Discovery of R-142086 as a Factor Xa (FXa) Inhibitor: Syntheses and Structure–Activity Relationships of Cinnamyl Derivatives[1,2)]

Tetsuji NOGUCHI,[a] Naoki TANAKA,*[,b] Toyoki NISHIMATA,[b] Riki GOTO,[b] Miho HAYAKAWA,[a] Atsuhiro SUGIDACHI,[b] Taketoshi OGAWA,[a] Yoichi NIITSU,[b] Fumitoshi ASAI,[b] Tomoko ISHIZUKA,[b] and Koichi FUJIMOTO[b,3)]

[a] *R&D Division, Daiichi Sankyo Co., Ltd.; 1–16–13 Kitakasai, Edogawa-ku, Tokyo 134–8630, Japan: and* [b] *R&D Division, Daiichi Sankyo Co., Ltd.; 1–2–58 Hiromachi, Shinagawa-ku, Tokyo 140–8710, Japan.*
Received July 28, 2008; accepted October 16, 2008; published online October 17, 2008

To develop a novel and effective anticoagulant with potent and selective factor Xa (FXa) inhibitory activity, a new series of cinnamyl derivatives with enhanced lipophilicity and prodrug forms were synthesized and their biological activities were evaluated. As a result, we found that cinnamyl derivative (*N*-{4-[1-(acetimidoyl)-piperidin-4-yloxy]-3-carbamoylphenyl}-*N*-[(*Z*)-3-(3-amidinophenyl)-2-fluoro-2-propenyl]sulfamoyl)acetic acid dihydrochloride (26d, R-142086) with a fluorine atom on the double bond exhibited potent anticoagulant activity and no mutagenic potential. Moreover, orally administered R-142086 exhibited potent anti-FXa activity and anticoagulant activity in dogs.

Key words factor Xa inhibitory activity; cinnamyl derivative; anticoagulant; prodrug; Ames test

Warfarin is widely used as a sole oral anticoagulant for the treatment and prevention of thromboembolic diseases. However, many reports have mentioned the defects of warfarin. It requires periodic monitoring because of its narrow therapeutic window and, in addition, warfarin interacts with many different foods and drugs.[4—6)] Therefore, new anticoagulants based on novel mechanisms need to be developed. Recently, blood coagulation factor Xa (FXa) has attracted considerable attention as a novel anticoagulation target.

FXa acts at the convergence point of the intrinsic pathway and the extrinsic pathway in a blood coagulation cascade.[7)] FXa converts prothrombin into thrombin and leads to fibrin clot formation. It is thought that the inhibition of FXa effectively diminishes the thrombin generation and, as a result, leads to the inhibition of clot formation. Indeed, many FXa inhibitors have been synthesized and their anticoagulant activities reported.[8,9)] In these reports, FXa inhibitors exhibit less bleeding risk than warfarin and thrombin inhibitors. We have also conducted research to discover orally-active novel FXa inhibitors.[10—13)]

Previously, we found that the series of cinnamyl derivatives represented by **1** and **2** produced potent *in vitro* FXa inhibitory activities and high selectivity. Moreover, these compounds also exhibited potent *ex vivo* anticoagulant activities in hamsters after oral administration.

However, regarding the chemical structure, these compounds are highly hydrophilic with two amidino groups. It seems that enhancement of these compounds' lipophilicity may improve the plasma concentration after oral administration and the resulting oral anticoagulant activity. Similarly, conversion of these compounds into their prodrug forms may be promising for high oral activity. Herein, we describe our synthetic efforts and further evaluations to discover R-142086 with *ex vivo* anticoagulant activity in dogs.

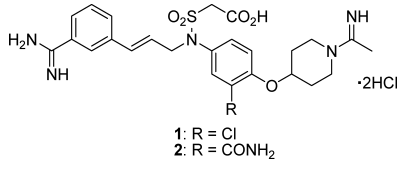


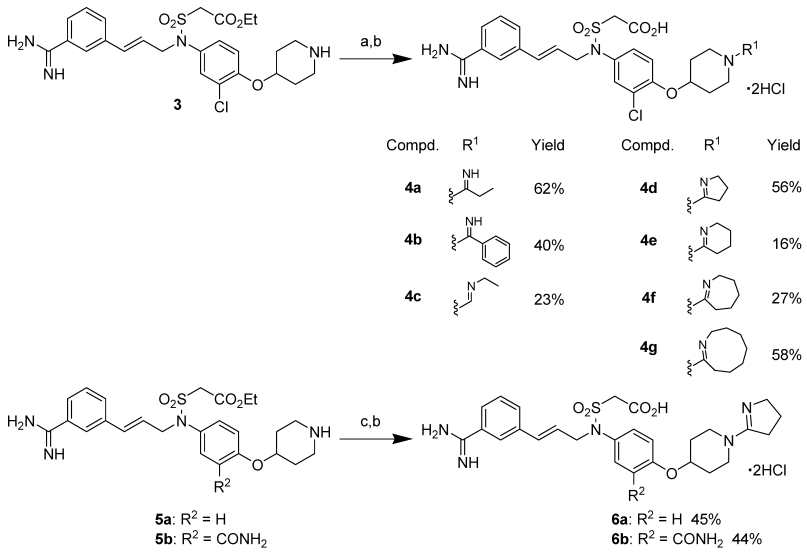
Fig. 1. Structures of Cinnamyl Derivatives **1** and **2**

Chemistry Cinnamyl derivatives with various imidoyl group on the piperidine ring were synthesized as shown in Chart 1. Piperidine **3**[13)] was reacted with iminoethers[14,15)] under basic conditions, followed by acid hydrolysis to give corresponding bisamidine derivatives **4a**—**g**. Other cinnamyl derivatives with a five-membered cyclic imidoyl group (**6a**, **6b**) were synthesized by the same methods as compound **4d**.

Monoamidine derivatives were synthesized as shown in Chart 2. A *t*-butoxycarbonyl (Boc) group of compound **7**[13)] was converted to a methyl group (**8a**) by treatment with formaldehyde solution and formic acid. Compound **7** was also deprotected under an acidic condition to give piperidine **9**. This compound was then subjected to a usual condition to give acetamide **8b**. Piperidine **9** was converted to corresponding *N*-alkyl or *N*-aryl compounds (**8c**—**k**) by reductive amination with aldehydes or ketones (method A), or treatment with alkyl- or arylbromide under a basic condition (method B), or Pd-catalyzed amination with arylbromide and phosphine **10** (method C).[16)] Reduction of the nitro group of compounds **8a**—**k** afforded aniline **11a**—**k**, respectively. An acetyl group of aniline **11b** was converted to an ethyl group (**11l**) by the treatment with $LiAlH_4$. These anilines **11a**, **11c**—**l** were subjected to methods similar to those of the other cinnamyl derivatives to give corresponding monoamidine derivatives **13a**, **13c**—**l**. A Boc group of known intermediate **14**[13)] was converted to *N*-(4-pyridylmethyl)piperidine compound **15** by 2 steps. This compound was also subjected to the similar methods described above to give corresponding monoamidine derivative **13m**.

Prodrugs of monoamidine derivative **16** were synthesized as shown in Chart 3. Monoamidine derivative **16**, synthesized as shown in Chart 2, was converted to its prodrugs **17a**—**i** by the treatment with symmetric carbonates or 4-nitrophenyl carbonates.[17,18)] Benzonitrile **18**, also synthesized as shown in Chart 2, was reacted with hydroxylamine under a basic condition to give amidoxime **17j**.

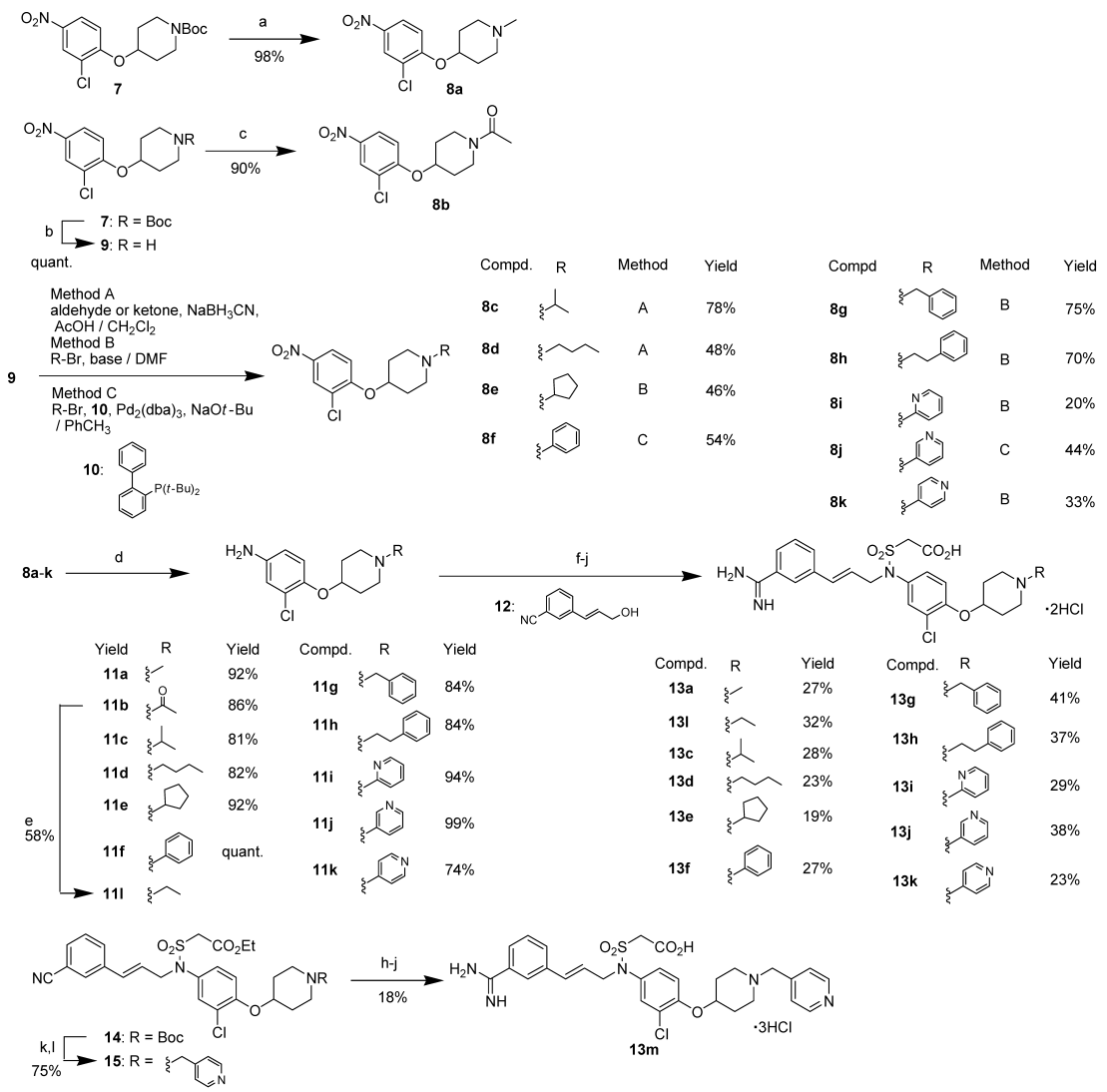
* To whom correspondence should be addressed. e-mail: tanaka.naoki.ri@daiichisankyo.co.jp



Compd.	R^1	Yield	Compd.	R^1	Yield
4a		62%	**4d**		56%
4b		40%	**4e**		16%
4c		23%	**4f**		27%
			4g		58%

Reagents : a) R^1-OMe or R^1-OEt ·HCl, Et_3N / EtOH; b) 3_N HCl; c) 5-methoxy-3,4-dihydro-2H-pyrrole, Et_3N / EtOH.

Chart 1



Compd.	R	Method	Yield
8c		A	78%
8d		A	48%
8e		B	46%
8f		C	54%

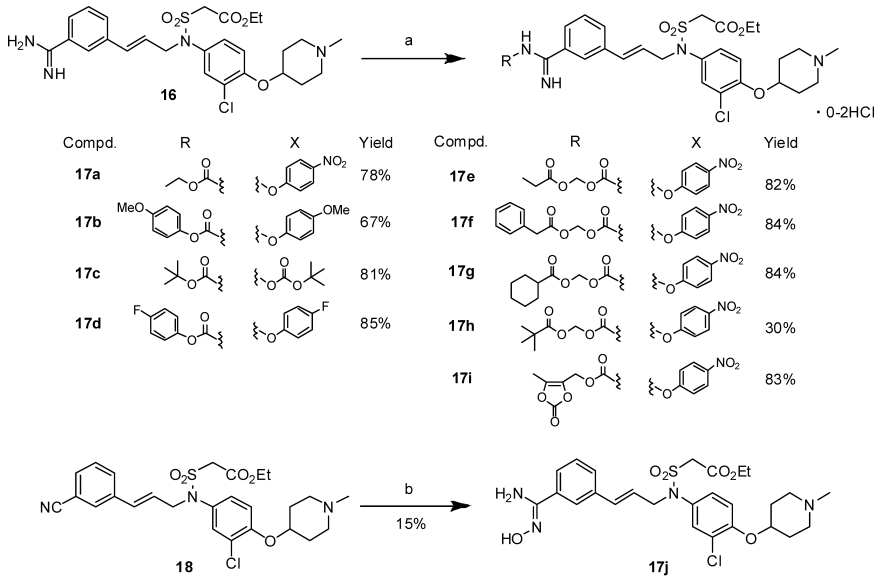
Compd	R	Method	Yield
8g		B	75%
8h		B	70%
8i		B	20%
8j		C	44%
8k		B	33%

Yield	R	Yield	Compd.	R	Yield
11a		92%	**11g**		84%
11b		86%	**11h**		84%
11c		81%	**11i**		94%
11d		82%	**11j**		99%
11e		92%	**11k**		74%
11f		quant.			
11l					

Compd.	R	Yield	Compd.	R	Yield
13a		27%	**13g**		41%
13l		32%	**13h**		37%
13c		28%	**13i**		29%
13d		23%	**13j**		38%
13e		19%	**13k**		23%
13f		27%			

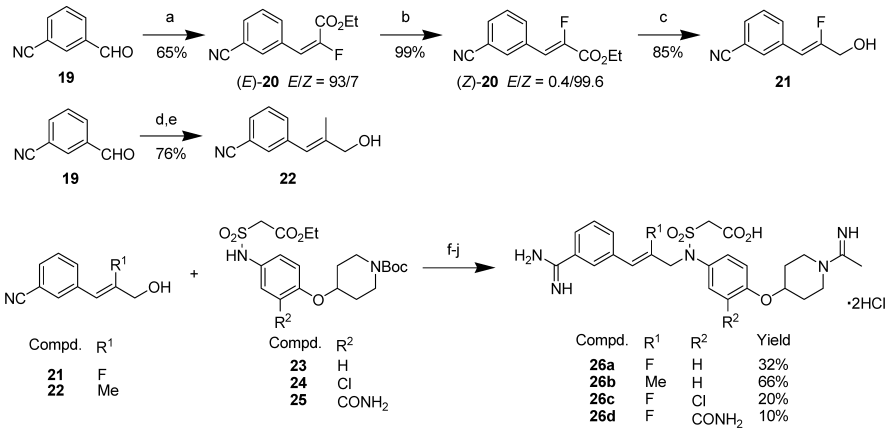
Reagents : a) HCHO aq., HCO_2H; b) HCl / dioxane; c) Ac_2O / Pyr.; d) Sn / AcOH; e) $LiAlH_4$ / THF; f) $EtO_2CCH_2SO_2Cl$, Pyr. / CH_2Cl_2; g) **12**, DEAD, PPh_3 / CH_2Cl_2; h) HCl g. / CH_2Cl_2-EtOH; i) NH_4Cl, NH_3 aq. / EtOH-H_2O; j) 3_N HCl; k) HCl / EtOH-dioxane; l) 4-(bromomethyl)pyridine · HBr, K_2CO_3 / DMF.

Chart 2



[a] Reagents : a) R-X, $NaHCO_3$ / CH_2Cl_2-H_2O; b) NH_2OH · HCl, Na_2CO_3 / EtOH.

Chart 3



Reagents : a) $(EtO)_2P(O)CHFCO_2Et$, NaH / THF; b) Br_2 / MeCN; c) $NaBH_4$ / EtOH; d) $Ph_3PC(Me)CHO$ / $PhCH_3$; e) $NaBH_4$, $CeCl_3$ · $7H_2O$ / EtOH-CH_2Cl_2; f) DEAD, PPh_3 / CH_2Cl_2; g) HCl g. / CH_2Cl_2-EtOH; h) NH_4Cl, NH_3 aq. / EtOH-H_2O; i) ethyl acetimidate · HCl, Et_3N / EtOH; j) 3_N HCl.

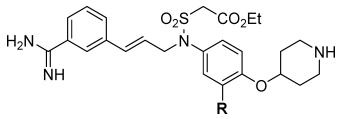
Chart 4

Cinnamyl derivatives with a substituent on the double bond were synthesized as shown in Chart 4. In the case of intermediate **21** with a fluorine atom, 3-cyanobenzaldehyde (**19**) was subjected to a Horner–Wittig reaction to give (*E*)-**20** and (*Z*)-**20** as an undesired mixture ratio (*E*/*Z*=93/7). Then, treated with bromine, the mixture was isomerized to give (*Z*)-**20** dominantly (*E*/*Z*=0.4/99.6).[19] This compound was treated with $NaBH_4$ to give *Z*-substituted fluoroallylalcohol **21**. In the case of intermediate **22** with a methyl group, 3-cyanobenzaldehyde **19** was also reacted with ylide, followed by Luche reduction[20] to give (*E*)-substituted methylallylalcohol **22**. Substituted allylalcohols **21** and **22** were coupled with sulfonamide **23**, **24** and **25** by means of a Mitsunobu reaction[21], followed by reactions similar to those of the other cinnamyl derivatives to give corresponding cinnamyl derivatives **26a**—**d**.

Results and Discussion

The *in vitro* FXa and trypsin inhibitory activities of all the compounds were evaluated and expressed as IC_{50} values. The *ex vivo* effects on prothrombin time (PT) in hamsters (*per os* (*p.o.*)) were also evaluated. Described above, this series of cinnamyl derivatives has two amidino groups in their structures. As a result, these compounds have high hydrophilicity. It seems that enhancement of these compounds' lipophilicity may improve their oral anticoagulant activity. As one of the approaches for the enhancement of lipophilicity, we attempted to remove the acetimidoyl group of these cinnamyl derivatives (Table 1).[22] Non-substituted piperidine compounds with various substituent patterns on the central benzene ring (**5a**, **5b**, **27**, **3**)[23] were synthesized and their biological activities were evaluated. Most of compounds exhibited significantly lower inhibitory activities than those of compound **1** and other acetimidoyl derivatives[13] *in vitro*. However, only chlorobenzene derivative **3** exhibited moderate *in vitro* FXa inhibitory activity. It seemed that the substituents on the benzene ring had a considerable effect on the FXa inhibitory activities of non-substituted piperidine compounds.

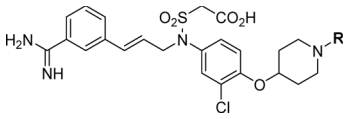
Table 1. Biological Activities of Compounds **5a**, **5b**, **27**, **3** and **1**

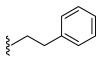


Compd.[a]	R	IC_{50} (nM)	
		FXa	Trypsin
5a	H	230	3300
5b	$CONH_2$	290	2100
27	F	250	2100
3	Cl	31	1800
1		7.4	520

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

Table 2. Biological Activities of Compounds **13a** and **13c**—**m**

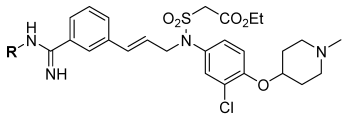


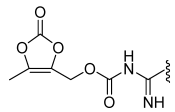
Compd.[a]	R	IC_{50} (nM)		Hamster *ex vivo* (*p.o.*, 1 h) CT_2 (mg/kg)[b]
		FXa	Trypsin	
13a		16	2900	48
13l		10	8700	77
13c		16	8700	>100
13d		24	8000	77
13e		12	5400	52
13f		170	2300	NT[c]
13g		15	990	NT[c]
13h		13	2200	NT[c]
13i		20	780	NT[c]
13j		32	590	NT[c]
13k		6.4	650	>100
13m		41	1600	NT[c]

a) All the compounds were synthesized and evaluated as their hydrochlorides. *b*) The concentration required to double the clotting time. *c*) Not tested.

Based on the results shown in Table 1, we synthesized monoamidine derivatives with non-amidine substituents *i.e.* alkyl, aryl, and arylalkyl groups on the nitrogen atom in the piperidine ring of chlorobenzene derivative **3**, and evaluated their biological activities (Table 2). Regarding alkyl derivatives (**13a**, **c**, **d**, **e**, **l**), these compounds exhibited potent FXa inhibitory activities (10—24 nM) *in vitro*. In particular, methyl derivative **13a** and cyclopentyl derivative **13e** also exhibited potent anticoagulant activities (*ex vivo*). On the other hand, phenyl derivative **13f** exhibited significantly lower FXa inhibitory activity than those of alkyl derivatives. However, the introduction of an alkyl chain (**13g**, **h**) between the piperidine ring and a phenyl group of **13f**, or conversion of one carbon atom on the phenyl group into a nitrogen atom (**13i**—**k**) improved the FXa inhibitory activities. Among them, 4-pyridyl derivative **13k** exhibited potent *in vitro* FXa inhibitory activity comparable to that of the bisamidine derivative **1**. However, in the *ex vivo* test by oral administration, compound **13k** exhibited almost no oral anticoagulant activity. From these results, a methyl group (**13a**) and a cyclopentyl group (**13e**) were favorable at this position.

Table 3. Biological Activities of Compounds **16**, **17a**—**j** and **13a**



17i: 

17j: 

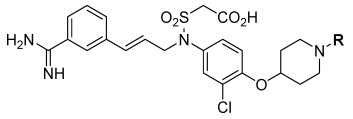
Compd.[a]	R	IC_{50} (nM)		Hamster *ex vivo* (*p.o.*, 1 h) CT_2 (mg/kg)[b]
		FXa	Trypsin	
16	–H	29	3200	56
17a	$–CO_2Et$	14000	NA[c]	43
17b	$–CO_2$(4-OMe-Ph)	1300	NA[c]	63
17c	$–CO_2t$-Bu	20000	NA[c]	>100
17d	$–CO_2$(4-F-Ph)	900	NA[c]	>100
17e	$–CO_2CH_2OCOEt$	960	NA[c]	>100
17f	$–CO_2CH_2OCOCH_2Ph$	320	97000	>100
17g	$–CO_2CH_2OCOc$-Hex	4500	NA[c]	>100
17h	$–CO_2CH_2OCOt$-Bu	9900	NA[c]	>100
17i		33	5700	>100
17j		12000	NA[c]	58
13a		16	2900	48

a) All the compounds were synthesized and evaluated as their hydrochlorides. *b*) The concentration required to double the clotting time. *c*) Not active (>100000).

As another approach to improve the lipophilicity and oral activity of monoamidine derivatives, we intended to convert **13a** to its prodrug form (Table 3). Compound **16** with an ester group instead of a carboxylic group exhibited oral anticoagulant activity similar to that of compound **13a**. Next, we attempted to convert an amidino moiety of compound **16** into its carbamate forms (**17a**—**i**) and amidoxime form (**17j**). Among these compounds, carbamate prodrugs **17a**, **17b** and amidoxime prodrug **17j** exhibited anticoagulant activities (*ex vivo*) similar to that of compound **13a**. However, as prodrugs, no advantages were observed. From the results shown in Tables 2 and 3, the conversion of bisamidine derivatives into monoamidine derivatives and their prodrugs could not improve the oral anticoagulant activity of bisamidine derivative **1**.

As an alternative approach to improve the lipophilicity of bisamidine derivative **1**, additional lipophilic imidoyl moieties other than an acetimidoyl group were introduced instead of an acetimidoyl group of compound **1**, and their biological activities were evaluated (Table 4). On the whole, most of the imidoyl compounds exhibited potent FXa inhibitory activi-

Table 4. Biological Activities of Compounds **1** and **4a**—**g**



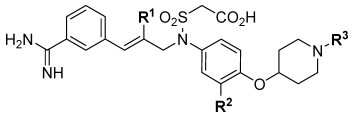
Compd.[a]	R	IC_{50} (nM)		Hamster *ex vivo* (*p.o.*, 1 h) CT_2 (mg/kg)[b]
		FXa	Trypsin	
1		7.4	520	14
4a		6.3	1200	2.2 fold@100 mg
4b		7.8	860	>100
4c		13	3500	NT[c]
4d		7.0	2200	27
4e		10	2000	47
4f		16	4000	NT[c]
4g		34	3400	NT[c]

a) All the compounds were synthesized and evaluated as their hydrochlorides. *b*) The concentration required to double the clotting time. *c*) Not tested.

ties *in vitro*. In particular, propioimidoyl (**4a**), benzimidoyl (**4b**), and five-membered cyclic imidoyl (**4d**) derivatives exhibited potent activities. Regarding cyclic imidoyl derivatives (**4d**—**g**), a tendency was observed indicating that a smaller ring size was suitable. In the *ex vivo* anticoagulant activities of these compounds, compound **4d** was as potent as compound **1** (27 mg/kg). From these results, we found that the acetimidoyl and five-membered cyclic imidoyl groups were suitable as this part.

Based on the results shown in Table 4, five-membered cyclic imidoyl derivatives **6a** and **6b** were synthesized and their biological activities were compared with those of corresponding acetimidoyl derivatives **28** and **2**, which exhibited favorable results in the previous report[13] (Table 5). Compounds **6a** and **6b** exhibited potent FXa inhibitory activities *in vitro*. In addition, these compounds exhibited improved enzyme selectivity over trypsin. However, we examined the mutagenic potential of these cinnamyl derivatives and found that all the derivatives exhibited positive results in Ames tests.[24] On the other hand, the reported naphthylamidine derivative YM-75466[25] (Fig. 2) exhibited a negative result in the test. In terms of structural differences between YM-75466 and our derivatives, YM-75466 has a naphthyl moiety whereas our derivatives have cinnamyl moieties. Therefore, we speculated that the cause of the positive result was the oxidation of the double bond. Based on this speculation, we introduced substituents at the β-position of the cinnamyl moiety of compound **28** and their mutagenic potentials as well as biological activities were examined. As a result, both compound **26a** with a fluorine atom and **26b** with a methyl group

Table 5. Biological Activities of Compounds **2**, **6a**, **6b**, **26a**—**d** and **28**



Compd.[a]	R^1	R^2	R^3	IC_{50} (nM)		Hamster *ex vivo* (*p.o.*, 1 h) CT_2 (mg/kg)[b]	Ames test
				FXa	Trypsin		
28	H	H		6.4	520	34	+
2	H	$CONH_2$		7.1	320	16	+
6a	H	H		14	3100	NT[c]	+
6b	H	$CONH_2$		9.8	4400	NT[c]	+
26a	F	H		9.3	960	38	−
26b	Me	H		10	1300	92	−
26c	F	Cl		7.4	3100	>100	NT[c]
26d	F	$CONH_2$		12	3100	33	−

a) All the compounds were synthesized and evaluated as their hydrochlorides. *b*) The concentration required to double the clotting time. *c*) Not tested.

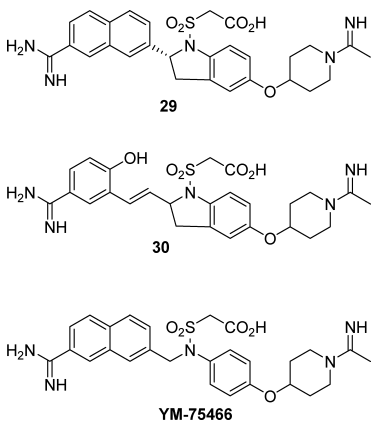


Fig. 2. Structures of Compounds **29**,[a] **30**[a] and YM-75466[b]
a) Hydrochloride. b) Methanesulfonate.

exhibited negative results in Ames tests. Compound **26a** also exhibited potent FXa inhibitory activity and oral anticoagulant activity similar to those of non-substituted derivative **28** in hamsters. To apply these findings to compounds **1** and **2**, we synthesized **26c** and **26d** with a fluorine atom and evaluated their activities. Both compounds exhibited potent FXa inhibitory activities *in vitro*. In the *ex vivo* tests, however, compound **26c** with a chlorine atom on the central benzene ring exhibited almost no oral anticoagulant activity. On the other hand, compound **26d** with a carbamoyl group at this position exhibited potent anticoagulant activity in hamsters (33 mg/kg, *p.o.*). Moreover, compound **26d** exhibited no mutagenic potential similar to those of **26a** and **26b**.

Cinnamyl derivatives with potent anticoagulant activities and no mutagenic potential (**1**, **26a**, **26b**, **26d**) in addition to our reported compounds (**29**, **30**) and YM-75466 (Fig. 2) were subjected to a pharmacokinetic study in dogs in order to assess the oral absorption of these derivatives (1 mg/kg) (Fig. 3). Compounds **1** and **26a** exhibited extremely low plasma concentrations, whereas compound **26d** exhibited an obviously high plasma concentration superior to those of the other tested compounds.

Moreover, compound **26d** exhibited a dose-dependent increase in plasma anti-FXa and anticoagulant activities after oral administration to dogs (Fig. 4).

From these results, compound **26d** (R-142086) has potent biological activities and a high plasma concentration by oral administration.

In conclusion, we synthesized many cinnamyl derivatives in order to develop compounds having potent oral anticoagulant activities. As a result, we found that cinnamyl derivatives with a fluorine atom or a methyl group on the double bond exhibited oral anticoagulant activities in hamsters and no mutagenic potential. Among them, **26d** (R-142086) exhibited potent oral anti-FXa and anticoagulant activity in addition to a high plasma concentration compared to the other indoline and cinnamyl derivatives in dogs.

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. The 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. 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, *t*-butyl methyl ether, and dimethylsulfoxide are abbreviated as THF, DMF, TBME and DMSO, respectively.

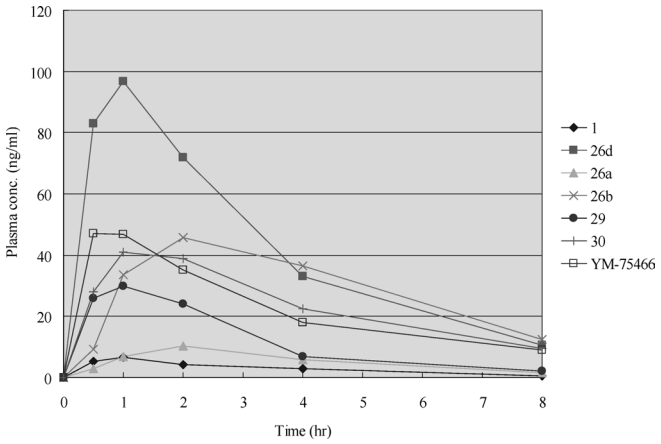


Fig. 3. Plasma Concentrations of Compounds **1**, **26a**, **26b**, **26d**, **29**, **30** and YM-75466 in Dogs after Oral Administration of Each Compound at a Dose of 1 mg/kg

(*N*-[(*E*)-3-(3-Amidinophenyl)-2-propenyl]-*N*-{3-chloro-4-[1-(1-iminopropyl)piperidin-4-yloxy]phenyl}sulfamoyl)acetic Acid Dihydrochloride (4a) To a solution of ethyl {*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[3-chloro-4-(piperidin-4-yloxy)phenyl]sulfamoyl}acetate dihydrochloride **3** (0.770 g, 1.27 mmol) in EtOH (25 ml) were added ethyl propionimidate hydrochloride (0.540 g, 3.92 mmol) and Et_3N (0.880 ml, 6.35 mmol) and the resulting mixture was allowed to stand at room temperature for 22 h. Ethyl propionimidate hydrochloride (0.180 g, 1.31 mmol) and Et_3N (0.350 ml, 2.52 mmol) were added and the mixture was stirred at room temperature for 4.5 h. A 4 N solution of hydrogen chloride in dioxane (10 ml) was added 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 EtOH (10 ml) and a 4 N solution of hydrogen chloride in dioxane (2 ml) and the mixture was concentrated. The resulting residue was dissolved in H_2O and the solution was lyophilized to give ethyl (*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-{3-chloro-4-[1-(1-iminopropyl)piperidin-4-yloxy]phenyl}sulfamoyl)acetate dihydrochloride (0.570 g, 0.860 mmol, 67%) as a colorless amorphous solid. This amorphous solid (0.420 g, 0.633 mmol) was dissolved in a 3 N solution of hydrogen chloride (15 ml) and stirred at 60 °C for 6.5 h. The reaction mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=41/9) to give an amorphous solid. This amorphous solid was dissolved in a 3 N solution of hydrogen chloride (3 ml) and the mixture was concentrated. The resulting residue was dissolved in H_2O and the solution was lyophilized to give **4a** (0.370 g, 0.583 mmol, 93%) as a colorless amorphous solid. MS *m*/*z*: 562 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, *J*=7.5 Hz), 1.71—1.87 (2H, m), 2.00—2.12 (2H, m), 2.63 (2H, q, *J*=7.5 Hz), 3.59—3.81 (4H, m), 4.30 (2H, s), 4.48 (2H, d, *J*=5.5 Hz), 4.81—4.88 (1H, m), 6.46 (1H, dt, *J*=16.0, 5.5 Hz), 6.58 (1H, d, *J*=16.0 Hz), 7.34 (1H, d, *J*=9.0 Hz), 7.43 (1H, dd, *J*=2.5, 9.0 Hz), 7.55 (1H, t, *J*=8.0 Hz), 7.60 (1H, d, *J*=2.5 Hz), 7.70—7.76 (2H, m), 7.94 (1H, s). IR (KBr) cm^{-1}: 1734, 1671, 1620, 1349, 1156. *Anal.* Calcd for $C_{26}H_{32}ClN_5O_5S \cdot 2.5HCl \cdot 0.4H_2O$: C, 47.28; H, 5.39; N, 10.60; Cl, 18.79; S, 4.85. Found: C, 47.12; H, 5.33; N, 10.71; Cl, 18.99; S, 4.86.

Similarly, compounds **4b**—**g** were prepared.

4b: MS *m*/*z*: 610 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.70—1.78 (1H, m), 1.88—2.02 (2H, m), 2.14—2.22 (1H, m), 3.28—3.50 (2H, m), 3.83—3.90 (1H, m), 3.91—4.01 (1H, m), 4.27 (2H, s), 4.45 (2H, d, *J*=5.0 Hz), 4.82—4.89 (1H, m), 6.44 (1H, dt, *J*=16.0, 5.0 Hz), 6.56 (1H, d, *J*=16.0 Hz), 7.32 (1H, d, *J*=9.0 Hz), 7.40 (1H, dd, *J*=2.5, 9.0 Hz), 7.51—7.71 (9H, m), 7.90 (1H, s). IR (KBr) cm^{-1}: 1733, 1673, 1605, 1349, 1155. *Anal.* Calcd for $C_{30}H_{32}ClN_5O_5S \cdot 2.2HCl \cdot 1.0H_2O$: C, 50.87; H, 5.15; N, 9.89; Cl, 16.02; S, 4.53. Found: C, 50.57; H, 5.02; N, 10.08; Cl, 15.95; S, 4.92.

4c: MS *m*/*z*: 562 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.19 (3H, t, *J*=7.0 Hz), 1.72—1.88 (2H, m), 1.98—2.09 (2H, m), 3.51—3.79 (6H, m), 4.28 (2H, s), 4.47 (2H, d, *J*=6.0 Hz), 4.80—4.87 (1H, m), 6.44 (1H, dt, *J*=16.0, 6.0 Hz), 6.57 (1H, d, *J*=16.0 Hz), 7.32 (1H, d, *J*=9.0 Hz), 7.41 (1H, dd, *J*=

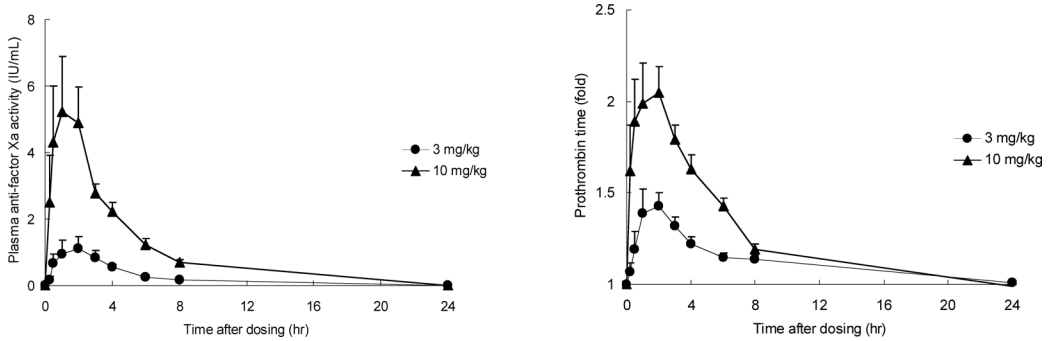


Fig. 4. Plasma Anti-FXa[a)] and Anticoagulant Activities after Oral Administration of R-142086 to Dogs

a) The activity was calibrated using the anti-FXa activity standard enoxaparin.

2.0, 9.0 Hz), 7.52—7.60 (2H, m), 7.68—7.75 (2H, m), 7.89 (1H, s), 8.13 (1H, d, J=13.5 Hz). IR (KBr) cm^{-1}: 1731, 1698, 1677, 1347, 1155. *Anal.* Calcd for $C_{26}H_{32}ClN_5O_5S \cdot 2.5HCl \cdot 0.2H_2O$: C, 47.54; H, 5.36; N, 10.66; Cl, 18.89; S, 4.88. Found: C, 47.47; H, 5.38; N, 10.72; Cl, 18.98; S, 4.90.

4d: MS m/z: 574 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.73—1.88 (2H, m), 2.00—2.14 (4H, m), 2.97 (2H, t, J=8.0 Hz), 3.50—3.88 (6H, m), 4.30 (2H, s), 4.47 (2H, d, J=5.5 Hz), 4.81—4.88 (1H, m), 6.46 (1H, dt, J=16.0, 5.5 Hz), 6.58 (1H, d, J=16.0 Hz), 7.34 (1H, d, J=9.0 Hz), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.59 (1H, d, J=2.5 Hz), 7.71—7.76 (2H, m), 7.93 (1H, s). IR (KBr) cm^{-1}: 1734, 1672, 1350, 1155. *Anal.* Calcd for $C_{27}H_{32}ClN_5O_5S \cdot 2.4HCl \cdot 0.7H_2O$: C, 48.10; H, 5.35; N, 10.39; Cl, 17.88; S, 4.76. Found: C, 48.06; H, 5.29; N, 10.45; Cl, 18.00; S, 4.69.

4e: MS m/z: 588 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.64—1.81 (6H, m), 1.99—2.08 (2H, m), 2.67—2.72 (2H, m), 3.30—3.37 (2H, m), 3.55—3.78 (4H, m), 4.28 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.80—4.87 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.32 (1H, d, J=9.0 Hz), 7.41 (1H, dd, J=2.5, 9.0 Hz), 7.53—7.59 (2H, m), 7.67—7.74 (2H, m), 7.88 (1H, s). IR (KBr) cm^{-1}: 1734, 1675, 1637, 1352, 1156. *Anal.* Calcd for $C_{28}H_{34}ClN_5O_5S \cdot 2.8HCl \cdot 1.2H_2O$: C, 47.25; H, 5.55; N, 9.84; Cl, 18.93; S, 4.50. Found: C, 46.88; H, 5.89; N, 10.12; Cl, 19.10; S, 5.09.

4f: MS m/z: 602 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.52—1.62 (4H, m), 1.67—1.82 (4H, m), 2.00—2.09 (2H, m), 2.84—2.88 (2H, m), 3.43—3.49 (2H, m), 3.63—3.91 (4H, m), 4.27 (2H, s), 4.46 (2H, d, J=5.5 Hz), 4.80—4.86 (1H, m), 6.44 (1H, dt, J=16.0, 5.5 Hz), 6.57 (1H, d, J=16.0 Hz), 7.32 (1H, d, J=9.0 Hz), 7.40 (1H, dd, J=2.5, 9.0 Hz), 7.51—7.61 (2H, m), 7.68—7.75 (2H, m), 7.89 (1H, s). IR (KBr) cm^{-1}: 1734, 1675, 1628, 1351, 1156. *Anal.* Calcd for $C_{29}H_{36}ClN_5O_5S \cdot 2.5HCl \cdot 1.2H_2O$: C, 48.72; H, 5.77; N, 9.80; Cl, 17.36; S, 4.48. Found: C, 48.93; H, 5.78; N, 9.51; Cl, 17.39; S, 4.62.

4g: MS m/z: 630 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.38—1.81 (12H, m), 2.00—2.09 (2H, m), 2.78—2.85 (2H, m), 3.48—3.57 (2H, m), 3.59—3.72 (2H, m), 3.73—3.86 (2H, m), 4.27 (2H, s), 4.46 (2H, d, J=5.5 Hz), 4.80—4.88 (1H, m), 6.44 (1H, dt, J=16.0, 5.5 Hz), 6.57 (1H, d, J=16.0 Hz), 7.31 (1H, d, J=9.0 Hz), 7.40 (1H, dd, J=2.5, 9.0 Hz), 7.51—7.60 (2H, m), 7.64—7.75 (2H, m), 7.87 (1H, s). IR (KBr) cm^{-1}: 1733, 1675, 1627, 1352, 1156. *Anal.* Calcd for $C_{31}H_{40}ClN_5O_5S \cdot 2.1HCl \cdot 1.7H_2O$: C, 50.49; H, 6.22; N, 9.50; Cl, 14.90; S, 4.35. Found: C, 50.40; H, 5.75; N, 9.64; Cl, 14.61; S, 4.63.

(*N*-[(*E*)-3-(3-Amidinophenyl)-2-propenyl]-*N*-{4-[1-(4,5-dihydro-3*H*-pyrrol-2-yl)piperidin-4-yloxy]phenyl}sulfamoyl)acetic Acid Dihydrochloride (6a) Ethyl {*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[4-(piperidin-4-yloxy)phenyl]sulfamoyl}acetate dihydrochloride **5a** was converted to **6a** by the same procedure as that for **4a**. Compound **6a** was obtained (45%, 2 steps) as a colorless amorphous solid. MS m/z: 540 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.68—1.80 (2H, m), 2.00—2.13 (4H, m), 2.96 (2H, t, J=8.0 Hz), 3.46—3.72 (5H, m), 3.83—3.92 (1H, m), 4.20 (2H, s), 4.45 (2H, d, J=5.5 Hz), 4.67—4.73 (1H, m), 6.45 (1H, dt, J=16.0, 5.5 Hz), 6.54 (1H, d, J=16.0 Hz), 7.04 (2H, d, J=9.0 Hz), 7.39 (2H, d, J=9.0 Hz), 7.54 (1H, t, J=8.0 Hz), 7.71 (2H, d, J=8.0 Hz), 7.90 (1H, s). IR (KBr) cm^{-1}: 1733, 1672, 1347, 1155. *Anal.* Calcd for $C_{27}H_{33}N_5O_5S \cdot 2.1HCl \cdot 1.6H_2O$: C, 50.28; H, 5.98; N, 10.86; Cl, 11.54; S, 4.97. Found: C, 50.12; H, 5.65; N, 10.96; Cl, 11.62; S, 4.99.

Similarly, compound **6b** was prepared.

6b: MS m/z: 583 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.80—1.95 (2H, m), 2.00—2.15 (4H, m), 2.96 (2H, m), 3.45—3.55 (1H, m), 3.55—3.75 (4H, m), 3.75—3.85 (1H, m), 4.24 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.82—4.88 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.57 (1H, d, J=16.0 Hz), 7.28 (1H, d, J=9.0 Hz), 7.52 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.67 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.77 (1H, d, J=2.5 Hz), 7.86 (1H, s). IR (KBr) cm^{-1}: 1731, 1670. *Anal.* Calcd for $C_{28}H_{34}N_6O_6S \cdot 2.9HCl \cdot 1.9H_2O$: C, 46.54; H, 5.68; N, 11.63; Cl, 14.23; S, 4.44. Found: C, 46.68; H, 5.68; N, 11.35; Cl, 14.15; S, 4.71.

3-Chloro-4-(1-methylpiperidin-4-yloxy)nitrobenzene (8a) To a suspension of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-chloronitrobenzene **7** (1.50 g, 4.20 mmol) in 90% HCO_2H (4.00 g) was added 37% HCHO solution (2.50 g) and the resulting mixture was stirred at 100 °C for 2 h. The mixture was neutralized with K_2CO_3 and extracted with EtOAc. The organic layer was washed with brine and dried. The organic layer was concentrated to give **8a** (1.12 g, 4.14 mmol, 98%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.10 (4H, m), 2.33 (3H, s), 2.35—2.45 (2H, m), 2.60—2.70 (2H, m), 4.54—4.61 (1H, m), 6.98 (1H, d, J=9.0 Hz), 8.13 (1H, dd, J=3.0, 9.0 Hz), 8.30 (1H, d, J=3.0 Hz).

3-Chloro-4-(piperidin-4-yloxy)nitrobenzene (9) To a solution of 4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-chloronitrobenzene **7** (7.91 g, 22.2 mmol) in dioxane (80 ml) was added a 4 N solution of hydrogen chloride in dioxane (70 ml), and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated and the resulting residue was dissolved in H_2O. The mixture was neutralized with $NaHCO_3$ to give crystals and the crystals were collected by filtration to give **9** (8.06 g, quant.) as pale yellow needles. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.60 (2H, m), 1.90—2.00 (2H, m), 2.57—2.68 (2H, m), 2.90—3.00 (2H, m), 3.93—3.99 (1H, m), 7.45 (1H, d, J=9.0 Hz), 8.18 (1H, dd, J=3.0, 9.0 Hz), 8.31 (1H, d, J=3.0 Hz).

4-(1-Acetylpiperidin-4-yloxy)-3-chloronitrobenzene (8b) To a solution of 3-chloro-4-(piperidin-4-yloxy)nitrobenzene **9** (1.00 g, 3.90 mmol) in pyridine (20 ml) was added Ac_2O (0.550 ml, 5.82 mmol) and the mixture was stirred at room temperature for 3 h. H_2O was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with $NaHCO_3$ solution and brine. The organic layer was dried and concentrated to give **8b** (1.05 g, 3.51 mmol, 90%) as a pale yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.03 (4H, m), 2.14 (3H, s), 3.50—3.63 (2H, m), 3.68—3.75 (1H, m), 3.91—3.97 (1H, m), 4.78—4.85 (1H, m), 7.01 (1H, d, J=9.0 Hz), 8.15 (1H, dd, J=2.5, 9.0 Hz), 8.32 (1H, d, J=2.5 Hz).

4-(1-Butylpiperidin-4-yloxy)-3-chloronitrobenzene (8d) (Method A) To a solution of 3-chloro-4-(piperidin-4-yloxy)nitrobenzene **9** (1.50 g, 5.84 mmol) and butyraldehyde (1.04 ml, 11.5 mmol) in CH_2Cl_2 (30 ml) were added AcOH (0.33 ml, 5.8 mmol) and $NaBH_3CN$ (0.18 g, 2.9 mmol) and the mixture was stirred at room temperature for 3 h. $NaBH_3CN$ (0.18 g, 2.9 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was concentrated and the resulting residue was diluted with EtOAc. The organic solution was washed with H_2O, $NaHCO_3$ solution and brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=20/1) to give **8d** (0.88 g, 2.81 mmol, 48%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.5 Hz), 1.31—1.39 (2H, m), 1.50—1.57 (2H, m), 1.92—2.04 (4H, m), 2.04—2.15 (2H, m), 2.40—2.48 (2H, m), 2.49—2.57 (2H, m), 2.70—2.80 (2H, m), 4.59—4.66 (1H, m), 6.99 (1H, d, J=9.0 Hz), 8.13 (1H, dd, J=2.5, 9.0 Hz), 8.30 (1H, d, J=2.5 Hz).

Similarly, compound **8c** was prepared.

8c: ^{1}H-NMR ($CDCl_3$) δ: 1.09 (6H, d, J=6.5 Hz), 1.90—2.00 (2H, m), 2.00—2.15 (2H, m), 2.45—2.60 (2H, m), 2.75—2.90 (3H, m), 4.55—4.63 (1H, m), 6.98 (1H, d, J=9.0 Hz), 8.13 (1H, dd, J=3.0, 9.0 Hz), 8.30 (1H, d, J=3.0 Hz).

3-Chloro-4-(1-cyclopentylpiperidin-4-yloxy)nitrobenzene (8e) (Method B) To a solution of 3-chloro-4-(piperidin-4-yloxy)nitrobenzene **9** (4.00 g, 15.6 mmol) in DMF (70 ml) were added cyclopentyl bromide (1.96 ml, 18.3 mmol) and K_2CO_3 (3.23 g, 23.4 mmol) and the mixture was stirred at 100 °C for 7 h. Cyclopentyl bromide (0.700 ml, 6.53 mmol) was added and the mixture was stirred at 100 °C for 2 h and at 120 °C for 5 h. The mixture was diluted with EtOAc and washed with brine. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=30/1—10/1) to give **8e** (2.35 g, 7.13 mmol, 46%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.37—1.48 (2H, m), 1.50—1.61 (2H, m), 1.65—1.76 (2H, m), 1.85—2.00 (4H, m), 2.00—2.10 (2H, m), 2.45—2.55 (2H, m), 2.53—2.60 (1H, m), 2.70—2.81 (2H, m), 4.56—4.64 (1H, m), 6.98 (1H, d, J=9.0 Hz), 8.13 (1H, dd, J=3.0, 9.0 Hz), 8.30 (1H, d, J=3.0 Hz).

Similarly, compounds **8g**—**i** and **8k** were prepared.

8g: ^{1}H-NMR ($CDCl_3$) δ: 1.88—1.98 (2H, m), 1.98—2.08 (2H, m), 2.37—2.48 (2H, m), 2.66—2.77 (2H, m), 3.55 (2H, s), 4.54—4.61 (1H, m), 6.97 (1H, d, J=9.0 Hz), 7.23—7.37 (5H, m), 8.12 (1H, dd, J=2.5, 9.0 Hz), 8.30 (1H, d, J=2.5 Hz).

8h: ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.03 (2H, m), 2.03—2.13 (2H, m), 2.46—2.59 (2H, m), 2.61—2.71 (2H, m), 2.73—2.88 (4H, m), 4.58—4.63 (1H, m), 6.99 (1H, d, J=9.0 Hz), 7.17—7.24 (3H, m), 7.24—7.34 (2H, m), 8.13 (1H, dd, J=3.0, 9.0 Hz), 8.31 (1H, d, J=3.0 Hz).

8i: ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.06 (2H, m), 2.06—2.17 (2H, m), 3.60—3.72 (2H, m), 3.79—3.90 (2H, m), 4.76—4.84 (1H, m), 6.64 (1H, dd, J=5.0, 7.0 Hz), 6.71 (1H, d, J=8.5 Hz), 7.04 (1H, d, J=9.0 Hz), 7.48—7.53 (1H, m), 8.16 (1H, dd, J=3.0, 9.0 Hz), 8.20 (1H, dd, J=2.0, 5.0 Hz), 8.32 (1H, d, J=3.0 Hz).

8k: ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.14 (4H, m), 3.46—3.55 (2H, m), 3.58—3.67 (2H, m), 4.80—4.87 (1H, m), 6.72 (2H, d, J=6.5 Hz), 7.03 (1H, d, J=9.0 Hz), 8.16 (1H, dd, J=3.0, 9.0 Hz), 8.28 (2H, d, J=6.5 Hz), 8.32 (1H, d, J=3.0 Hz).

3-Chloro-4-(1-phenylpiperidin-4-yloxy)nitrobenzene (8f) (Method C) To a solution of 3-chloro-4-(piperidin-4-yloxy)nitrobenzene **9** (2.68 g, 10.4 mmol), bromobenzene (1.97 g, 12.5 mmol), 2-(di-*t*-butylphosphino)biphenyl **10** (0.62 g, 2.1 mmol) and $Pd_2(dba)_3$ (0.95 g, 1.0 mmol) in toluene (30 ml)

was added NaO*t*-Bu (1.20 g, 12.5 mmol) and the mixture was stirred at 80 °C for 2 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=4/1) to give **8f** (1.86 g, 5.59 mmol, 54%) as a yellow solid. ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.10 (2H, m), 2.11—2.21 (2H, m), 3.19—3.29 (2H, m), 3.44—3.53 (2H, m), 4.70—4.77 (1H, m), 6.88 (1H, t, J=7.5 Hz), 6.95—7.00 (2H, m), 7.03 (1H, d, J=9.0 Hz), 7.25—7.32 (2H, m), 8.15 (1H, dd, J=3.0, 9.0 Hz), 8.31 (1H, d, J=3.0 Hz).

Similarly, compound **8j** was prepared.

8j: ^{1}H-NMR ($CDCl_3$) δ: 2.03—2.22 (4H, m), 3.26—3.37 (2H, m), 3.44—3.54 (2H, m), 4.74—4.81 (1H, m), 7.03 (1H, d, J=9.0 Hz), 7.18 (1H, dd, J=4.5, 8.5 Hz), 7.22—7.26 (1H, m), 8.12 (1H, dd, J=1.5, 4.5 Hz), 8.16 (1H, dd, J=3.0, 9.0 Hz), 8.32 (1H, d, J=3.0 Hz), 8.36 (1H, d, J=3.0 Hz).

3-Chloro-4-(1-methylpiperidin-4-yloxy)aniline (11a) To a solution of 3-chloro-4-(1-methylpiperidin-4-yloxy)nitrobenzene **8a** (8.48 g, 31.3 mmol) in AcOH (200 ml) was added tin powder (18.59 g, 156.6 mmol) and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated. The resulting residue was neutralized with K_2CO_3 solution and the mixture was extracted with EtOAc. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=3/1) to give **11a** (6.95 g, 28.9 mmol, 92%) as a red-brown solid. ^{1}H-NMR ($CDCl_3$) δ: 1.82—2.02 (4H, m), 2.20—2.30 (2H, m), 2.30 (3H, s), 2.68—2.78 (2H, m), 4.09—4.16 (1H, m), 6.51 (1H, dd, J=3.0, 8.5 Hz), 6.72 (1H, d, J=3.0 Hz), 6.81 (1H, d, J=8.5 Hz).

Similarly, compounds **11b**—**k** were prepared.

11b: ^{1}H-NMR ($CDCl_3$) δ: 1.78—1.94 (4H, m), 2.11 (3H, s), 3.33—3.43 (1H, m), 3.60—3.70 (1H, m), 3.70—3.82 (2H, m), 4.32—4.39 (1H, m), 6.53 (1H, dd, J=3.0, 8.5 Hz), 6.74 (1H, d, J=3.0 Hz), 6.81 (1H, d, J=8.5 Hz).

11c: ^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J=6.5 Hz), 1.80—2.20 (4H, m), 2.61—2.71 (2H, m), 2.91—3.00 (2H, m), 3.00—3.06 (1H, m), 4.24—4.31 (1H, m), 6.52 (1H, dd, J=3.0, 8.5 Hz), 6.73 (1H, d, J=3.0 Hz), 6.80 (1H, d, J=8.5 Hz).

11d: ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.5 Hz), 1.30—1.38 (2H, m), 1.55—1.64 (2H, m), 1.92—2.02 (2H, m), 2.08—2.18 (2H, m), 2.58—2.67 (2H, m), 2.74—2.84 (2H, m), 2.90—2.98 (2H, m), 4.28—4.34 (1H, m), 6.52 (1H, dd, J=3.0, 8.5 Hz), 6.73 (1H, d, J=3.0 Hz), 6.79 (1H, d, J=8.5 Hz).

11e: ^{1}H-NMR ($CDCl_3$) δ: 1.48—1.61 (2H, m), 1.61—1.78 (4H, m), 1.86—2.02 (4H, m), 2.06—2.19 (2H, m), 2.71—2.98 (5H, m), 4.26—4.33 (1H, m), 6.52 (1H, dd, J=2.5, 8.5 Hz), 6.73 (1H, d, J=2.5 Hz), 6.79 (1H, d, J=8.5 Hz).

11f: ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.01 (2H, m), 2.03—2.12 (2H, m), 3.02—3.12 (2H, m), 3.50—3.61 (2H, m), 4.23—4.30 (1H, m), 6.53 (1H, dd, J=3.0, 8.5 Hz), 6.74 (1H, d, J=3.0 Hz), 6.81—6.87 (1H, m), 6.84 (1H, d, J=8.5 Hz), 6.96 (2H, d, J=8.0 Hz), 7.23—7.29 (2H, m).

11g: ^{1}H-NMR ($CDCl_3$) δ: 1.80—1.90 (2H, m), 1.90—2.00 (2H, m), 2.21—2.32 (2H, m), 2.71—2.81 (2H, m), 3.52 (2H, s), 4.08—4.15 (1H, m), 6.50 (1H, dd, J=3.0, 8.5 Hz), 6.72 (1H, d, J=3.0 Hz), 6.80 (1H, d, J=8.5 Hz), 7.22—7.28 (1H, m), 7.28—7.36 (4H, m).

11h: ^{1}H-NMR ($CDCl_3$) δ: 1.83—1.95 (2H, m), 1.95—2.06 (2H, m), 2.32—2.42 (2H, m), 2.58—2.67 (2H, m), 2.77—2.91 (4H, m), 4.12—4.20 (1H, m), 6.52 (1H, dd, J=3.0, 8.5 Hz), 6.73 (1H, d, J=3.0 Hz), 6.82 (1H, d, J=8.5 Hz), 7.17—7.24 (3H, m), 7.24—7.32 (2H, m).

11i: ^{1}H-NMR ($CDCl_3$) δ: 1.83—1.95 (2H, m), 1.97—2.07 (2H, m), 3.36—3.47 (2H, m), 3.90—4.01 (2H, m), 4.30—4.37 (1H, m), 6.53 (1H, dd, J=3.0, 8.5 Hz), 6.59 (1H, dd, J=5.5, 7.0 Hz), 6.69 (1H, d, J=8.5 Hz), 6.74 (1H, d, J=3.0 Hz), 6.85 (1H, d, J=8.5 Hz), 7.45—7.49 (1H, m), 8.17—8.22 (1H, m).

11j: ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.11 (4H, m), 3.08—3.19 (2H, m), 3.51—3.61 (2H, m), 4.27—4.34 (1H, m), 6.53 (1H, dd, J=2.0, 9.0 Hz), 6.74 (1H, d, J=2.0 Hz), 6.84 (1H, d, J=9.0 Hz), 7.16 (1H, dd, J=4.5, 8.5 Hz), 7.18—7.23 (1H, m), 8.08 (1H, d, J=4.5 Hz), 8.34 (1H, d, J=2.5 Hz).

11k: ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.05 (4H, m), 3.30—3.38 (2H, m), 3.65—3.73 (2H, m), 4.34—4.41 (1H, m), 6.54 (1H, dd, J=3.0, 8.5 Hz), 6.69 (2H, dd, J=1.5, 5.0 Hz), 6.74 (1H, d, J=3.0 Hz), 6.83 (1H, d, J=8.5 Hz), 8.25 (2H, dd, J=1.5, 5.0 Hz).

3-Chloro-4-(1-ethylpiperidin-4-yloxy)aniline (11l) A solution of 4-(1-acetylpiperidin-4-yloxy)-3-chloroaniline **11b** (820 mg, 3.05 mmol) in THF (10 ml) was added to a suspension of $LiAlH_4$ (230 mg, 6.06 mmol) in THF (5 ml) and the mixture was refluxed for 3.5 h. $LiAlH_4$ (115 mg, 3.03 mmol) was added and the mixture was refluxed for 2 h. $Na_2SO_4 \cdot 10H_2O$ was added and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=3/1—1/2) to give **11l** (448 mg, 1.76 mmol, 58%) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, t, J=7.0 Hz), 1.82—2.04 (4H, m), 2.24—2.34 (2H, m), 2.45 (2H, q, J=7.0 Hz), 2.73—2.83 (2H, m), 4.11—4.18 (1H, m), 6.51 (1H, dd, J=3.0, 8.5 Hz), 6.73 (1H, d, J=3.0 Hz), 6.81 (1H, d, J=8.5 Hz).

{*N*-[(*E*)-3-(3-Amidinophenyl)-2-propenyl]-*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]sulfamoyl}acetic Acid Dihydrochloride (13a) To a solution of 3-chloro-4-(1-methylpiperidin-4-yloxy)aniline **11a** (6.95 g, 28.9 mmol) in CH_2Cl_2 (150 ml) were added $EtO_2CCH_2SO_2Cl$ (3.88 ml, 28.9 mmol) and pyridine (4.67 ml, 57.7 mmol) and the mixture was stirred at room temperature for 5 h. H_2O was added and the mixture was extracted with EtOAc. The organic layer was dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH=4/1—1/1) to give ethyl {*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]sulfamoyl}acetate (9.12 g, 23.3 mmol, 81%) as a brown amorphous solid. This amorphous solid (7.37 g, 18.9 mmol), (*E*)-3-(3-cyanophenyl)-2-propen-1-ol **12** (3.30 g, 20.7 mmol) and PPh_3 (5.93 g, 22.6 mmol) were dissolved in CH_2Cl_2 (200 ml) and the mixture was treated with diethyl azodicarboxylate (DEAD) (3.49 ml, 22.2 mmol). The resulting mixture was stirred overnight at room temperature and the mixture was concentrated. The resulting residue was chromatographed on a silica gel column (EtOAc/MeOH=3/1—1/2) to give ethyl {*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl}acetate (7.29 g, 13.7 mmol, 73%) as an orange amorphous solid. Into a solution of this amorphous solid (938 mg, 1.76 mmol) in CH_2Cl_2 (30 ml) and EtOH (15 ml) was bubbled hydrogen chloride under ice-cooling, and the resulting mixture was stirred at room temperature under tightly sealed conditions for 5 h. The reaction mixture was concentrated and the resulting residue was dissolved in EtOH (20 ml). The solution was treated with NH_4Cl (189 mg, 3.53 mmol) in H_2O (10 ml) and NH_3 solution (0.350 ml, 5.75 mmol) and the mixture was stirred overnight at room temperature. The mixture was treated with a 4 N solution of hydrogen chloride in dioxane and concentrated. The resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=39/11) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride and the mixture was concentrated. The resulting residue was lyophilized to give ethyl {*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]sulfamoyl}acetate dihydrochloride (841 mg, 1.35 mmol, 77%) as a colorless amorphous solid. This amorphous solid (435 mg, 0.699 mmol) was dissolved in a 3 N solution of hydrogen chloride (20 ml) and stirred at 60 °C for 6.5 h. The reaction mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=87/13) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride (1 ml) and the mixture was concentrated. The resulting residue was lyophilized to give **13a** (243 mg, 0.409 mmol, 59%) as a colorless amorphous solid. MS *m/z*: 521 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.90—2.07 (2H, m), 2.13—2.24 (2H, m), 2.68—2.80 (3H, m), 3.00—3.09 (2H, m), 3.30—3.51 (2H, m), 4.28 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.60—4.88 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.29—7.33 (1H, m), 7.38—7.43 (1H, m), 7.55 (1H, t, J=8.0 Hz), 7.57—7.61 (1H, m), 7.69 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1732, 1676, 1348, 1155. *Anal.* Calcd for $C_{24}H_{29}ClN_4O_5S \cdot 2.1HCl \cdot 1.6H_2O$: C, 46.02; H, 5.52; N, 8.94; Cl, 17.54; S, 5.12. Found: C, 45.95; H, 5.44; N, 8.99; Cl, 17.34; S, 5.31.

Similarly, compounds **13c**—**l** were prepared.

13c: MS *m/z*: 549 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, d, J=6.5 Hz), 1.91—2.03 (2H, m), 2.13—2.23 (2H, m), 2.92—3.38 (5H, m), 3.99 (2H, s), 4.48 (2H, d, J=6.0 Hz), 4.72—4.79 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.55 (1H, d, J=16.0 Hz), 7.27 (1H, d, J=9.0 Hz), 7.46 (1H, dd, J=2.5, 9.0 Hz), 7.54 (1H, t, J=8.0 Hz), 7.65 (1H, d, J=2.5 Hz), 7.67 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 7.87 (1H, s). IR (KBr) cm^{-1}: 1677, 1344, 1151. *Anal.* Calcd for $C_{26}H_{33}ClN_4O_5S \cdot 1.3HCl \cdot 2.3H_2O$: C, 48.95; H, 6.15; N, 8.78; Cl, 12.78; S, 5.03. Found: C, 48.77; H, 6.05; N, 9.09; Cl, 12.76; S, 5.31.

13d: MS *m/z*: 563 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, J=7.5 Hz), 1.26—1.35 (2H, m), 1.56—1.65 (2H, m), 1.86—1.98 (2H, m), 2.09—2.18 (2H, m), 2.83—3.18 (6H, m), 4.03 (2H, s), 4.48 (2H, d, J=6.0 Hz), 4.67—4.74 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.56 (1H, d, J=16.0 Hz), 7.27 (1H, d, J=9.0 Hz), 7.45 (1H, dd, J=2.5, 9.0 Hz), 7.54 (1H, t, J=8.0 Hz), 7.64 (1H, d, J=2.5 Hz), 7.67 (1H, d, J=8.0 Hz), 7.71 (1H, d, J=8.0 Hz), 7.86 (1H, s). IR (KBr) cm^{-1}: 1676, 1347, 1153. *Anal.* Calcd for $C_{27}H_{35}ClN_4O_5S \cdot 1.4HCl \cdot 2.0H_2O$: C, 49.88; H, 6.26; N, 8.62; Cl, 13.09; S, 4.93. Found: C, 49.58; H, 6.09; N, 8.76; Cl, 13.30; S, 5.04.

13e: MS *m/z*: 575 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.48—1.63 (2H, m), 1.63—1.76 (2H, m), 1.76—1.88 (2H, m), 1.93—2.10 (4H, m), 2.15—2.35 (2H, m), 2.91—3.13 (2H, m), 3.20—3.59 (3H, m), 4.26 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.64—4.93 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.31 (1H, d, J=9.0 Hz), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.61 (1H, d, J=2.5 Hz), 7.69 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.90 (1H, s). IR (KBr) cm^{-1}: 1732, 1676, 1348, 1155. *Anal.* Calcd for $C_{28}H_{35}ClN_4O_5S \cdot 2.0HCl \cdot 1.7H_2O$: C, 49.55; H, 6.00; N, 8.26; Cl, 15.67; S, 4.72. Found: C, 49.57; H, 5.81; N, 8.48; Cl, 15.56; S, 4.95.

13f: MS *m/z*: 583 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.88—2.08 (2H, m), 2.10—2.32 (2H, m), 3.04—3.91 (4H, m), 4.28 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.79—4.85 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.09—7.14 (1H, m), 7.26—7.49 (4H, m), 7.32 (1H, d, J=9.0 Hz), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.60 (1H, d, J=2.5 Hz), 7.68 (1H, d, J=8.0 Hz), 7.74 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1733, 1676, 1349, 1155. *Anal.* Calcd for $C_{29}H_{31}ClN_4O_5S \cdot 2.0HCl \cdot 1.9H_2O$: C, 50.46; H, 5.37; N, 8.12; Cl, 15.41; S, 4.65. Found: C, 50.79; H, 5.07; N, 7.93; Cl, 15.22; S, 4.78.

13g: MS *m/z*: 597 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.90—2.08 (2H, m), 2.12—2.26 (2H, m), 2.92—3.02 (2H, m), 3.20—3.50 (2H, m), 4.20—4.38 (2H, m), 4.25 (2H, s), 4.46 (2H, d, J=6.0 Hz), 4.59—4.85 (1H, m), 6.42 (1H, dt, J=16.0, 6.0 Hz), 6.56 (1H, d, J=16.0 Hz), 7.27 (1H, d, J=9.0 Hz), 7.39 (1H, dd, J=2.5, 9.0 Hz), 7.40—7.50 (3H, m), 7.54 (1H, t, J=8.0 Hz), 7.55—7.65 (3H, m), 7.66 (1H, d, J=8.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.85 (1H, s). IR (KBr) cm^{-1}: 1732, 1675, 1349, 1154. *Anal.* Calcd for $C_{30}H_{33}ClN_4O_5S \cdot 1.9HCl \cdot 1.8H_2O$: C, 51.56; H, 5.55; N, 8.02; Cl, 14.71; S, 4.59. Found: C, 51.43; H, 5.54; N, 8.03; Cl, 14.52; S, 4.92.

13h: MS *m/z*: 611 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.96—2.08 (2H, m), 2.18—2.28 (2H, m), 3.00—3.14 (4H, m), 3.20—3.50 (4H, m), 4.26 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.80—4.87 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.22—7.39 (6H, m), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.60 (1H, d, J=2.5 Hz), 7.67 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.87 (1H, s). IR (KBr) cm^{-1}: 1732, 1675, 1349, 1154. *Anal.* Calcd for $C_{31}H_{35}ClN_4O_5S \cdot 1.9HCl \cdot 1.6H_2O$: C, 52.50; H, 5.70; N, 7.90; Cl, 14.50; S, 4.52. Found: C, 52.52; H, 5.49; N, 7.96; Cl, 14.44; S, 4.62.

13i: MS *m/z*: 584 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.71—1.82 (2H, m), 2.01—2.12 (2H, m), 3.63—3.75 (2H, m), 3.85—3.97 (2H, m), 4.28 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.80—4.87 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 6.87—6.92 (1H, m), 7.30—7.40 (1H, m), 7.33 (1H, d, J=9.0 Hz), 7.41 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.59 (1H, d, J=2.5 Hz), 7.68 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s), 7.90—7.96 (1H, m), 8.02 (1H, d, J=6.0 Hz). IR (KBr) cm^{-1}: 1733, 1676, 1349, 1155. *Anal.* Calcd for $C_{28}H_{30}ClN_5O_5S \cdot 1.8HCl \cdot 2.0H_2O$: C, 49.04; H, 5.26; N, 10.21; Cl, 14.48; S, 4.68. Found: C, 48.75; H, 4.87; N, 10.24; Cl, 14.34; S, 4.80.

13j: MS *m/z*: 584 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.69—1.81 (2H, m), 1.97—2.08 (2H, m), 3.37—3.48 (2H, m), 3.62—3.72 (2H, m), 4.29 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.77—4.84 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.33 (1H, d, J=9.0 Hz), 7.41 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.59 (1H, d, J=2.5 Hz), 7.69 (1H, d, J=8.0 Hz), 7.74 (1H, d, J=8.0 Hz), 7.77 (1H, dd, J=5.5, 9.0 Hz), 7.89 (1H, s), 8.04 (1H, dd, J=2.0, 9.0 Hz), 8.15 (1H, d, J=5.5 Hz), 8.48 (1H, d, J=2.0 Hz). IR (KBr) cm^{-1}: 1731, 1675, 1348, 1154. *Anal.* Calcd for $C_{28}H_{30}ClN_5O_5S \cdot 2.2HCl \cdot 1.8H_2O$: C, 48.27; H, 5.18; N, 10.05; Cl, 16.28; S, 4.60. Found: C, 48.19; H, 4.97; N, 10.13; Cl, 16.13; S, 4.76.

13k: MS *m/z*: 584 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.70—1.80 (2H, m), 1.99—2.09 (2H, m), 3.64—3.75 (2H, m), 3.80—3.90 (2H, m), 4.26 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.83—4.90 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.22 (2H, d, J=7.5 Hz), 7.33 (1H, d, J=9.0 Hz), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55 (1H, t, J=8.0 Hz), 7.59 (1H, d, J=2.5 Hz), 7.69 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.89 (1H, s), 8.24 (2H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 1731, 1675, 1347, 1154. *Anal.* Calcd for $C_{28}H_{30}ClN_5O_5S \cdot 1.7HCl \cdot 2.3H_2O$: C, 48.92; H, 5.32; N, 10.19; Cl, 13.92; S, 4.66. Found: C, 49.11; H, 5.08; N, 10.22; Cl, 13.87; S, 4.72.

13l: MS *m/z*: 535 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.5 Hz), 1.92—2.05 (2H, m), 2.14—2.24 (2H, m), 2.99—3.10 (2H, m), 3.02—3.49 (4H, m), 4.15 (2H, s), 4.48 (2H, d, J=6.0 Hz), 4.72—4.79 (1H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.57 (1H, d, J=16.0 Hz), 7.29 (1H, d, J=9.0 Hz), 7.43 (1H, dd, J=2.5, 9.0 Hz), 7.54 (1H, t, J=8.0 Hz), 7.62 (1H, d, J=2.5 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}: 1731, 1676, 1348, 1154. *Anal.* Calcd for $C_{25}H_{31}ClN_4O_5S \cdot 2.2HCl \cdot 1.4H_2O$: C, 46.88; H, 5.67; N, 8.75; Cl, 17.71; S, 5.01. Found: C, 46.75; H, 5.70; N, 8.48; Cl, 17.57; S, 5.37.

Ethyl (*N*-{3-Chloro-4-[1-(4-pyridylmethyl)piperidin-4-yloxy]phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate (15) To a solution of ethyl (*N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-chlorophenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate **14** (1.25 g, 2.02 mmol) in EtOH (15 ml) was added a 4 N solution of hydrogen chloride in dioxane (15 ml) and the resulting mixture was stirred at room temperature for 4 h. The mixture was concentrated and the resulting residue was diluted with EtOAc. The organic solution was washed with $NaHCO_3$ and brine, dried and concentrated to give ethyl {*N*-[3-chloro-4-(piperidin-4-yloxy)phenyl]-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl}acetate (1.10 g, quant.) as a pale yellow oil. This oil (1.10 g) was dissolved in DMF (30 ml) and treated with 4-(bromomethyl)pyridine hydrobromide (590 mg, 2.33 mmol) and K_2CO_3 (590 mg, 4.27 mmol). The mixture was stirred overnight at room temperature and the mixture was diluted with EtOAc. The mixture was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (EtOAc/MeOH=10/1) to give **15** (970 mg, 1.60 mmol, 75%) as a pale yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.0 Hz), 1.86—1.95 (2H, m), 1.95—2.04 (2H, m), 2.33—2.43 (2H, m), 2.65—2.74 (2H, m), 3.53 (2H, s), 3.98 (2H, s), 4.31 (2H, q, J=7.0 Hz), 4.40—4.47 (1H, m), 4.46 (2H, d, J=6.5 Hz), 6.22 (1H, dt, J=16.0, 6.5 Hz), 6.41 (1H, d, J=16.0 Hz), 6.92 (1H, d, J=9.0 Hz), 7.28 (2H, d, J=6.0 Hz), 7.31 (1H, dd, J=2.5, 9.0 Hz), 7.40 (1H, t, J=8.0 Hz), 7.49—7.54 (2H, m), 7.53 (1H, d, J=2.5 Hz), 7.55 (1H, s), 8.54 (2H, d, J=6.0 Hz).

(*N*-[(*E*)-3-(3-Amidinophenyl)-2-propenyl]-*N*-{3-chloro-4-[1-(4-pyridylmethyl)piperidin-4-yloxy]phenyl}sulfamoyl)acetic Acid Trihydrochloride (13m) Ethyl (*N*-{3-chloro-4-[1-(4-pyridylmethyl)piperidin-4-yloxy]-phenyl}-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl)acetate **15** was converted to **13m** by the same procedure as that for **13a**. Compound **13m** was obtained (18%, 3 steps) as a colorless amorphous solid. MS *m/z*: 598 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.97—2.16 (2H, m), 2.16—2.40 (2H, m), 3.05—3.16 (2H, m), 3.30—3.46 (2H, m), 4.28 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.52—4.92 (3H, m), 6.44 (1H, dt, J=16.0, 6.0 Hz), 6.57 (1H, d, J=16.0 Hz), 7.28—7.33 (1H, m), 7.38—7.44 (1H, m), 7.54 (1H, t, J=8.0 Hz), 7.59 (1H, s), 7.68—7.74 (2H, m), 7.90 (1H, s), 8.14—8.22 (2H, m), 8.88—8.93 (2H, m). IR (KBr) cm^{-1}: 1731, 1675, 1347, 1154. *Anal.* Calcd for $C_{29}H_{32}ClN_5O_5S \cdot 3.2HCl \cdot 1.7H_2O$: C, 46.73; H, 5.22; N, 9.40; Cl, 19.98; S, 4.30. Found: C, 46.65; H, 5.22; N, 9.45; Cl, 20.00; S, 4.44.

Ethyl (*N*-[3-Chloro-4-(1-methylpiperidin-4-yloxy)phenyl]-*N*-{(*E*)-3-[3-(etoxycarbonylamino)(imino)methylphenyl]-2-propenyl}sulfamoyl)-acetate Dihydrochloride (17a) To a solution of ethyl {*N*-[(*E*)-3-(3-amidinophenyl)-2-propenyl]-*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]sulfamoyl}acetate dihydrochloride **16** (0.420 g, 0.675 mmol) in H_2O (5 ml) were added ethyl 4-nitrophenyl carbonate (0.140 g, 0.663 mmol) in CH_2Cl_2 (5 ml) and $NaHCO_3$ (0.110 g, 1.31 mmol) and the mixture was stirred at room temperature for 3 h. $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was washed with $NaHCO_3$ solution, dried and concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2/EtOH=1/1) to give an amorphous solid. This amorphous solid was dissolved in EtOH (5 ml) and a 1 N solution of hydrogen chloride (1.4 ml) and the mixture was concentrated. The resulting residue was dissolved in H_2O and the solution was lyophilized to give **17a** (0.360 g, 0.519 mmol, 78%) as a colorless amorphous solid. MS *m/z*: 621 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.33 (3H, t, J=7.0 Hz), 1.90—2.07 (2H, m), 2.15—2.25 (2H, m), 2.69—2.78 (3H, m), 3.00—3.10 (2H, m), 3.29—3.37 (1H, m), 3.40—3.50 (1H, m), 4.19 (2H, q, J=7.0 Hz), 4.35 (2H, q, J=7.0 Hz), 4.42 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.60—4.89 (1H, m), 6.42 (1H, dt, J=16.0, 6.0 Hz), 6.59 (1H, d, J=16.0 Hz), 7.29—7.33 (1H, m), 7.38—7.43 (1H, m), 7.54 (1H, t, J=8.0 Hz), 7.57—7.62 (1H, m), 7.66 (1H, d, J=8.0 Hz), 7.75 (1H, d, J=8.0 Hz), 7.86 (1H, s). IR (KBr) cm^{-1}: 1742, 1674, 1354, 1157. *Anal.* Calcd for $C_{29}H_{37}ClN_4O_7S \cdot 2.3HCl \cdot 1.5H_2O$: C, 47.58; H, 5.82; N, 7.65; Cl, 15.98; S, 4.38. Found: C, 47.36; H, 5.93; N, 7.71; Cl, 15.94; S, 4.54.

Similarly, compounds **17b**—**i** were prepared.

17b: MS *m/z*: 699 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.83—1.93 (1H, m), 2.00—2.18 (2H, m), 2.20—2.27 (1H, m), 2.71—2.82 (3H, m), 3.00—3.10 (2H, m), 3.30—3.50 (2H, m), 3.77 (3H, s), 4.19 (2H, q, J=7.0 Hz), 4.42 (2H, s), 4.48 (2H, d, J=6.0 Hz), 4.58—4.87 (1H, m), 6.39 (1H, dt, J=16.0, 6.0 Hz), 6.59 (1H, d, J=16.0 Hz), 6.99 (2H, d, J=9.0 Hz), 7.17 (2H, d, J=9.0 Hz), 7.29—7.33 (1H, m), 7.39—7.43 (1H, m), 7.51 (1H, t, J=7.5 Hz), 7.58—7.63 (1H, m), 7.69 (1H, d, J=7.5 Hz), 7.80 (1H, d, J=7.5 Hz), 7.97 (1H, s). IR (KBr) cm^{-1}: 1740, 1671, 1354, 1161. *Anal.* Calcd for $C_{34}H_{39}ClN_4O_8S \cdot 2.0HCl \cdot 2.0H_2O$: C, 50.53; H, 5.61; N, 6.93; Cl, 13.16; S, 3.97. Found: C, 50.24; H, 5.75; N, 6.98; Cl, 12.90; S,

4.45.

17c: MS *m/z*: 649 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (3H, t, J=7.0 Hz), 1.54 (9H, s), 1.87—1.96 (2H, m), 1.97—2.06 (2H, m), 2.32 (3H, s), 2.34—2.44 (2H, m), 2.64—2.73 (2H, m), 3.99 (2H, s), 4.30 (2H, q, J=7.0 Hz), 4.37—4.44 (1H, m), 4.44 (2H, d, J=6.5 Hz), 6.22 (1H, dt, J=16.0, 6.5 Hz), 6.42 (1H, d, J=16.0 Hz), 6.91 (1H, d, J=9.0 Hz), 7.27—7.32 (1H, m), 7.34 (1H, t, J=8.0 Hz), 7.45 (1H, d, J=8.0 Hz), 7.52 (1H, d, J=2.5 Hz), 7.66 (1H, d, J=8.0 Hz), 7.78 (1H, s). IR (KBr) cm^{-1}: 1740, 1655, 1365, 1163. *Anal.* Calcd for $C_{31}H_{41}ClN_4O_7S\cdot0.1HCl\cdot0.7H_2O$: C, 55.95; H, 6.44; N, 8.42; Cl, 5.86; S, 4.82. Found: C, 56.24; H, 6.27; N, 8.27; Cl, 5.85; S, 4.79.

17d: MS *m/z*: 687 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (3H, t, J=7.0 Hz), 1.86—1.95 (2H, m), 1.95—2.04 (2H, m), 2.31 (3H, s), 2.32—2.40 (2H, m), 2.60—2.72 (2H, m), 3.99 (2H, s), 4.31 (2H, q, J=7.0 Hz), 4.36—4.44 (1H, m), 4.46 (2H, d, J=6.5 Hz), 6.26 (1H, dt, J=16.0, 6.5 Hz), 6.47 (1H, d, J=16.0 Hz), 6.91 (1H, d, J=9.0 Hz), 7.04—7.12 (2H, m), 7.13—7.20 (2H, m), 7.31 (1H, dd, J=2.5, 9.0 Hz), 7.42 (1H, t, J=8.0 Hz), 7.53 (1H, d, J=2.5 Hz), 7.54 (1H, d, J=8.0 Hz), 7.75 (1H, d, J=8.0 Hz), 7.86 (1H, s). IR (KBr) cm^{-1}: 1739, 1668, 1355, 1162. *Anal.* Calcd for $C_{33}H_{36}ClFN_4O_7S\cdot0.9HCl\cdot0.5H_2O$: C, 54.37; H, 5.24; N, 7.69; Cl, 9.24; F, 2.61; S, 4.40. Found: C, 54.40; H, 5.38; N, 7.34; Cl, 9.25; F, 2.69; S, 4.54.

17e: MS *m/z*: 679 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=7.5 Hz), 1.36 (3H, t, J=7.0 Hz), 1.87—2.05 (4H, m), 2.32 (3H, s), 2.33—2.43 (4H, m), 2.63—2.72 (2H, m), 3.99 (2H, s), 4.31 (2H, q, J=7.0 Hz), 4.36—4.47 (3H, m), 5.88 (2H, s), 6.25 (1H, dt, J=15.5, 7.0 Hz), 6.45 (1H, d, J=15.5 Hz), 6.91 (1H, d, J=9.0 Hz), 7.28—7.42 (2H, m), 7.50—7.54 (2H, m), 7.72 (1H, d, J=8.0 Hz), 7.82 (1H, s). IR (KBr) cm^{-1}: 1741, 1667, 1354, 1158. *Anal.* Calcd for $C_{31}H_{39}ClN_4O_9S\cdot0.1HCl\cdot0.3H_2O$: C, 54.10; H, 5.81; N, 8.14; Cl, 5.67; S, 4.66. Found: C, 53.81; H, 5.71; N, 8.42; Cl, 5.61; S, 4.79.

17f: MS *m/z*: 741 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (3H, t, J=7.5 Hz), 1.86—2.05 (4H, m), 2.29—2.42 (5H, m), 2.61—2.72 (2H, m), 3.69 (2H, s), 3.99 (2H, s), 4.31 (2H, q, J=7.5 Hz), 4.36—4.49 (3H, m), 5.89 (2H, s), 6.25 (1H, dt, J=15.5, 7.0 Hz), 6.45 (1H, d, J=15.5 Hz), 6.91 (1H, d, J=9.5 Hz), 7.23—7.42 (7H, m), 7.50—7.54 (2H, m), 7.71 (1H, d, J=8.0 Hz), 7.81 (1H, s). IR (KBr) cm^{-1}: 1741, 1667, 1354, 1156. *Anal.* Calcd for $C_{36}H_{41}ClN_4O_9S\cdot0.1HCl\cdot0.3H_2O$: C, 57.63; H, 5.60; N, 7.47; Cl, 5.20; S, 4.27. Found: C, 57.39; H, 5.38; N, 7.48; Cl, 5.29; S, 4.57.

17g: MS *m/z*: 733 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.18—1.51 (8H, m), 1.60—1.80 (3H, m), 1.86—2.05 (6H, m), 2.28—2.43 (6H, m), 2.61—2.72 (2H, m), 3.99 (2H, s), 4.30 (2H, q, J=7.0 Hz), 4.36—4.48 (3H, m), 5.87 (2H, s), 6.25 (1H, dt, J=16.5, 6.0 Hz), 6.45 (1H, d, J=16.5 Hz), 6.91 (1H, d, J=9.0 Hz), 7.30 (1H, dd, J=3.0, 9.0 Hz), 7.39 (1H, t, J=8.0 Hz), 7.50—7.54 (2H, m), 7.72 (1H, d, J=8.0 Hz), 7.82 (1H, s). IR (KBr) cm^{-1}: 1740, 1667, 1356, 1157. *Anal.* Calcd for $C_{35}H_{45}ClN_4O_9S\cdot0.1HCl\cdot0.2H_2O$: C, 56.77; H, 6.19; N, 7.57; Cl, 5.27; S, 4.33. Found: C, 56.66; H, 6.24; N, 7.39; Cl, 5.39; S, 4.47.

17h: MS *m/z*: 707 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (9H, s), 1.35 (3H, t, J=8.0 Hz), 1.87—2.05 (4H, m), 2.29—2.44 (5H, m), 2.61—2.73 (2H, m), 3.99 (2H, s), 4.30 (2H, q, J=8.0 Hz), 4.36—4.49 (3H, m), 5.87 (2H, s), 6.25 (1H, dt, J=16.5, 6.0 Hz), 6.45 (1H, d, J=16.5 Hz), 6.91 (1H, d, J=9.0 Hz), 7.30 (1H, dd, J=3.0, 9.0 Hz), 7.40 (1H, t, J=8.0 Hz), 7.50—7.54 (2H, m), 7.72 (1H, d, J=8.0 Hz), 7.82 (1H, s). IR (KBr) cm^{-1}: 1741, 1668, 1356, 1156. *Anal.* Calcd for $C_{33}H_{43}ClN_4O_9S\cdot0.3HCl\cdot0.3H_2O$: C, 54.78; H, 6.12; N, 7.74; Cl, 6.37; S, 4.43. Found: C, 54.77; H, 6.13; N, 7.70; Cl, 6.31; S, 4.73.

17i: MS *m/z*: 705 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (3H, t, J=7.5 Hz), 1.83—2.05 (4H, m), 2.19 (3H, s), 2.27—2.43 (5H, m), 2.61—3.73 (2H, m), 3.99 (2H, s), 4.31 (2H, q, J=7.5 Hz), 4.35—4.49 (3H, m), 4.93 (2H, s), 6.24 (1H, dt, J=15.5, 6.5 Hz), 6.45 (1H, d, J=15.5 Hz), 6.91 (1H, d, J=9.0 Hz), 7.28—7.41 (2H, m), 7.49—7.54 (2H, m), 7.71 (1H, d, J=8.0 Hz), 7.80 (1H, s). IR (KBr) cm^{-1}: 1739, 1659, 1354, 1155. *Anal.* Calcd for $C_{32}H_{37}ClN_4O_{10}S\cdot0.2HCl$: C, 53.95; H, 5.26; N, 7.86; Cl, 5.97; S, 4.50. Found: C, 54.03; H, 5.26; N, 7.71; Cl, 5.94; S, 4.44.

Ethyl (*N*-{(*E*)-3-[3-(Amino)(hydroxyimino)methylphenyl]-2-propenyl}-*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]sulfamoyl)acetate Dihydrochloride (17j) To a solution of ethyl {*N*-[3-chloro-4-(1-methylpiperidin-4-yloxy)phenyl]-*N*-[(*E*)-3-(3-cyanophenyl)-2-propenyl]sulfamoyl}acetate **18** (800 mg, 1.50 mmol) in EtOH (20 ml) were added hydroxylamine hydrochloride (350 mg, 5.04 mmol) and Na_2CO_3 (240 mg, 2.26 mmol) and the mixture was stirred overnight at room temperature and refluxed for 9 h. The mixture was concentrated and the resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN+13/7) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride and the mixture was concentrated. The resulting residue was dissolved in H_2O and the solution was lyophilized to give **17j** (148 mg, 0.232 mmol, 15%) as a colorless amorphous solid. MS *m/z*: 565 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.86—2.27 (4H, m), 2.71—2.80 (3H, m), 2.98—3.11 (2H, m), 3.40—3.52 (2H, m), 4.19 (2H, q, J=7.0 Hz), 4.37—4.49 (4H, m), 4.57—4.89 (1H, m), 6.40 (1H, dt, J=15.5, 6.0 Hz), 6.57 (1H, d, J=15.5 Hz), 7.30 (1H, t, J=9.0 Hz), 7.38—7.69 (5H, m), 7.77 (1H, s). IR (KBr) cm^{-1}: 1737, 1666, 1352, 1156. *Anal.* Calcd for $C_{26}H_{33}N_4O_6S\cdot2.2HCl\cdot2.0H_2O$: C, 45.83; H, 5.80; N, 8.22; Cl, 16.65; S, 4.71. Found: C, 45.50; H, 5.78; N, 8.59; Cl, 16.80; S, 4.66.

(*Z*)-3-(3-Cyanophenyl)-2-fluoro-2-propen-1-ol (21) To a solution of ethyl 2-(diethylphosphono)-2-fluoroacetate (9.82 g, 40.5 mmol) in THF (160 ml) was added NaH (2.12 g, 48.6 mmol, as a 55% (w/w) dispersion in mineral oil) at −15 °C and the mixture was stirred at −15 °C for 10 min. 3-Cyanobenzaldehyde **19** (5.58 g, 42.6 mmol) in THF (40 ml) was added and the mixture was stirred at −15 °C for 3 h. The reaction mixture was quenched with NH_4Cl solution 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/CH_2Cl_2=5/2/3) to give a mixture of (*E*)- and (*Z*)-**20** (6.07 g, 27.7 mmol, 65%) as a colorless solid. This solid (6.07 g, 27.7 mmol) was dissolved in MeCN (100 ml), and the solution was treated with bromine (3 drops, catalytic amount). The resulting mixture was stirred at room temperature for 1 h and the mixture was concentrated to give (*Z*)-**20** (6.03 g, 27.5 mmol, 99%) as a pale yellow solid. This solid (6.01 g, 27.4 mmol) was suspended in EtOH (100 ml) and the suspension was treated with $NaBH_4$ (2.07 g, 54.7 mmol). The mixture was stirred at 40 °C for 1 h. NH_4Cl solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and concentrated. The resulting residue was chromatographed on a silica gel column (hexane/EtOAc/CH_2Cl_2=4/3/3) to give **21** (4.12 g, 23.3 mmol, 85%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 4.32 (2H, dd, J=5.5, 12.5 Hz), 5.82 (1H, d, J=37.5 Hz), 7.45 (1H, t, J=8.0 Hz), 7.53 (1H, d, J=8.0 Hz), 7.70 (1H, d, J=8.0 Hz), 7.81 (1H, s).

(*E*)-3-(3-Cyanophenyl)-2-methyl-2-propen-1-ol (22) A solution of 3-cyanobenzaldehyde **19** (5.00 g, 38.1 mmol) and 2-(triphenylphosphoranylidene)propionaldehyde (15.8 g, 49.6 mmol) in toluene (170 ml) was stirred at 70 °C for 7 h and the reaction mixture was concentrated. The resulting residue was chromatographed on a silica gel column (CH_2Cl_2) to give a yellow solid. This yellow solid was recrystallized from Et_2O and hexane (1/9) to give (*E*)-3-(3-cyanophenyl)-2-methyl-2-propenal (5.19 g, 30.3 mmol, 80 %) as colorless crystals. These crystals (4.69 g, 27.4 mmol) were dissolved in CH_2Cl_2 (30 ml) and EtOH (60 ml) and the mixture was treated with $NaBH_4$ (518 mg, 13.7 mmol) and $CeCl_3\cdot7H_2O$ (3.57 g, 9.58 mmol). The mixture was stirred at 0 °C for 2 h and then $NaBH_4$ (518 mg, 13.7 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h and quenched with NH_4Cl solution. The mixture was then extracted with EtOAc and 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 **22** (4.50 g, 26.0 mmol, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.87 (3H, s), 4.21 (2H, s), 6.52 (1H, s), 7.40—7.57 (4H, m).

(*N*-{4-[1-(Acetimidoyl)piperidin-4-yloxy]-3-carbamoylphenyl}-*N*-[(*Z*)-3-(3-amidinophenyl)-2-fluoro-2-propenyl]sulfamoyl)acetic Acid Dihydrochloride (26d) DEAD (0.860 ml, 5.48 mmol) was added to a solution of ethyl (*N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-cabamoylphenyl}-sulfamoyl)acetate **25** (2.20 g, 4.53 mmol), (*Z*)-3-(3-cyanophenyl)-2-fluoro-2-propen-1-ol **21** (800 mg, 4.51 mmol) and PPh_3 (1.50 g, 5.72 mmol) in CH_2Cl_2 (50 ml) and the resulting mixture was stirred at room temperature for 2.5 h. The mixture was concentrated and the resulting residue was chromatographed on a silica gel column (hexane/EtOAc=1/2—1/4) to give ethyl (*N*-{4-[1-(*t*-butoxycarbonyl)piperidin-4-yloxy]-3-carbamoylphenyl}-*N*-[(*Z*)-3-(3-cyanophenyl)-2-fluoro-2-propenyl]sulfamoyl)acetate (3.40 g, quant.) as a pale yellow amorphous solid. Into a solution of this amorphous solid (2.90 g, 4.50 mmol) in CH_2Cl_2 (30 ml) and EtOH (30 ml) was bubbled hydrogen chloride under ice-cooling and the resulting mixture was stirred at room temperature under tightly sealed conditions for 75 min. The reaction mixture was concentrated and the resulting residue was dissolved in EtOH (30 ml) and H_2O (5 ml). The solution was treated with NH_4Cl (540 mg, 10.1 mmol) and NH_3 solution (1.20 ml, 19.8 mmol) and the mixture was allowed to stand at room temperature overnight. The 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 ethyl {*N*-[(*Z*)-3-(3-amidinophenyl)-2-fluoro-2-propenyl]-*N*-[3-carbamoyl-4-(piperidin-4-

yloxy)phenyl]sulfamoyl}acetate (1.04 g, 1.85 mmol, 41%) as a colorless amorphous solid. This amorphous solid (1.00 g, 1.78 mmol) was dissolved in EtOH (30 ml) and the mixture was treated with ethyl acetimidate hydrochloride (450 mg, 3.64 mmol) and Et_3N (1.00 ml, 7.21 mmol). The resulting mixture was stirred overnight at room temperature and the reaction mixture was concentrated. The resulting residue was purified by a preparative HPLC (YMC-pack ODS, YMC Corp., H_2O/MeCN=41/9) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride (5.6 ml) and the mixture was concentrated to give ethyl (*N*-{4-[1-(acetimidoyl)piperidin-4-yloxy]-3-carbamoylphenyl}-*N*-[(*Z*)-3-(3-amidinophenyl)-2-fluoro-2-propenyl]sulfamoyl)acetate dihydrochloride (1.06 g, 1.57 mmol, 88%) as a colorless amorphous solid. This amorphous solid (910 mg, 1.35 mmol) was dissolved in a 3 N solution of hydrogen chloride (20 ml) and the mixture was stirred at 70 °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=9/1) to give an amorphous solid. This amorphous solid was dissolved in a 1 N solution of hydrogen chloride (4 ml) and the mixture was concentrated. The resulting residue was lyophilized to give **26d** (240 mg, 0.370 mmol, 27%) as a colorless amorphous solid. MS *m/z*: 575 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.79—1.92 (2H, m), 2.01—2.12 (2H, m), 2.30 (3H, s), 3.48—3.86 (4H, m), 4.27 (2H, s), 4.62 (2H, d, J=16.5 Hz), 4.83—4.90 (1H, m), 5.98 (1H, d, J=39.0 Hz), 7.30 (1H, d, J=9.5 Hz), 7.51—7.61 (2H, m), 7.69 (1H, d, J=8.0 Hz), 7.74—7.83 (3H, m). IR (KBr) cm^{-1}: 1672, 1352, 1158. *Anal.* Calcd for $C_{26}H_{31}FN_6O_6S \cdot 2.0HCl \cdot 0.5H_2O$: C, 47.56; H, 5.22; N, 12.80; Cl, 10.80; F, 2.89; S, 4.88. Found: C, 47.26; H, 5.08; N, 12.68; Cl, 10.87; F, 2.90; S, 4.82.

Similarly, compounds **26a**—**c** were prepared.

26a: MS *m/z*: 532 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.68—1.81 (2H, m), 1.99—2.11 (2H, m), 2.29 (3H, s), 3.47—3.57 (2H, m), 3.67—3.75 (1H, m), 3.78—3.85 (1H, m), 4.20 (2H, s), 4.59 (2H, d, J=15.5 Hz), 4.68—4.74 (1H, m), 5.95 (1H, d, J=38.0 Hz), 7.06 (2H, d, J=9.0 Hz), 7.42 (2H, d, J=9.0 Hz), 7.59 (1H, t, J=8.0 Hz), 7.68 (1H, d, J=8.0 Hz), 7.76 (1H, d, J=8.0 Hz), 7.81 (1H, s). IR (KBr) cm^{-1}: 1673, 1627, 1350, 1157. *Anal.* Calcd for $C_{25}H_{30}FN_5O_5S \cdot 2.3HCl \cdot 2.6H_2O$: C, 45.34; H, 5.71; N, 10.57; Cl, 12.31; F, 2.87; S, 4.84. Found: C, 45.26; H, 5.59; N, 10.64; Cl, 12.36; F, 2.84; S, 5.05.

26b: MS *m/z*: 528 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.63—1.82 (2H, m), 1.88 (3H, s), 1.99—2.11 (2H, m), 2.30 (3H, s), 3.44—3.90 (4H, m), 4.19 (2H, s), 4.37 (2H, s), 4.67—4.75 (1H, m), 6.33 (1H, s), 7.05 (2H, d, J=9.0 Hz), 7.41 (2H, d, J=9.0 Hz), 7.48 (1H, d, J=8.0 Hz), 7.53—7.58 (2H, m), 7.67 (1H, d, J=8.0 Hz). IR (KBr) cm^{-1}: 1672, 1627, 1345, 1156. *Anal.* Calcd for $C_{26}H_{33}N_5O_5S \cdot 2.5HCl \cdot 1.2H_2O$: C, 48.76; H, 5.97; N, 10.94; Cl, 13.84; S, 5.01. Found: C, 48.75; H, 6.16; N, 10.87; Cl, 13.94; S, 4.84.

26c: MS *m/z*: 566 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.69—1.87 (2H, m), 1.97—2.11 (2H, m), 2.29 (3H, s), 3.46—3.81 (4H, m), 4.30 (2H, s), 4.61 (2H, d, J=16.5 Hz), 4.79—4.88 (1H, m), 5.98 (1H, d, J=38.5 Hz), 7.34 (1H, d, J=9.0 Hz), 7.42 (1H, dd, J=2.5, 9.0 Hz), 7.55—7.61 (2H, m), 7.69 (1H, d, J=7.5 Hz), 7.76 (1H, d, J=7.5 Hz), 7.81 (1H, s). IR (KBr) cm^{-1}: 1736, 1675, 1625, 1351, 1157. *Anal.* Calcd for $C_{25}H_{29}ClFN_5O_5S \cdot 2.2HCl \cdot 1.3H_2O$: C, 44.84; H, 5.09; N, 10.46; Cl, 16.94; F, 2.84; S, 4.79. Found: C, 44.58; H, 5.07; N, 10.25; Cl, 17.00; F, 3.02; S, 4.77.

Biology. Anti-FXa and Trypsin Assay The hydrolysis of chromogenic substrates was assayed by continuously measuring the 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 enzymes 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 the dose–response curves. The enzymes and substrates used were 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 hamsters (Japan SLC). Platelet-poor plasma was prepared by centrifugation at 2000×***g*** for 10 min and stored at −20 °C until use. The plasma clotting times were determined using a COAGMASTER II (Sankyo, Japan) and an ACL9000 (Instrumentation Laboratories, MA, U.S.A.). The prothrombin time (PT) was measured using SIMPLASTIN EXCEL (Organon Teknika, NC, U.S.A.) and HemosILTM RecombiPlastin (Instrumentation Laboratories, MA, U.S.A.). The activated partial thromboplastin time (APTT) was measured using Platelin LS (Organon Teknika, NC, U.S.A.) and HemosILTM SynthASil (Instrumentation Laboratories, MA, U.S.A.). The coagulation times for each compound were compared with the 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.

Pharmacokinetic Study Each compound was orally administered to 3 dogs at a dose of 1 mg/kg. The compounds were dissolved in saline and used as the dosing solutions. Blood samples were collected at each time. The blood was transferred into tubes containing sodium citrate. The plasma concentrations of the compounds were determined by LC-MS/MS using multiple reaction monitoring in positive electrospray ionization mode on a Micromass Quattro LC mass spectrometer coupled with a Waters Alliance 2790 HPLC. Each compound was separated on an Atlantis HILIC Silica column.

Plasma Anti-FXa and Anticoagulant Assay in Dogs The plasma anti-FXa activity was assessed by an amidolytic assay using a fluorogenic FXa substrate, Z-Pyr-Gly-Arg-MCA3, and the activity (IU/ml) was calibrated using an anti-FXa activity standard, enoxaparin, a low molecular weight heparin. Frozen plasma samples were thawed rapidly in a 37 °C water bath and placed on ice. An aliquot each of 5 μl plasma sample, 40 μl of buffer A (0.1 M Tris–HCl–0.2 M NaCl, pH 8.4) and 5 μl of 2 U/ml AT-III (final concentration (f.c.) of 0.1 U/ml) were added to each well of a 96-well plate and the plate was briefly shaken. After the addition of 30 μl of 0.33 IU/ml FXa (f.c. 0.1 IU/ml) and 20 μl of 1 mM Z-Pyr-Gly-Arg-MCA (f.c. 0.2 mM) to each reaction mixture, the plate was briefly shaken and incubated for 10 min at room temperature under light-shielded conditions. The reaction was stopped by adding 50 μl of 60% (v/v) acetic acid solution to each well and the fluorescent intensity (excitation 380 nm, emission 440 nm) was measured by a multilabel counter (Wallac 1420 ARVOsx, PerkinElmer, Inc.). Anti-FXa activity (IU/ml) in each plasma sample was calibrated with two-fold serial dilutions (0.000—2.000 anti-FXa IU/ml plasma) of enoxaparin in pooled rat plasma using 4-parameter analysis (SOFTmax PRO 3.1.1, Molecular Devices Corp.).

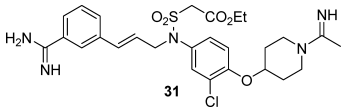
PT was used to determine the *ex vivo* anticoagulant activities of the test compound. Plasma samples (50 μl) were each added to test tubes and placed in a coagulometer (KC-10A micro, Heinrich Amelung GmbH), and 100 μl of PT reagent (Thromboplastin C plus, Dade Behring Marburg GmbH) was added to the plasma to start the clotting after 1 min incubation at 37 °C.

Acknowledgments We wish to thank Ms. Ikuko Shimada, Ms. Naoko Suzuki and Ms. Yumiko Fujisawa for their expert synthetic and technical assistance, as well as Dr. Ken-ichi Otsuguro for his many helpful discussions.

References and Notes

1) Fujimoto K., Tanaka N., Shimada I., Asai F., WO 02/081448 (2002).
2) Fujimoto K., Tanaka N., Shimada I., Asai F., Inoue K., Okada J., WO 02/089803 (2002).
3) Present address: *General Administration Department, Daiichi Sankyo Business Associe Co., Ltd.*
4) Harder S., Thurmann P., *Clin. Pharmacokinet.*, **30**, 416—444 (1996).
5) Hirsh J., *N. Engl. J. Med.*, **324**, 1865—1875 (1991).
6) Wells P. S., Holbrook A. M., Crowther N. R., Hirsh J., *Ann. Intern. Med.*, **121**, 676—683 (1994).
7) Davie E. W., Fujisawa K., Kisiel W., *Biochemistry*, **30**, 10363—10370 (1991).
8) Hara T., Yokoyama A., Tanabe K., Ishihara H., Iwamoto M., *Thromb. Haemost.*, **74**, 635—639 (1995).
9) Sato K., Kawasaki T., Hisamichi N., Taniuchi Y., Hirayama F., Koshio H., Matsumoto Y., *Br. J. Pharmacol.*, **123**, 92—96 (1998).
10) Noguchi T., Tanaka N., Nishimata T., Goto R., Hayakawa M., Sugidachi A., Ogawa T., Asai F., Matsui Y., Fujimoto K., *Chem. Pharm. Bull.*, **54**, 163—174 (2006).
11) Noguchi T., Tanaka N., Nishimata T., Goto R., Hayakawa M., Sugidachi A., Ogawa T., Asai F., Ozeki T., Fujimoto K., *Chem. Pharm. Bull.*, **55**, 393—402 (2007).
12) Noguchi T., Tanaka N., Nishimata T., Goto R., Hayakawa M., Sugidachi A., Ogawa T., Asai F., Fujimoto K., *Chem. Pharm. Bull.*, **55**, 1494—1504 (2007).
13) Noguchi T., Tanaka N., Nishimata T., Goto R., Hayakawa M., Sugidachi A., Ogawa T., Asai F., Fujimoto K., *Chem. Pharm. Bull.*, **56**, 758—770 (2008).
14) Meyers A. I., Knaus G., Kamata K., Ford M. E., *J. Am. Chem. Soc.*, **98**, 567—576 (1976).
15) Bredereck H., Effenberger F., Henseleit E., *Angew. Chem.*, **75**, 790—791 (1963).
16) Guram A. S., Rennels R. A., Buchwald S. L., *Angew. Chem. Int. Ed.*

Engl., **34**, 1348—1350 (1995).
17) Folkmann M., Lund F. J., *Synthesis*, **1990**, 1159—1166 (1990).
18) Alexander J., Bindra D. S., Glass J. D., Holahan M. A., Renyer M. L., Rork G. S., Sitko G. R., Stranieri M. T., Stupienski R. F., Veerapanane H., Cook J. J., *J. Med. Chem.*, **39**, 480—486 (1996).
19) Eddarir S., Francesch C., Mestdagh H., Rolando C., *Tetrahedron Lett.*, **31**, 4449—4452 (1990).
20) Gemal A. L., Luche J. L., *Tetrahedron Lett.*, **22**, 4077—4080 (1981).
21) Mitsunobu O., *Synthesis*, **1981**, 1—28 (1981).
22) In fact, the cLogP values of cinnamyl derivatives were increased by the removal of the acetimidoyl group or the conversion of carboxyl group into its ethyl ester form. For example, the cLogP values of compounds **1**, **31** and **3** were 0.13±0.70, 1.12±0.71, and 2.29±0.50, respectively.



31

23) These compounds were synthesized in the previous report (see ref. 11). The physical data of these compounds are as follows. **5a**: MS *m*/*z*: 501 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.78—1.90 (2H, m), 2.05—2.15 (2H, m), 2.98—3.09 (2H, m), 3.13—3.23 (2H, m), 4.20 (2H, q, J=7.0 Hz), 4.34 (2H, s), 4.45 (2H, d, J=6.0 Hz), 4.62—4.69 (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). IR (KBr) cm^{-1}: 1737, 1675. *Anal.* Calcd for $C_{25}H_{32}N_4O_5S\cdot 1.9HCl\cdot 2.4H_2O$: C, 48.97; H, 6.36; N, 9.14; Cl, 10.99; S, 5.23. Found: C, 49.29; H, 6.20; N, 8.84; Cl, 11.01; S, 4.98. **5b**: MS *m*/*z*: 544 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.87—1.97 (2H, m), 2.08—2.17 (2H, m), 3.01—3.11 (2H, m), 3.15—3.24 (2H, m), 4.20 (2H, q, J=7.0 Hz), 4.38 (2H, s), 4.47 (2H, d, J=6.0 Hz), 4.77—4.84 (1H, m), 6.45 (1H, dt, J=16.0, 6.0 Hz), 6.58 (1H, d, J=16.0 Hz), 7.24 (1H, d, J=9.0 Hz), 7.47—7.74 (5H, m), 7.90 (1H, s). IR (KBr) cm^{-1}: 1736, 1671, 1658. *Anal.* Calcd for $C_{26}H_{33}N_5O_6S\cdot 2.2HCl\cdot 1.2H_2O$: C, 48.38; H, 5.87; N, 10.85; Cl, 12.08; S, 4.97. Found: C, 48.74; H, 6.30; N, 11.11; Cl, 12.09; S, 5.04. **27**: MS *m*/*z*: 519 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.79—1.91 (2H, m), 2.04—2.15 (2H, m), 3.00—3.11 (2H, m), 3.13—3.24 (2H, m), 4.19 (2H, q, J=7.0 Hz), 4.40 (2H, s), 4.47 (2H, d, J=7.0 Hz), 4.64—4.71 (1H, m), 6.37—6.48 (1H, m), 6.58 (1H, d, J=16.0 Hz), 7.25 (1H, dd, J=2.5, 9.0 Hz), 7.31 (1H, t, J=9.0 Hz), 7.43 (1H, dd, J=2.5, 12.5 Hz), 7.55 (1H, t, J=8.0 Hz), 7.66—7.71 (1H, m), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1737, 1675. *Anal.* Calcd for $C_{25}H_{31}FN_4O_5S\cdot 2.0HCl\cdot 2.0H_2O$: C, 47.85; H, 5.94; N, 8.93; Cl, 11.30; F, 3.03; S, 5.11. Found: C, 48.02; H, 5.70; N, 8.86; Cl, 11.60; F, 3.03; S, 4.92. **3**: MS *m*/*z*: 535 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.0 Hz), 1.82—1.94 (2H, m), 2.05—2.16 (2H, m), 3.03—3.12 (2H, m), 3.13—3.24 (2H, m), 4.19 (2H, q, J=7.0 Hz), 4.41 (2H, s), 4.47 (2H, d, J=6.5 Hz), 4.74—4.81 (1H, m), 6.44 (1H, dt, J=16.0, 6.5 Hz), 6.57 (1H, d, J=16.0 Hz), 7.30 (1H, d, J=9.5 Hz), 7.41 (1H, dd, J=2.5, 9.5 Hz), 7.55 (1H, t, J=8.0 Hz), 7.59 (1H, d, J=2.5 Hz), 7.69 (1H, d, J=8.0 Hz), 7.73 (1H, d, J=8.0 Hz), 7.88 (1H, s). IR (KBr) cm^{-1}: 1737, 1675. *Anal.* Calcd for $C_{25}H_{31}ClN_4O_5S\cdot 1.8HCl\cdot 2.0H_2O$: C, 47.16; H, 5.83; N, 8.80; Cl, 15.59; S, 5.04. Found: C, 47.31; H, 5.67; N, 8.53; Cl, 15.84; S, 4.86.
24) Ames B. N., Gurney E. G., Miller J. A., Bartsch H., *Proc. Nat. Acad. Sci. U.S.A.*, **69**, 3128—3132 (1972).
25) Hirayama F., Koshio H., Katayama N., Kurihara H., Taniuchi Y., Sato K., Hisamichi N., Sakai-Moritani Y., Kawasaki T., Matsumoto Y., Yanagisawa I., *Bioorg. Med. Chem.*, **10**, 1509—1523 (2002).