 4.41 (2H, d, J=7.0 Hz), 4.64—4.72 (1H, m), 6.33 (1H, dt, J=15.5, 7.0 Hz), 6.46 (1H, d, J=15.5 Hz), 7.00 (2H, d, J=9.0 Hz), 7.27—7.38 (5H, m), 7.48 (1H, s). IR (KBr) cm^{-1}: 1672, 1623, 1334, 1146. *Anal.* Calcd for $C_{24}H_{30}ClN_3O_3S \cdot 1.0HCl \cdot 0.5H_2O$: C, 55.28; H, 6.19; N, 8.06; Cl, 13.60; S, 6.15. Found: C, 55.30; H, 5.89; N, 7.95; Cl, 13.69; S, 6.17.

28c: MS *m/z*: 520 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7.5 Hz), 1.64—1.79 (2H, m), 1.98—2.10 (2H, m), 2.28 (3H, s), 3.17 (2H, q, J=7.5 Hz), 3.44—3.57 (2H, m), 3.66—3.82 (2H, m), 4.40 (2H, d, J=6.0 Hz), 4.64—4.72 (1H, m), 6.32 (1H, dt, J=16.0, 6.0 Hz), 6.44 (1H, d, J=16.0 Hz), 6.99 (2H, d, J=8.5 Hz), 7.23—7.44 (5H, m), 7.61 (1H, s). IR (KBr) cm^{-1}: 1672, 1624, 1334, 1146. *Anal.* Calcd for $C_{24}H_{30}BrN_3O_3S \cdot 1.1HCl \cdot 1.4H_2O$: C, 49.21; H, 5.83; N, 7.17; Br, 13.64; Cl, 6.66; S, 5.47. Found: C, 48.83; H, 5.74; N, 7.20; Br, 14.07; Cl, 6.64; S, 5.45.

28d: MS *m/z*: 485 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7.5 Hz), 1.66—1.79 (2H, m), 1.98—2.09 (2H, m), 2.28 (3H, s), 3.18 (2H, q, J=7.5 Hz), 3.45—3.57 (2H, m), 3.67—3.81 (2H, m), 4.43 (2H, d, J=6.0 Hz), 4.63—4.72 (1H, m), 6.32 (1H, dt, J=16.0, 6.0 Hz), 6.49 (1H, d, J=16.0 Hz), 7.00 (2H, d, J=9.0 Hz), 7.31—7.42 (3H, m), 7.50 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1671, 1618, 1331, 1145. *Anal.* Calcd for $C_{25}H_{32}N_4O_4S \cdot 1.2HCl \cdot 1.5H_2O$: C, 54.07; H, 6.57; N, 10.09; Cl, 7.66; S, 5.77. Found: C, 53.85; H, 6.33; N, 10.15; Cl, 7.68; S, 6.18.

28e: MS *m/z*: 510 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7.0 Hz), 1.67—1.79 (2H, m), 2.00—2.09 (2H, m), 2.29 (3H, s), 3.18 (2H, q, J=7.0 Hz), 3.45—3.83 (4H, m), 4.43 (2H, d, J=5.5 Hz), 4.64—4.72 (1H, m), 6.42 (1H, dt, J=16.5, 5.5 Hz), 6.58 (1H, d, J=16.5 Hz), 7.00 (2H, d, J=9.0 Hz), 7.38 (2H, d, J=9.0 Hz), 7.51—7.75 (4H, m). IR (KBr) cm^{-1}: 1672, 1623, 1333, 1146. *Anal.* Calcd for $C_{25}H_{30}F_3N_3O_3S \cdot 1.0HCl \cdot 1.0H_2O$: C, 53.23; H, 5.90; N, 7.45; Cl, 6.29; F, 10.10; S, 5.68. Found: C, 52.98; H, 6.01; N, 7.42; Cl, 6.28; F, 10.13; S, 5.56.

28f: MS *m/z*: 521 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.5 Hz), 1.66—1.78 (2H, m), 1.99—2.09 (2H, m), 2.28 (3H, s), 3.18 (2H, q, J=7.5 Hz), 3.44—3.82 (4H, m), 4.44 (2H, d, J=5.5 Hz), 4.65—4.72 (1H, m), 6.33 (1H, dt, J=16.5, 5.5 Hz), 6.54 (1H, d, J=16.5 Hz), 7.00 (2H, d, J=9.0 Hz), 7.36 (2H, d, J=9.0 Hz), 7.48—7.69 (3H, m), 7.81 (1H, s). IR (KBr) cm^{-1}: 1672, 1627, 1331, 1147. *Anal.* Calcd for $C_{24}H_{32}N_4O_5S_2 \cdot 1.0HCl \cdot 1.1H_2O$: C, 49.96; H, 6.15; N, 9.71; Cl, 6.14; S, 11.11. Found: C, 49.83; H, 6.11; N, 9.92; Cl, 6.03; S, 11.13.

28g: MS *m/z*: 442 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.5 Hz), 1.63—1.82 (2H, m), 1.96—2.10 (2H, m), 2.29 (3H, s), 3.17 (2H, q, J=7.5 Hz), 3.43—3.86 (4H, m), 4.40 (2H, d, J=6.0 Hz), 4.64—4.73 (1H, m), 6.20 (1H, dt, J=16.0, 6.0 Hz), 6.45 (1H, d, J=16.0 Hz), 7.00 (2H, d, J=9.0 Hz), 7.20—7.39 (7H, m). IR (KBr) cm^{-1}: 1672, 1623, 1334, 1146. *Anal.* Calcd for $C_{24}H_{31}N_3O_3S \cdot 1.1HCl \cdot 1.5H_2O$: C, 56.66; H, 6.95; N, 8.26; Cl, 7.67; S, 6.30. Found: C, 56.65; H, 6.85; N, 8.08; Cl, 7.73; S, 6.35.

Ethyl (*N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}sulfamoyl)-acetate (29) To a solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]aniline **4** (4.39 g, 15.0 mmol) in CH_2Cl_2 (30 ml) and pyridine (2.40 ml, 29.7 mmol) was added $EtO_2CCH_2SO_2Cl$ (2.40 ml, 17.9 mmol) and the mixture was stirred at room temperature for 13 h. MeOH (0.5 ml) was added, and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **29** (4.96 g, 11.2 mmol, 75%) as a pale red oil. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.0 Hz), 1.47 (9H, s), 1.69—1.81 (2H, m), 1.85—1.94 (2H, m), 3.30—3.39 (2H, m), 3.64—3.73 (2H, m), 3.89 (2H, s), 4.29 (2H, q, J=7.0 Hz), 4.41—4.48 (1H, m), 6.79 (1H, br s), 6.89 (2H, d, J=8.5 Hz), 7.27 (2H, d, J=8.5 Hz).

Ethyl (*N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate (30) DEAD (1.00 ml, 6.35 mmol) was added to a solution of ethyl (*N*-{4-[1-(*t*-butoxycarbonyl)-piperidin-4-yloxy]phenyl}sulfamoyl)acetate **29** (2.21 g, 4.99 mmol), (*E*)-3-(3-cyanophenyl)-2-propen-1-ol **7** (796 mg, 5.00 mmol) and PPh_3 (1.70 g, 6.48 mmol) in CH_2Cl_2 (40 ml), and the resulting mixture was stirred at 0 °C for 2 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=10/1) to give **30** (2.15 g, 3.68 mmol, 74%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 1.47 (9H, s), 1.68—1.81 (2H, m), 1.85—1.95 (2H, m), 3.30—3.38 (2H, m), 3.65—3.72 (2H, m), 3.98 (2H, s), 4.30 (2H, q, J=7.0 Hz), 4.42—4.49 (1H, m), 4.47 (2H, d, J=6.0 Hz), 6.24 (1H, dt, J=15.5, 6.0 Hz), 6.40 (1H, d, J=15.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.35—7.42 (3H, m), 7.49—7.54 (2H, m), 7.55 (1H, s).

Ethyl {*N*-[(*E*)-3-(3-Amidinophenyl)-2-propenyl]-*N*-[4-(piperidin-4-yloxy)phenyl]sulfamoyl}acetate Dihydrochloride (31) Into a solution of ethyl (*N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate **30** (1.46 g, 2.50 mmol) in CH_2Cl_2 (50 ml) and EtOH (25 ml) was bubbled hydrogen chloride under ice-cooling, and the resulting mixture was stirred at room temperature under tightly sealed condition for 8 h. The reaction mixture was concentrated and the resulting residue was dissolved in EtOH (40 ml). The solution was treated with NH_4Cl (299 mg, 5.59 mmol) in H_2O (15 ml) and NH_3 solution (0.575 ml, 9.45 mmol) and the mixture was allowed to stand at room temperature overnight. The mixture was treated with a 4 N solution of hydrogen chloride in dioxane (2 ml) and concentrated. The resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=17/3) to give **31** (979 mg, 1.71 mmol, 68%) as a pale yellow amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.77—1.89 (2H, m), 2.05—2.14 (2H, m), 2.99—3.10 (2H, m), 3.15—3.24 (2H, m), 4.20 (2H, q, J=7.0 Hz), 4.34 (2H, s), 4.45 (2H, d, J=6.0 Hz), 4.62—4.70 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.55 (1H, d, J=16.0 Hz), 7.04 (2H, d, J=8.5 Hz), 7.39 (2H, d, J=8.5 Hz), 7.55 (1H, t, J=8.0 Hz), 7.69 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.89 (1H, s).

Ethyl (*N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetate Dihydrochloride (32) To a solution of ethyl {*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[4-(piperidin-4-yloxy)phenyl]sulfamoyl}acetate dihydrochloride **31** (1.09 g, 1.90 mmol) in EtOH (40 ml) were added ethyl acetimidate hydrochloride (705 mg, 5.70 mmol) and Et_3N (1.30 ml, 9.38 mmol). The resulting mixture was stirred at room temperature for 6 h and the reaction mixture was concentrated. The resulting residue was dissolved in MeOH (15 ml) and a 4 N solution of hydrogen chloride in dioxane (2 ml) and the mixture was concentrated. The resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=4/1) to give an amorphous solid. This amorphous solid was dissolved in MeOH (15 ml) and a 4 N solution of hydrogen chloride in dioxane (1 ml) and the mixture was concentrated to give **32** (812 mg, 1.32 mmol, 70%) as a colorless amorphous solid. MS *m/z*: 542 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.67—1.79 (2H, m), 1.99—2.09 (2H, m), 2.29 (3H, s), 3.44—3.56 (2H, m), 3.68—3.77 (1H, m), 3.77—3.84 (1H, m), 4.19 (2H, q, J=7.0 Hz), 4.34 (2H, s), 4.44 (2H, d, J=6.0 Hz), 4.67—4.74 (1H, m), 6.45 (1H, dt, J=16.5, 6.0 Hz), 6.55 (1H, d, J=16.5 Hz), 7.04 (2H, d, J=9.5 Hz), 7.39 (2H, d, J=9.5 Hz), 7.54 (1H, t, J=8.0 Hz), 7.69 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1738, 1673, 1626. *Anal.* Calcd for $C_{27}H_{35}N_5O_5S \cdot 2.1HCl \cdot 1.7H_2O$: C, 49.98; H, 6.29; N, 10.79; Cl, 11.47; S, 4.94. Found: C, 50.29; H, 6.45; N, 10.39; Cl, 11.57; S, 5.06.

(*N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetic Acid Dihydrochloride (33) Ethyl (*N*-{4-[1-(acetimidoyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetate dihydrochloride **32** (440 mg, 0.716 mmol) was dissolved in a 3 N solution of hydrogen chloride (30 ml) and stirred at 80 °C for 3 h. The reaction mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=17/3) to give an amorphous solid. This amorphous solid was dissolved in MeOH (15 ml) and a 4 N solution of hydrogen chloride in dioxane (1 ml) and the mixture was concentrated. The resulting residue was dissolved in H_2O (15 ml) and the solution was lyophilized to

give **33** (331 mg, 0.564 mmol, 78%) as a colorless amorphous solid. MS *m/z*: 514 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.68—1.79 (2H, m), 1.98—2.08 (2H, m), 2.29 (3H, s), 3.46—3.57 (2H, m), 3.68—3.76 (1H, m), 3.77—3.84 (1H, m), 4.18 (2H, s), 4.45 (2H, d, J=6.0 Hz), 4.66—4.74 (1H, m), 6.44 (1H, dt, J=16.5, 6.0 Hz), 6.55 (1H, d, J=16.5 Hz), 7.03 (2H, d, J=8.5 Hz), 7.40 (2H, d, J=8.5 Hz), 7.54 (1H, t, J=8.0 Hz), 7.68 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 7.87 (1H, s). IR (KBr) cm^{-1}: 1733, 1673, 1627. *Anal.* Calcd for $C_{25}H_{31}N_5O_5S\cdot 2.1HCl\cdot 1.7H_2O$: C, 48.37; H, 5.93; N, 11.28; Cl, 11.99; S, 5.16. Found: C, 48.20; H, 6.05; N, 11.29; Cl, 11.76; S, 5.47.

3-((*E*)-3-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenylamino}-1-propenyl)benzonitrile (34a) Molecular sieves 5A (15 g) was added to a solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]aniline **4** (11.3 g, 38.6 mmol) and 3-cyanocinnamaldehyde **6** (6.00 g, 38.2 mmol) in toluene (30 ml), and the resulting suspension was refluxed for 2 h. The mixture was filtered through a pad of celite and the filtrate was concentrated. The resulting residue was recrystallized from CH_2Cl_2 and Et_2O to give an imine derivative (12.9 g). The imine derivative was suspended in EtOH (200 ml) and the resulting mixture were treated with $CeCl_3\cdot 7H_2O$ (catalytic amount) and $NaBH_4$ (1.13 g, 29.9 mmol). The reaction mixture was stirred at 0 °C for 1 h and the mixture was concentrated. 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 a yellow solid. The solid was washed with *i*-Pr_2O to give **34a** (10.0 g, 23.1 mmol, 60%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.62—1.77 (2H, m), 1.81—1.93 (2H, m), 3.22—3.35 (2H, m), 3.67—3.80 (2H, m), 3.93 (2H, dd, J=1.0, 5.5 Hz), 4.24—4.31 (1H, m), 6.39 (1H, dt, J=16.0, 5.5 Hz), 6.61 (1H, d, J=16.0 Hz), 6.61 (2H, d, J=9.0 Hz), 6.81 (2H, d, J=9.0 Hz), 7.41 (1H, t, J=7.5 Hz), 7.51 (1H, d, J=7.5 Hz), 7.57 (1H, d, J=7.5 Hz), 7.63 (1H, s).

3-[(*E*)-3-(*N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-methylamino)-1-propenyl]benzonitrile (34b) (Method C) To a suspension of 3-((*E*)-3-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenylamino}-1-propenyl)benzonitrile **34a** (1.00 g, 2.31 mmol) and paraformaldehyde (138 mg, 4.60 mmol) in CH_2Cl_2 (20 ml) were added AcOH (0.260 ml, 4.54 mmol) and $NaBH_3CN$ (144 mg, 2.29 mmol), and the resulting suspension was stirred overnight at room temperature. MeOH (20 ml) was added, and the mixture was stirred at 30 °C for 5 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=3/2) to give **34b** (761 mg, 1.70 mmol, 74%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.65—1.78 (2H, m), 1.82—1.93 (2H, m), 2.92 (3H, s), 3.21—3.34 (2H, m), 3.66—3.76 (2H, m), 4.02 (2H, d, J=5.0 Hz), 4.25—4.32 (1H, m), 6.32 (1H, dt, J=16.0, 5.0 Hz), 6.51 (1H, d, J=16.0 Hz), 6.72 (2H, d, J=9.0 Hz), 6.86 (2H, d, J=9.0 Hz), 7.39 (1H, t, J=7.5 Hz), 7.49 (1H, d, J=7.5 Hz), 7.56 (1H, d, J=7.5 Hz), 7.62 (1H, s).

Similarly, compounds **34c**—**e** were prepared.

34c: ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7.0 Hz), 1.46 (9H, s), 1.67—1.77 (2H, m), 1.82—1.93 (2H, m), 3.20—3.29 (2H, m), 3.36 (2H, q, J=7.0 Hz), 3.66—3.76 (2H, m), 4.01 (2H, d, J=5.0 Hz), 4.23—4.29 (1H, m), 6.31 (1H, dt, J=16.0, 5.0 Hz), 6.50 (1H, d, J=16.0 Hz), 6.69 (2H, d, J=9.0 Hz), 6.84 (2H, d, J=9.0 Hz), 7.39 (1H, t, J=7.5 Hz), 7.49 (1H, d, J=7.5 Hz), 7.55 (1H, d, J=7.5 Hz), 7.61 (1H, s).

34d: ^{1}H-NMR ($CDCl_3$) δ: 1.18 (6H, d, J=6.5 Hz), 1.46 (9H, s), 1.63—1.76 (2H, m), 1.83—1.93 (2H, m), 3.21—3.30 (2H, m), 3.65—3.76 (2H, m), 3.91 (2H, d, J=4.5 Hz), 3.97—4.04 (1H, m), 4.23—4.30 (1H, m), 6.33 (1H, dt, J=16.0, 4.5 Hz), 6.53 (1H, d, J=16.0 Hz), 6.73 (2H, d, J=9.0 Hz), 6.82 (2H, d, J=9.0 Hz), 7.38 (1H, t, J=7.5 Hz), 7.47 (1H, d, J=7.5 Hz), 7.53 (1H, d, J=7.5 Hz), 7.60 (1H, s).

34e: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.65—1.75 (2H, m), 1.83—1.92 (2H, m), 3.22—3.32 (2H, m), 3.64—3.75 (2H, m), 4.11 (2H, d, J=5.0 Hz), 4.23—4.29 (1H, m), 4.52 (2H, s), 6.32 (1H, dt, J=16.0, 5.0 Hz), 6.48 (1H, d, J=16.0 Hz), 6.71 (2H, d, J=9.0 Hz), 6.81 (2H, d, J=9.0 Hz), 7.20—7.60 (9H, m).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]acetamide (34f) (Method D)** To a solution of 3-((*E*)-3-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenylamino}-1-propenyl)benzonitrile **34a** (503 mg, 1.16 mmol) in CH_2Cl_2 (10 ml) were added pyridine (0.140 ml, 1.73 mmol) and acetic anhydride (0.130 ml, 1.38 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1—0/1) to give **34f** (403 mg, 0.847 mmol, 73%) as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.71—1.93 (4H, m), 1.88 (3H, s), 3.28—3.38 (2H, m), 3.65—3.75 (2H, m), 4.41 (2H, d, J=5.5 Hz), 4.44—4.50 (1H, m), 6.32 (1H, dt, J=16.0, 5.5 Hz), 6.38 (1H, d, J=16.0 Hz), 6.91 (2H, d, J=9.0 Hz), 7.07 (2H, d, J=9.0 Hz), 7.40 (1H, t, J=8.0 Hz), 7.51 (1H, d, J=8.0 Hz), 7.55 (1H, d, J=8.0 Hz), 7.58 (1H, s).

Similarly, compound **34g** was prepared.

34g: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.68—1.99 (4H, m), 2.15 (3H, s), 3.28—3.40 (2H, m), 3.64—3.76 (2H, m), 4.32—4.53 (5H, m), 6.23—6.46 (2H, m), 6.93 (2H, d, J=9.0 Hz), 7.14 (2H, d, J=9.0 Hz), 7.35—7.59 (4H, m).

***N*-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]-2-hydroxyacetamide (34h)** To a solution of *N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]-2-acetoxyacetamide **34g** (1232 mg, 2.31 mmol) in MeOH (20 ml) was added K_2CO_3 (640 mg, 4.63 mmol), and the resulting mixture was stirred at room temperature for 1 h. H_2O was added, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/2) to give **34h** (977 mg, 1.99 mmol, 86%) as colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.71—1.83 (2H, m), 1.88—1.99 (2H, m), 3.28—3.40 (3H, m), 3.60—3.78 (2H, m), 3.81 (2H, d, J=4.5 Hz), 4.46 (2H, d, J=6.5 Hz), 4.44—4.51 (1H, m), 6.30 (1H, dt, J=16.0, 6.5 Hz), 6.44 (1H, d, J=16.0 Hz), 6.93 (2H, d, J=9.0 Hz), 7.07 (2H, d, J=9.0 Hz), 7.42 (1H, t, J=7.5 Hz), 7.53 (1H, d, J=7.5 Hz), 7.56 (1H, d, J=7.5 Hz), 7.59 (1H, s).

3-((*E*)-3-{4-[1-(Acetimidoyl)piperidin-4-yloxy]phenylamino}-1-propenyl)benzamidine Trihydrochloride (35a) 3-((*E*)-3-{4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]phenylamino}-1-propenyl)benzonitrile **34a** was converted to **35a** by the same procedure as that for **32**. Compound **35a** was obtained (55%, 3 steps) as a yellow amorphous solid. MS *m/z*: 392 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.67—1.78 (2H, m), 1.99—2.10 (2H, m), 2.30 (3H, s), 3.40—3.95 (4H, m), 4.06 (2H, d, J=6.5 Hz), 4.65—4.72 (1H, m), 6.56 (1H, dt, J=16.0, 6.5 Hz), 6.80 (1H, d, J=16.0 Hz), 7.10 (2H, d, J=9.0 Hz), 7.35—7.55 (2H, m), 7.60 (1H, t, J=8.0 Hz), 7.70—7.80 (2H, m), 7.87 (1H, s). IR (KBr) cm^{-1}: 1672, 1625. *Anal.* Calcd for $C_{23}H_{29}N_5O\cdot 3.0HCl\cdot 2.6H_2O$: C, 50.44; H, 6.85; N, 12.79; Cl, 19.42. Found: C, 50.49; H, 6.97; N, 12.88; Cl, 19.27.

Similarly, compounds **35b**—**35f**, **35h** were prepared.

35b: MS *m/z*: 406 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.66—1.77 (2H, m), 1.97—2.08 (2H, m), 2.31 (3H, s), 3.13 (3H, s), 3.40—3.70 (4H, m), 4.29 (2H, d, J=7.0 Hz), 4.71—4.78 (1H, m), 6.50 (1H, dt, J=16.0, 7.0 Hz), 6.76 (1H, d, J=16.0 Hz), 7.15 (2H, d, J=9.0 Hz), 7.58 (1H, t, J=7.5 Hz), 7.69 (1H, d, J=7.5 Hz), 7.70—7.85 (3H, m), 7.92 (1H, s). IR (KBr) cm^{-1}: 1672, 1625. *Anal.* Calcd for $C_{24}H_{31}N_5O\cdot 3.6HCl\cdot 2.9H_2O$: C, 48.94; H, 6.91; N, 11.89; Cl, 21.67. Found: C, 48.75; H, 6.77; N, 12.04; Cl, 21.90.

35c: MS *m/z*: 420 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.09 (3H, t, J=7.0 Hz), 1.66—1.76 (2H, m), 1.98—2.09 (2H, m), 2.32 (3H, s), 3.50—3.95 (6H, m), 4.24—4.36 (2H, m), 4.71—4.79 (1H, m), 6.49 (1H, dt, J=16.0, 6.5 Hz), 6.73 (1H, d, J=16.0 Hz), 7.00—7.30 (2H, m), 7.58 (1H, t, J=7.5 Hz), 7.67 (1H, d, J=7.5 Hz), 7.75—7.90 (4H, m). IR (KBr) cm^{-1}: 1673, 1623. *Anal.* Calcd for $C_{25}H_{33}N_5O\cdot 3.0HCl\cdot 2.1H_2O$: C, 52.98; H, 7.15; N, 12.36; Cl, 18.77. Found: C, 52.83; H, 7.19; N, 12.44; Cl, 18.97.

35d: MS *m/z*: 434 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6.0 Hz), 1.43 (3H, d, J=6.0 Hz), 1.65—1.75 (2H, m), 1.99—2.08 (2H, m), 2.31 (3H, s), 3.45—4.05 (5H, m), 4.37—4.45 (2H, m), 4.71—4.78 (1H, m), 6.42 (1H, dt, J=16.0, 7.0 Hz), 6.73 (1H, d, J=16.0 Hz), 7.15 (2H, d, J=8.5 Hz), 7.50—7.65 (2H, m), 7.70—7.90 (4H, m). IR (KBr) cm^{-1}: 1672, 1623. *Anal.* Calcd for $C_{26}H_{35}N_5O\cdot 3.1HCl\cdot 1.9H_2O$: C, 53.76; H, 7.27; N, 12.06; Cl, 18.92. Found: C, 53.62; H, 7.56; N, 12.09; Cl, 18.97.

35e: MS *m/z*: 482 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.50—1.75 (2H, m), 1.91—2.02 (2H, m), 2.29 (3H, s), 3.40—3.90 (4H, m), 4.37—4.44 (2H, m), 4.50—4.90 (3H, m), 6.63 (1H, dt, J=16.0, 6.0 Hz), 6.74 (1H, d, J=16.0 Hz), 6.97 (2H, d, J=8.5 Hz), 7.15—7.30 (3H, m), 7.40—7.60 (4H, m), 7.56 (1H, t, J=7.5 Hz), 7.66 (1H, d, J=7.5 Hz), 7.77 (1H, d, J=7.5 Hz), 7.92 (1H, s). IR (KBr) cm^{-1}: 1672, 1624. *Anal.* Calcd for $C_{30}H_{35}N_5O\cdot 3.6HCl\cdot 1.7H_2O$: C, 55.99; H, 6.58; N, 10.88; Cl, 19.83. Found: C, 56.13; H, 6.71; N, 10.67; Cl, 20.09.

35f: MS *m/z*: 434 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.69—1.80 (2H, m), 1.78 (3H, s), 1.99—2.09 (2H, m), 2.31 (3H, s), 3.45—3.95 (4H, m), 4.36—4.44 (2H, m), 4.62—4.78 (1H, m), 6.42—6.60 (2H, m), 7.05 (2H, d, J=8.5 Hz), 7.28 (2H, d, J=8.5 Hz), 7.55 (1H, t, J=7.5 Hz), 7.65—7.79 (2H, m), 7.95 (1H, s). IR (KBr) cm^{-1}: 1672, 1624. *Anal.* Calcd for $C_{25}H_{31}N_5O_2\cdot 2.9HCl\cdot 2.6H_2O$: C, 51.23; H, 6.72; N, 11.95; Cl, 17.54. Found: C, 51.01; H, 6.90; N, 11.87; Cl, 17.78.

35h: MS *m/z*: 450 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.67—1.79 (2H, m), 2.00—2.11 (2H, m), 2.30 (3H, s), 3.32—3.90 (6H, m), 4.35—4.43 (2H, m), 4.66—4.73 (1H, m), 6.42—6.59 (2H, m), 7.04 (2H, d, J=9.0 Hz), 7.28 (2H, d, J=9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.66—7.79 (2H, m), 7.93 (1H, s). IR (KBr) cm^{-1}: 1671. *Anal.* Calcd for $C_{25}H_{31}N_5O_3 \cdot 1.7HCl \cdot 2.8H_2O$: C, 53.43; H, 6.87; N, 12.46; Cl, 10.72. Found: C, 53.21; H, 6.53; N, 12.77; Cl, 10.95.

Ethyl {*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]-*N*-(3-hydroxyphenyl)sulfamoyl}acetate (38) To a solution of 3-(methoxymethoxy)aniline **36** (13.1 g, 85.5 mmol) in CH_2Cl_2 (150 ml) were added $EtO_2CCH_2SO_2Cl$ (16.0 g, 85.7 mmol) and pyridine (7.00 ml, 86.5 mmol), and the mixture was stirred at 0 °C for 2.5 h and allowed to stand overnight at room temperature. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=4/1) to give ethyl {*N*-[3-(methoxymethoxy)phenyl]sulfamoyl}acetate (25.2 g, 83.1 mmol, 97%) as a red oil. This oil (4.00 g, 13.2 mmol), (*E*)-3-(3-cyanophenyl)-2-propen-1-ol **7** (2.10 g, 13.2 mmol) and PPh_3 (5.00 g, 19.1 mmol) were dissolved in CH_2Cl_2 (120 ml), and treated with DEAD (3.00 ml, 19.0 mmol). The resulting mixture was stirred at room temperature for 4 h and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOAc=19/1) to give ethyl {*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]-*N*-[3-(methoxymethoxy)phenyl]sulfamoyl}acetate (4.60 g, 10.3 mmol, 78%) as an amorphous solid. This amorphous solid (4.60 g, 10.3 mmol) was dissolved in EtOAc (80 ml), and treated with a 4 N solution of hydrogen chloride in EtOAc (12 ml). The mixture was stirred at room temperature for 5.5 h and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **38** (3.60 g, 8.99 mmol, 86%) as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.1 Hz), 4.01 (2H, s), 4.30 (2H, q, J=7.1 Hz), 4.52 (2H, d, J=6.4 Hz), 6.23 (1H, dt, J=16.0, 6.4 Hz), 6.42 (1H, d, J=16.0 Hz), 6.80—6.90 (1H, m), 6.95—7.10 (2H, m), 7.25—7.29 (1H, m), 7.36—7.41 (1H, m), 7.45—7.60 (3H, m).

Similarly, compound **39** was prepared.

39: ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 3.98 (2H, s), 4.30 (2H, q, J=7.0 Hz), 4.46 (2H, d, J=6.0 Hz), 6.23 (1H, dt, J=16.0, 6.0 Hz), 6.39 (1H, d, J=16.0 Hz), 6.84 (2H, d, J=9.0 Hz), 7.34 (2H, d, J=9.0 Hz), 7.39 (1H, t, J=7.5 Hz), 7.47—7.53 (2H, m), 7.54 (1H, s).

Ethyl (*N*-{3-[1-(*t*-Butoxycarbonyl)piperidin-3-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate (40c) DEAD (3.20 ml, 20.3 mmol) was added to a solution of 1-(*t*-butoxycarbonyl)-3-hydroxypiperidine (4.00 g, 19.9 mmol), ethyl {*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]-*N*-(3-hydroxyphenyl)sulfamoyl}acetate **38** (2.00 g, 4.99 mmol) and PPh_3 (5.20 g, 19.8 mmol) in THF (100 ml), and the resulting mixture was stirred at 70 °C for 5 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (PhH/EtOAc=9/1) to give **40c** (0.790 g, 1.35 mmol, 27%) as a pale yellow oil. MS *m/z*: 584 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.2 Hz), 1.40 (9H, s), 1.44—2.06 (4H, m), 2.94—3.87 (4H, m), 4.01 (2H, s), 4.21—4.28 (1H, m), 4.29 (2H, q, J=7.2 Hz), 4.52 (2H, d, J=6.4 Hz), 6.24 (1H, dt, J=15.9, 6.4 Hz), 6.44 (1H, d, J=15.9 Hz), 6.85—6.95 (1H, m), 7.00—7.15 (2H, m), 7.28—7.33 (1H, m), 7.37—7.41 (1H, m), 7.45—7.60 (3H, m).

Similarly, compounds **40a**, **40b**, **40d** and **40e** were prepared.

40a: MS *m/z*: 584 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.5 Hz), 1.40 (9H, s), 1.45—2.06 (4H, m), 2.89—3.79 (4H, m), 3.97 (2H, s), 4.18—4.25 (1H, m), 4.31 (2H, q, J=7.5 Hz), 4.47 (2H, d, J=6.5 Hz), 6.24 (1H, dt, J=16.0, 6.5 Hz), 6.40 (1H, d, J=16.0 Hz), 6.93 (2H, d, J=8.5 Hz), 7.35—7.43 (3H, m), 7.47—7.57 (3H, m).

40b: MS *m/z*: 570 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.0 Hz), 1.46 (9H, s), 2.01—2.25 (2H, m), 3.41—3.68 (4H, m), 3.98 (2H, s), 4.31 (2H, q, J=7.0 Hz), 4.48 (2H, d, J=6.5 Hz), 4.82—4.88 (1H, m), 6.24 (1H, dt, J=16.0, 6.5 Hz), 6.41 (1H, d, J=16.0 Hz), 6.87 (2H, d, J=9.0 Hz), 7.35—7.60 (6H, m).

40d: MS *m/z*: 570 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.1 Hz), 1.47 (9H, s), 2.00—2.20 (2H, m), 3.39—3.63 (4H, m), 3.99 (2H, s), 4.30 (2H, q, J=7.1 Hz), 4.52 (2H, d, J=6.4 Hz), 4.83—4.90 (1H, m), 6.24 (1H, dt, J=15.9, 6.4 Hz), 6.43 (1H, d, J=15.9 Hz), 6.80—6.90 (1H, m), 7.00—7.15 (2H, m), 7.24—7.43 (2H, m), 7.45—7.60 (3H, m).

40e: MS *m/z*: 558 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.0 Hz), 1.45 (9H, s), 2.96 (3H, s), 3.55—3.62 (2H, m), 4.00 (2H, s), 4.03—4.34 (4H, m), 4.53 (2H, d, J=6.5 Hz), 6.24 (1H, dt, J=16.0, 6.5 Hz), 6.43 (1H, d, J=16.0 Hz), 6.85—6.90 (1H, m), 7.00—7.11 (2H, m), 7.25—7.42 (2H, m), 7.47—7.56 (3H, m).

Ethyl (*N*-{3-[1-(Acetimidoyl)piperidin-3-yloxy]phenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetate Dihydrochloride (41c) Ethyl (*N*-{3-[1-(*t*-butoxycarbonyl)piperidin-3-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate **40c** was converted to **41c** by the same procedure as that for **32**. Compound **41c** was obtained (30%, 3 steps) as a colorless amorphous solid. MS *m/z*: 542 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.1 Hz), 1.50—2.00 (4H, m), 2.11, 2.34 (together 3H, each singlet), 3.40—3.90 (4H, m), 4.19 (2H, q, J=7.1 Hz), 4.40 (2H, s), 4.50 (2H, d, J=5.2 Hz), 4.69—4.76 (1H, m), 6.46 (1H, dt, J=15.9, 5.2 Hz), 6.57 (1H, d, J=15.9 Hz), 6.92—6.99 (1H, m), 7.07—7.14 (2H, m), 7.31—7.37 (1H, m), 7.50—7.57 (1H, m), 7.68—7.74 (2H, m), 7.91—7.99 (1H, m). IR (KBr) cm^{-1}: 1738, 1672, 1622. *Anal.* Calcd for $C_{27}H_{35}N_5O_5S \cdot 2.2HCl \cdot 0.9H_2O$: C, 50.82; H, 6.16; N, 10.98; Cl, 12.22; S, 5.02. Found: C, 50.47; H, 6.37; N, 10.84; Cl, 12.60; S, 4.87.

Similarly, compounds **41a**, **41b**, **41d** and **41e** were prepared.

41a: MS *m/z*: 542 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz), 1.58—1.99 (4H, m), 2.15, 2.33 (together 3H, each singlet), 3.28—3.86 (4H, m), 4.20 (2H, q, J=7.0 Hz), 4.34 (2H, s), 4.45 (2H, d, J=6.0 Hz), 4.64—4.74 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.53, 6.57 (together 1H, each doublet, J=16.0 Hz), 6.98—7.03 (2H, m), 7.38—7.89 (6H, m). IR (KBr) cm^{-1}: 1738, 1673, 1623. *Anal.* Calcd for $C_{27}H_{35}N_5O_5S \cdot 2.1HCl \cdot 3.0H_2O$: C, 48.24; H, 6.46; N, 10.42; Cl, 11.07; S, 4.77. Found: C, 48.47; H, 6.17; N, 10.28; Cl, 11.24; S, 4.59.

41b: MS *m/z*: 528 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 2.10—2.30 (2H, m), 2.26, 2.29 (together 3H, each singlet), 3.40—4.05 (4H, m), 4.19 (2H, q, J=7.0 Hz), 4.34 (2H, s), 4.45 (2H, d, J=5.5 Hz), 5.10—5.30 (1H, m), 6.44 (1H, dt, J=16.0, 5.5 Hz), 6.56 (1H, d, J=16.0 Hz), 7.01, 7.02 (together 2H, each doublet, J=9.0 Hz), 7.42, 7.43 (together 2H, each doublet, J=9.0 Hz), 7.54 (1H, t, J=7.5 Hz), 7.65—7.75 (2H, m), 7.91 (1H, s). IR (KBr) cm^{-1}: 1738, 1672, 1629. *Anal.* Calcd for $C_{26}H_{33}N_5O_5S \cdot 2.0HCl \cdot 2.4H_2O$: C, 48.51; H, 6.23; N, 10.88; Cl, 11.01; S, 4.98. Found: C, 48.32; H, 5.97; N, 10.99; Cl, 11.25; S, 4.95.

41d: MS *m/z*: 528 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.1 Hz), 2.10—2.35 (5H, m), 3.35—4.05 (4H, m), 4.19 (2H, q, J=7.1 Hz), 4.40 (2H, s), 4.51 (2H, d, J=5.9 Hz), 5.18—5.25 (1H, m), 6.46 (1H, dt, J=16.0, 5.9 Hz), 6.59 (1H, d, J=16.0 Hz), 6.95—7.01 (1H, m), 7.09—7.16 (2H, m), 7.35—7.41 (1H, m), 7.51—7.57 (1H, m), 7.66—7.73 (2H, m), 7.92 (1H, s). IR (KBr) cm^{-1}: 1737, 1672, 1629. *Anal.* Calcd for $C_{26}H_{33}N_5O_5S \cdot 2.3HCl \cdot 1.7H_2O$: C, 48.63; H, 6.07; N, 10.91; Cl, 12.70; S, 4.99. Found: C, 48.54; H, 5.72; N, 10.90; Cl, 12.95; S, 4.87.

41e: MS *m/z*: 516 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.1 Hz), 2.28, 2.36 (together 3H, each singlet), 3.12, 3.19 (together 3H, each singlet), 3.81—3.93 (2H, m), 4.16—4.29 (2H, m), 4.19 (2H, q, J=7.1 Hz), 4.39 (2H, s), 4.51 (2H, d, J=6.1 Hz), 6.45 (1H, dt, J=15.9, 6.1 Hz), 6.58 (1H, d, J=15.9 Hz), 6.90—6.99 (1H, m), 7.02—7.14 (2H, m), 7.31—7.40 (1H, m), 7.53—7.58 (1H, m), 7.67—7.74 (2H, m), 7.92 (1H, s). IR (KBr) cm^{-1}: 1737, 1672, 1626. *Anal.* Calcd for $C_{25}H_{33}N_5O_5S \cdot 2.6HCl \cdot 1.5H_2O$: C, 47.11; H, 6.10; N, 10.99; Cl, 14.46; S, 5.03. Found: C, 46.89; H, 6.15; N, 10.96; Cl, 14.77; S, 5.07.

4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-3-chloronitrobenzene (43b) DEAD (3.10 ml, 19.7 mmol) was added to a solution of 1-(*t*-butoxycarbonyl)-4-hydroxypiperidine (3.32 g, 16.5 mmol), 2-chloro-4-nitrophenol **42b** (2.36 g, 13.6 mmol) and PPh_3 (5.11 g, 19.5 mmol) in CH_2Cl_2 (60 ml), and the resulting 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 **43b** (3.90 g, 10.9 mmol, 80%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.84—1.98 (4H, m), 3.47—3.58 (2H, m), 3.60—3.65 (2H, m), 4.69—4.76 (1H, m), 7.00 (1H, d, J=9.0 Hz), 8.14 (1H, dd, J=3.0, 9.0 Hz), 8.31 (1H, d, J=3.0 Hz).

Similarly, compounds **43a** and **43c**—**i** were prepared.

4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-3-carbamoylnitrobenzene (43j) To a solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-(ethoxycarbonyl)nitrobenzene **43f** (1.00 g, 2.54 mmol) in EtOH (10 ml) was added KOH (0.200 g, 3.56 mmol) in H_2O (0.5 ml), and the resulting mixture was refluxed for 2 h. The mixture was neutralized with a 1 N solution of hydrogen chloride and the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried and concentrated. The resulting residue was dissolved in CH_2Cl_2 (20 ml) and treated with $ClCO_2i$-Bu (0.330 ml, 2.53 mmol) and Et_3N (0.400 ml, 2.89 mmol). The solution was stirred at 0 °C for 1 h and the solution was added NH_3 solution (0.200 ml, 3.29 mmol). The mixture was stirred at room temperature for 1 h and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=19/1) to give **43j** (0.90 g, 2.46 mmol, 97%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.80—1.90 (2H, m), 2.08—2.20 (2H, m), 3.30—3.40 (2H, m), 3.75—3.88 (2H, m), 4.78—4.84 (1H, m), 7.11 (1H, d, J=9.0 Hz), 8.33 (1H, dd, J=3.0, 9.0 Hz), 9.09

(1H, d, J=3.0 Hz).

4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-3-fluoroaniline (44a) (Method E) A solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-fluoronitrobenzene **43a** (3.71 g, 10.9 mmol) in MeOH (50 ml) was hydrogenated over 10% Pd–C (0.30 g) at room temperature for 4 h with stirring. The catalyst was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **44a** (3.27 g, 10.5 mmol, 97%) as a pale red solid. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.66—1.78 (2H, m), 1.81—1.91 (2H, m), 3.18—3.29 (2H, m), 3.55 (2H, br s), 3.69—3.80 (2H, m), 4.13—4.20 (1H, m), 6.35 (1H, dd, J=3.0, 8.5 Hz), 6.44 (1H, dd, J=3.0, 12.5 Hz), 6.82 (1H, dd, J=8.5, 9.0 Hz).

Similarly, compounds **44c**—**e**, **44j**, **44g** and **44i** were prepared.

44c: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.69—1.78 (2H, m), 1.82—1.93 (2H, m), 2.17 (3H, s), 3.25—3.34 (2H, m), 3.63—3.73 (2H, m), 4.21—4.28 (1H, m), 6.47 (1H, dd, J=2.5, 8.5 Hz), 6.53 (1H, d, J=2.5 Hz), 6.68 (1H, d, J=8.5 Hz).

44d: ^{1}H-NMR ($CDCl_3$) δ: 1.18 (6H, d, J=7.5 Hz), 1.47 (9H, s), 1.68—1.80 (2H, m), 1.84—1.93 (2H, m), 3.24—3.38 (3H, m), 3.62—3.74 (2H, m), 4.25—4.33 (1H, m), 6.48 (1H, dd, J=3.0, 9.0 Hz), 6.60 (1H, d, J=3.0 Hz), 6.68 (1H, d, J=9.0 Hz).

44e: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.76—1.88 (4H, m), 3.38—3.47 (2H, m), 3.54—3.64 (2H, m), 4.43—4.50 (1H, m), 6.78 (1H, dd, J=3.0, 9.0 Hz), 6.83 (1H, d, J=9.0 Hz), 6.91 (1H, d, J=3.0 Hz).

44j: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.65—1.80 (2H, m), 1.95—2.05 (2H, m), 3.14—3.25 (2H, m), 3.75—3.85 (2H, m), 4.40—4.47 (1H, m), 6.78 (1H, dd, J=3.0, 9.0 Hz), 6.84 (1H, d, J=9.0 Hz), 7.50 (1H, d, J=3.0 Hz).

44g: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.69—1.91 (4H, m), 3.17—3.28 (2H, m), 3.71—3.82 (2H, m), 4.07—4.15 (1H, m), 6.21 (2H, d, J=9.5 Hz).

44i: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.57—1.72 (2H, m), 1.88—1.97 (2H, m), 2.18 (6H, s), 2.80—2.91 (2H, m), 3.75—3.83 (1H, m), 3.95—4.08 (2H, m), 6.36 (2H, s).

4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-3-chloroaniline (44b) (Method F) To a solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-chloronitrobenzene **43b** (2.40 g, 6.73 mmol) in AcOH (50 ml) was added zinc powder (5.60 g, 85.6 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered away, and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/1) to give **44b** (1.99 g, 6.09 mmol, 90%) as an orange oil. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.71—1.83 (2H, m), 1.82—1.92 (2H, m), 3.25—3.36 (2H, m), 3.53 (2H, br s), 3.67—3.78 (2H, m), 4.22—4.30 (1H, m), 6.52 (1H, dd, J=3.0, 9.0 Hz), 6.73 (1H, d, J=3.0 Hz), 6.80 (1H, d, J=9.0 Hz).

Similarly, compound **44h** was prepared.

44h: ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 1.78—1.96 (4H, m), 3.05—3.14 (2H, m), 3.87—3.99 (2H, m), 4.18—4.25 (1H, m), 6.62 (2H, s).

(*N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]-3-chlorophenyl}-*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]sulfamoyl)acetic Acid Dihydrochloride (45b) 4-[1-(*t*-Butoxycarbonyl)piperidin-4-yloxy]-3-chloroaniline **44b** was converted to **45b** by the same procedure as that for **33**. Compound **45b** was obtained (13%, 6 steps) as a colorless amorphous solid. MS m/z: 548 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.74—1.85 (2H, m), 2.00—2.10 (2H, m), 2.29 (3H, s), 3.54—3.75 (4H, m), 4.23 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.80—4.87 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.57 (1H, d, J=16.0 Hz), 7.32 (1H, d, J=9.0 Hz), 7.38—7.44 (1H, m), 7.55 (1H, t, J=8.0 Hz), 7.57—7.62 (1H, m), 7.68 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1734, 1673, 1625. *Anal.* Calcd for $C_{25}H_{30}ClN_5O_5S\cdot 2.5HCl\cdot 1.7H_2O$: C, 44.83; H, 5.40; N, 10.46; Cl, 18.52; S, 4.79. Found: C, 44.87; H, 5.31; N, 10.47; Cl, 18.33; S, 4.83.

Similarly, compounds **45a**, **45c**—**e** and **45g**—**j** were prepared.

45a: MS m/z: 532 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.72—1.82 (2H, m), 2.00—2.11 (2H, m), 2.29 (3H, s), 3.47—3.58 (2H, m), 3.67—3.75 (1H, m), 3.77—3.84 (1H, m), 4.23 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.69—4.76 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.57 (1H, d, J=16.0 Hz), 7.23—7.28 (1H, m), 7.32 (1H, t, J=8.5 Hz), 7.43 (1H, dd, J=2.0, 13.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.68 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 3295, 1733, 1673, 1624. *Anal.* Calcd for $C_{25}H_{30}FN_5O_5S\cdot 2.0HCl\cdot 1.8H_2O$: C, 47.14; H, 5.63; N, 10.99; Cl, 11.13; F, 2.98; S, 5.03. Found: C, 47.17; H, 5.40; N, 10.94; Cl, 11.50; F, 2.92; S, 4.77.

45c: MS m/z: 528 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.73—1.82 (2H, m), 1.97—2.07 (2H, m), 2.14 (3H, s), 2.29 (3H, s), 3.54—3.70 (4H, m), 3.71 (2H, s), 4.46 (2H, d, J=6.0 Hz), 4.67—4.74 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.50 (1H, d, J=16.0 Hz), 7.02 (1H, d, J=8.5 Hz), 7.36 (1H, s), 7.37 (1H, d, J=8.5 Hz), 7.52 (1H, t, J=8.0 Hz), 7.67 (1H, d, J=7.5 Hz), 7.69 (1H, d, J=8.0 Hz), 7.86 (1H, s). IR (KBr) cm^{-1}: 1678, 1608, 1367, 1151. *Anal.* Calcd for $C_{26}H_{33}N_5O_5S\cdot 2.3HCl\cdot 1.8H_2O$: C, 48.50; H, 6.09; N, 10.88; Cl, 12.66; S, 4.98. Found: C, 48.45; H, 6.14; N, 10.72; Cl, 12.83; S, 4.92.

45d: MS m/z: 556 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (6H, d, J=7.0 Hz), 1.70—1.86 (2H, m), 1.98—2.13 (2H, m), 2.30 (3H, s), 3.17—3.26 (1H, m), 3.50—3.81 (4H, m), 4.21 (2H, s), 4.45 (2H, d, J=6.0 Hz), 4.70—4.77 (1H, m), 6.46 (1H, dt, J=15.5, 6.0 Hz), 6.55 (1H, d, J=15.5 Hz), 7.07 (1H, d, J=8.0 Hz), 7.22—7.31 (2H, m), 7.55 (1H, t, J=8.0 Hz), 7.69—7.73 (2H, m), 7.91 (1H, s). IR (KBr) cm^{-1}: 1673, 1625, 1344, 1155. *Anal.* Calcd for $C_{28}H_{37}N_5O_5S\cdot 2.4HCl\cdot 1.4H_2O$: C, 50.31; H, 6.36; N, 10.48; Cl, 12.73; S, 4.80. Found: C, 50.11; H, 6.80; N, 10.31; Cl, 12.88; S, 4.85.

45e: MS m/z: 582 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.74—1.84 (2H, m), 2.00—2.11 (2H, m), 2.31 (3H, s), 3.40—3.75 (4H, m), 4.32 (2H, s), 4.50 (2H, d, J=6.0 Hz), 4.93—5.00 (1H, m), 6.47 (1H, dt, J=17.0, 7.0 Hz), 6.57 (1H, d, J=17.0 Hz), 7.43 (1H, d, J=10.0 Hz), 7.55 (1H, t, J=7.5 Hz), 7.64—7.78 (4H, m), 7.92 (1H, s). IR (KBr) cm^{-1}: 1675, 1618, 1349, 1142. *Anal.* Calcd for $C_{26}H_{30}F_3N_5O_5S\cdot 2.0HCl\cdot 2.0H_2O$: C, 45.22; H, 5.26; N, 10.14; Cl, 10.27; F, 8.25; S, 4.64. Found: C, 45.41; H, 5.25; N, 10.28; Cl, 10.50; F, 8.06; S, 4.49.

45g: MS m/z: 550 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.69—1.88 (2H, m), 1.93—2.07 (2H, m), 2.29 (3H, s), 3.42—3.56 (2H, m), 3.68—3.87 (2H, m), 4.37 (2H, s), 4.41—4.57 (3H, m), 6.43 (1H, dt, J=16.0, 5.5 Hz), 6.62 (1H, d, J=16.0 Hz), 7.32—7.42 (2H, m), 7.55 (1H, t, J=7.5 Hz), 7.66—7.78 (2H, m), 7.89 (1H, s). IR (KBr) cm^{-1}: 1733, 1674, 1626. *Anal.* Calcd for $C_{25}H_{29}F_2N_5O_5S\cdot 2.4HCl\cdot 1.6H_2O$: C, 45.09; H, 5.24; N, 10.52; Cl, 12.78; F, 5.71; S, 4.81. Found: C, 44.93; H, 4.99; N, 10.58; Cl, 12.76; F, 6.03; S, 5.10.

45h: MS m/z: 582 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.80—2.09 (4H, m), 2.30 (3H, s), 3.40—3.53 (2H, m), 3.78—3.87 (1H, m), 3.91—4.00 (1H, m), 4.39 (2H, s), 4.48—4.59 (3H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.62 (1H, d, J=16.0 Hz), 7.56 (1H, t, J=8.0 Hz), 7.67—7.78 (4H, m), 7.90 (1H, s). IR (KBr) cm^{-1}: 1733, 1673, 1625. *Anal.* Calcd for $C_{25}H_{29}Cl_2N_5O_5S\cdot 2.1HCl\cdot 2.0H_2O$: C, 43.20; H, 5.09; N, 10.08; Cl, 20.91; S, 4.61. Found: C, 43.44; H, 4.64; N, 10.22; Cl, 21.11; S, 4.22.

45i: MS m/z: 542 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.67—1.82 (2H, m), 1.93—2.04 (2H, m), 2.23 (6H, s), 2.29 (3H, s), 3.22—3.48 (2H, m), 3.81—3.88 (1H, m), 3.99—4.07 (1H, m), 4.13—4.23 (3H, m), 4.45 (2H, d, J=6.0 Hz), 6.43 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.17 (2H, s), 7.55 (1H, t, J=7.5 Hz), 7.67—7.75 (2H, m), 7.88 (1H, s). IR (KBr) cm^{-1}: 1733, 1673, 1626. *Anal.* Calcd for $C_{27}H_{35}N_5O_5S\cdot 2.1HCl\cdot 2.5H_2O$: C, 48.89; H, 6.40; N, 10.56; Cl, 11.22; S, 4.83. Found: C, 48.61; H, 6.22; N, 10.56; Cl, 11.21; S, 5.32.

45j: MS m/z: 557 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.78—1.93 (2H, m), 2.00—2.13 (2H, m), 2.30 (3H, s), 3.49—3.80 (4H, m), 4.24 (2H, s), 4.49 (2H, d, J=6.0 Hz), 4.82—4.91 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.28 (1H, d, J=9.5 Hz), 7.50—7.79 (5H, m), 7.89 (1H, s). IR (KBr) cm^{-1}: 1672, 1347, 1156. *Anal.* Calcd for $C_{26}H_{32}N_6O_6S\cdot 3.5HCl\cdot 2.9H_2O$: C, 42.40; H, 5.65; N, 11.41; Cl, 16.85; S, 4.35. Found: C, 42.05; H, 5.23; N, 11.39; Cl, 17.09; S, 4.78.

Biology. Anti-FXa and Trypsin 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). 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).

Coagulation Assay Citrated blood samples were collected from healthy male volunteers and male hamster (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) or an ACL9000 (Instrumentation Laboratories, MA, U.S.A.). Prothrombin time (PT) was measured using SIMPLASTIN EXCEL (Organon Teknika, NC, U.S.A.) or HemosILTM RecombiPlasTin (Instrumentation Laboratories, MA, U.S.A.). Activated partial thromboplastin time (APTT) was measured using Platelin LS (Organon Teknika, NC, U.S.A.) or HemosILTM SynthASil (Instrumentation Laboratories, MA, U.S.A.). 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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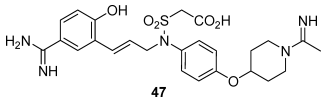

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