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Orally active factor Xa inhibitor: synthesis and biological activity of masked amidines as prodrugs of novel 1,4-diazepane derivatives

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Abstract—Factor Xa (fXa) is a serine protease, which plays a pivotal role in the coagulation cascade. To improve the oral anticoagulant activity of fXa inhibitors containing a 1,4-diazepane moiety as the P4 part, a prodrug strategy was examined. Among the compounds evaluated in this study, amidoxime prodrugs bearing an ester moiety, such as compounds **21** and **30**, showed effective oral anticoagulant activity in mice.

1. Introduction

Myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism are major causes of mortality in the industrialized world. Therefore, the prevention of blood coagulation is a major target for new therapeutic agents. Factor Xa (fXa) is strategically located at the junction of the intrinsic and extrinsic arms of the coagulation cascade, and it is thought that its inhibition may be more effective than direct inhibition of thrombin in interrupting the cascade and that fXa inhibitors may involve a lesser risk of bleeding than thrombin inhibitors.[1,2]

We have previously reported the potent and selective bisamidine type fXa inhibitors YM-60828 and YM-96765, which contained an amidine moiety as their P1 parts and an acetoamidine moiety as their P4 parts.[3–5] These compounds displayed effective oral antithrombotic activity in rats without prolongation of bleeding time.[4,5] We also discovered a potent orally active monoamidine fXa inhibitor **1**, which lacked a strongly basic acetoamidine moiety as the P4 part.[4] The amidine moiety possessed by each of these compounds as the P1 part was considered essential for fXa inhibitory activity. In addition, each compound contained a polar functional group, such as a carboxyl moiety. However, such polar functional groups are considered unfavorable in terms of their effects on oral absorption and the pharmacokinetic properties required by oral antithrombotic agents. In this paper, we discuss modification of these polar functional groups by means of a prodrug strategy with the goal of improving oral anticoagulant activity (Fig. 1).

2. Chemistry

The synthesis of the intermediate cyanonapthalene derivatives **6**–**12** is illustrated in Scheme 1. Treatment of **2** with 1-methyl-1,4-diazepane provided 4-substituted nitrobenzene **3**. The intermediate **5** was synthesized by reduction of the nitro group of **3**, followed by reductive alkylation with 7-formyl-2-naphthonitrile. Acylation of **5** with various sulfonylchlorides gave sulfonamide derivatives **6**–**8** and **12**. The removal of the *tert*-butoxycarbonyl (Boc) protecting group from **8** under acidic

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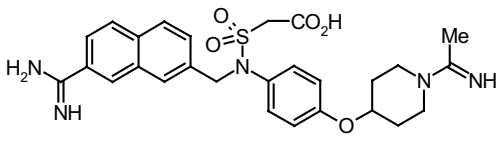
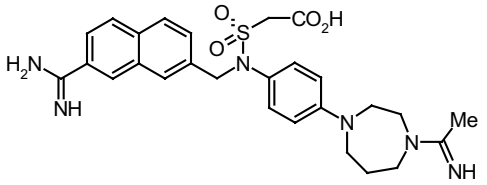


YM-60828



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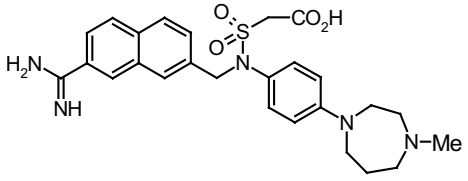

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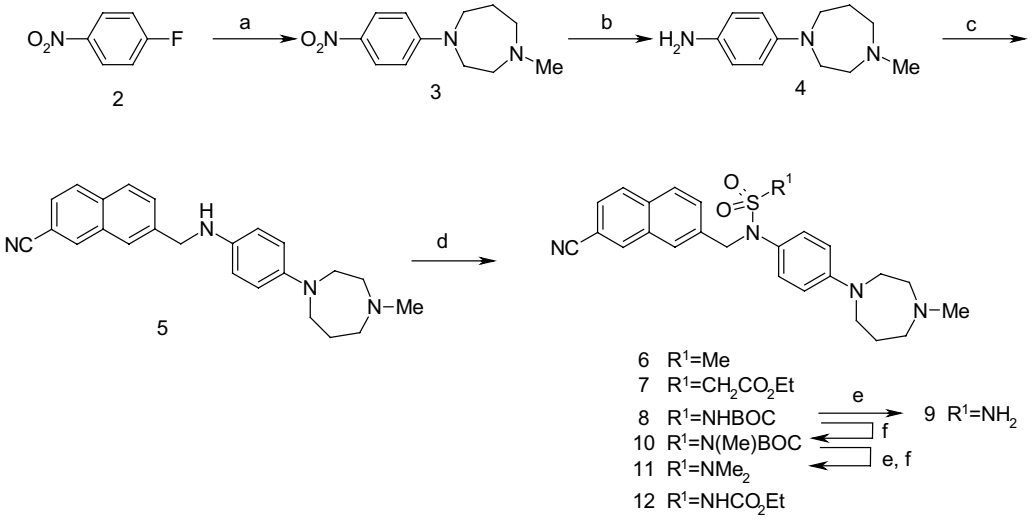
Figure 1. YM-60828 and related compounds.

conditions gave intermediate **9**. Sulfonyl carbamate derivative **8** was alkylated with methanol under Mitsunobu conditions to produce **10**. Dimethyl sulfamide derivative **11** was prepared by removal of the Boc protecting group from **10** followed by alkylation using the same Mitsunobu conditions. Synthesis of the naphthamidine and naphthamidoxime derivatives **13**–**23** is shown in Scheme 2. Treatment of intermediates **6**, **7**, **9**, and **12** under Pinner conditions (HCl/EtOH) converted them to the imidates, which were immediately reacted with excess ammonium acetate to provide the corresponding amidine derivatives **13**, **15**, **20**, and **22**. Treatment of intermediates **6**, **7**, **9**, **11**, and **12** with hydroxylamine hydrochloride provided the amidoxime derivatives **14**, **16**, **18**, **21**, and **23**. Hydrolysis of **21** with 1 N NaOH provided carboxy derivative **19**. Hydrogenolysis of **18** in the presence of 10% Pd–C gave the amidine derivative **17**.

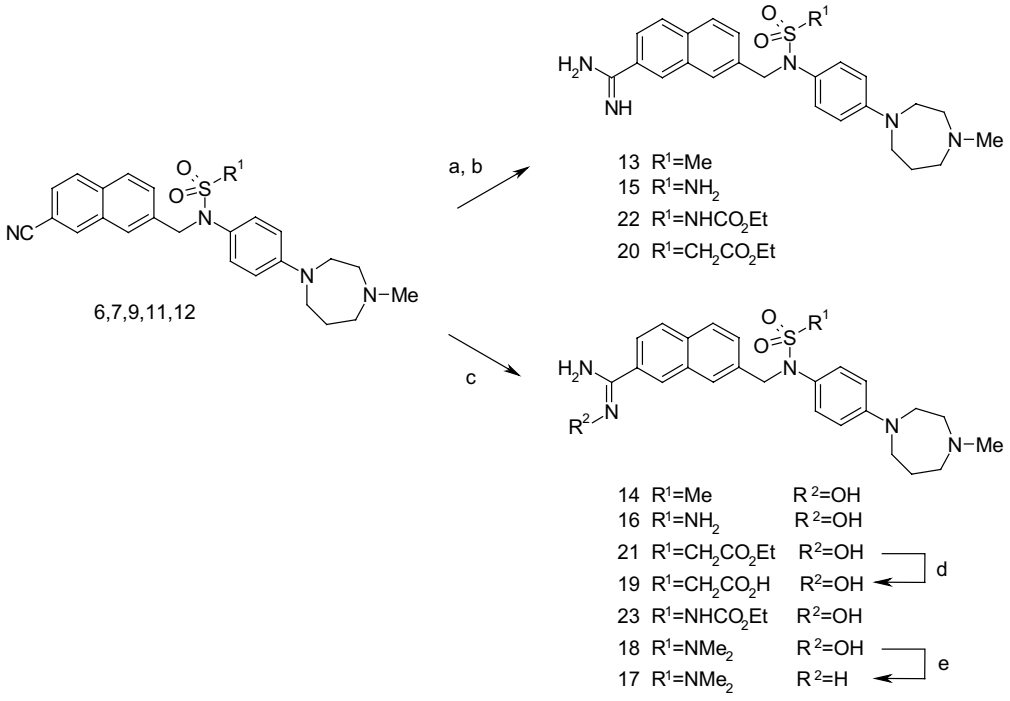
Schemes 3 and 4 show the synthesis of styrylamidine and related prodrug derivatives. Intermediate **25** was obtained by the same procedure as used to produce **5** using cinnamaldehyde **24**[3] instead of 7-formyl-2-naphthonitrile. In the manner described above, **25** was converted to sulfonamide derivatives **26** and **27**. Compound **26** was also converted to amidine derivative **29** and amidoxime derivatives **30** and **31** under the conditions described above. Hydrolysis of **29** under acidic conditions provided carboxy derivative **28**. The method of preparing carbamate derivatives **33** and **34** from amidine **29** involved reaction with an appropriate chloroformate in the presence of aqueous sodium hydroxide. Acylation of **30** with acetic anhydride gave acetyl amidoxime derivative **32**. Hydrolysis of **30** with 1 N NaOH provided carboxy derivative **35**. Esterification with various alcohols gave **36**, **37**, and **39**. Isopropyl ester derivative **38** was prepared from benzonitrile derivative **27** under the conditions described above.

3. Results and discussion

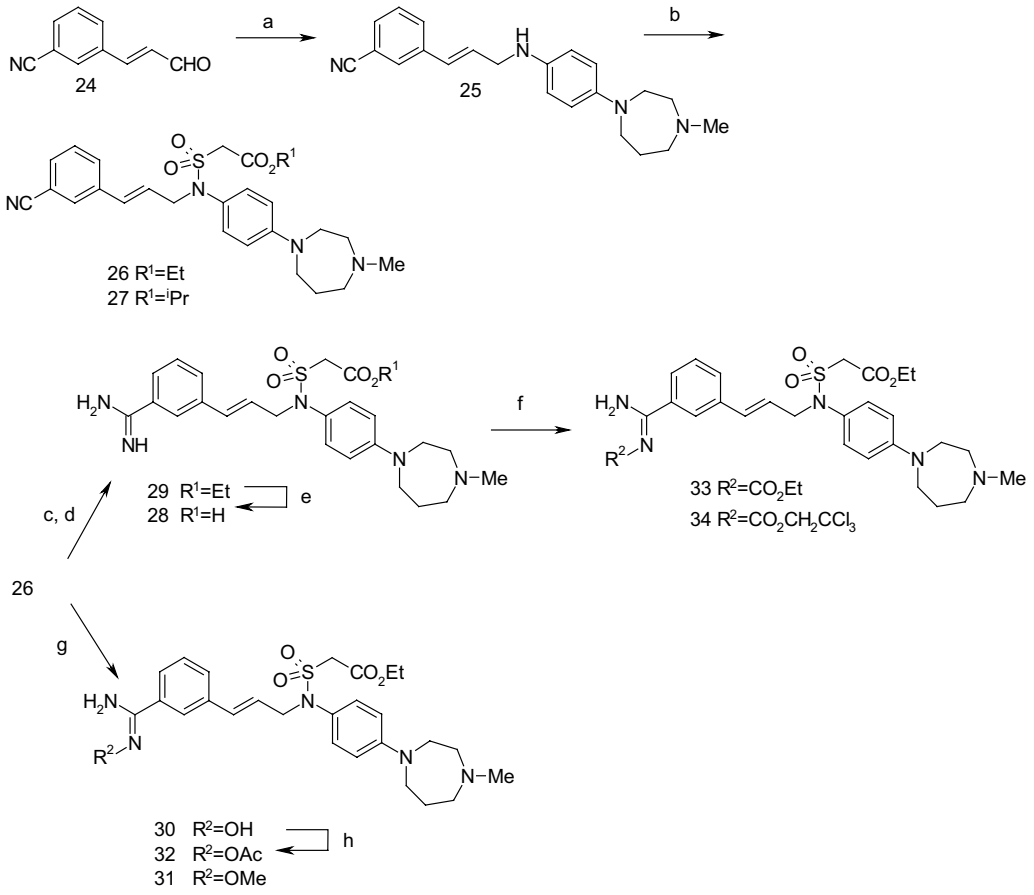
Compounds were evaluated for FXa inhibitory activity according to their IC_{50} values, and for anticoagulant activity in vitro by the CT2 values of their prothrombin times (PT). The CT2 value was defined as the concentration required to double the clotting time. In addition, oral anticoagulant activity was evaluated by the ability of compounds to prolong PT following oral administration in mice.



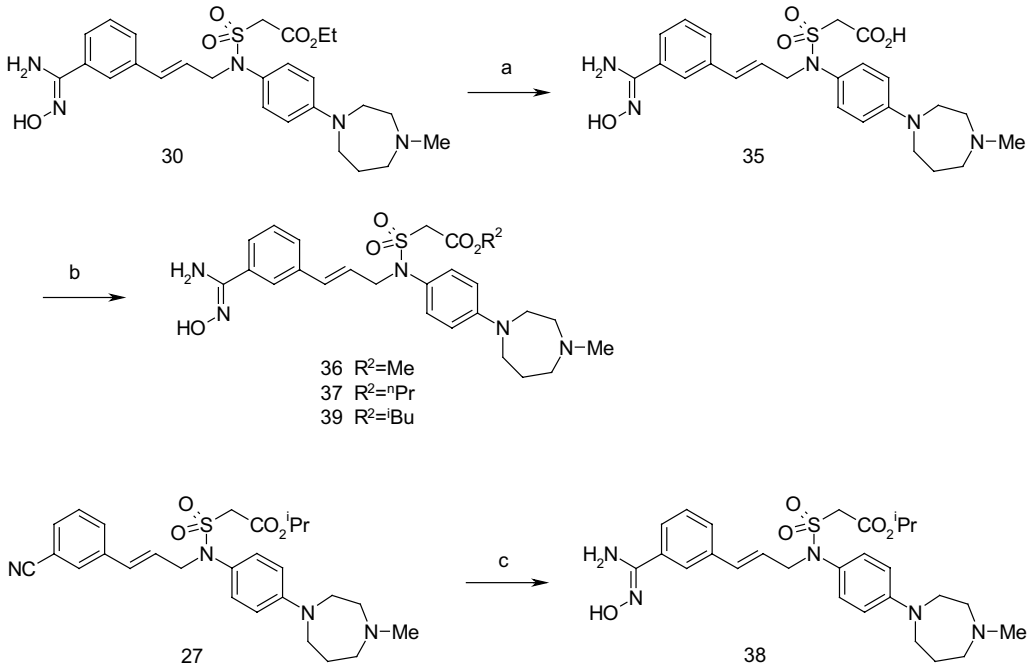
Scheme 1. Reagents and conditions: (a) 1-methyl-1,4-diazepane, K_2CO_3, DMF; (b) H_2, 10% Pd–C, EtOH; (c) 7-formyl-2-naphthonitrile, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane; (d) R^1SO_2Cl, pyridine, 1,2-dichloroethane; (e) HCl, $CHCl_3$, EtOAc; (f) MeOH, PPh_3, diethyl azodicarboxylate (DEAD), THF.



Scheme 2. Reagents and conditions: (a) HCl, EtOH; (b) NH_4OAc, EtOH for **6**, **7**, **9**, and **12**; (c) $H_2NOH{\cdot}HCl$, Et_3N, EtOH for **6**, **7**, **9**, **11**, and **12**; (d) 1 N NaOH; (e) H_2, 10% Pd–C, Ac_2O, AcOH.



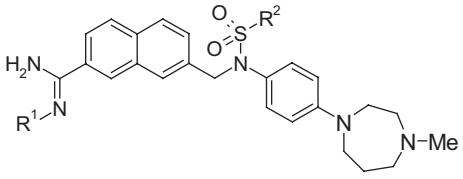
Scheme 3. Reagents and conditions: (a) **4**, $NaB(OAc)_3H$, AcOH, 1,2-dichloroethane; (b) $ClO_2SCH_2CO_2R^1$, pyridine; (c) HCl, EtOH; (d) NH_4OAc, EtOH; (e) concd HCl; (f) R^2OCOCl, 0.1 N NaOH, $CHCl_3$; (g) $H_2NOH{\cdot}HCl$ for **30**, Et_3N, EtOH, $H_2NOMe{\cdot}HCl$ for **31**, Et_3N, EtOH; (h) Ac_2O, pyridine, DMF.



Scheme 4. Reagents and conditions: (a) NaOH, EtOH, H_2O; (b) R^2OH, HCl, 1,4-dioxane; (c) $H_2NOH{\cdot}HCl$, Et_3N, ^{i}PrOH.

It has previously been shown that amidoxime compounds can be used as prodrugs of corresponding amidine compounds and that they can be converted to parent amidines in vivo by liver microsomal enzymes.[6] Weller et al. have demonstrated that amidoxime derivatives are effective as prodrugs of monoamidine fibrinogen antagonists, and possess significantly improved oral bioavailability.[7] In the present study, we applied the amidoxime prodrug strategy to our amidine-containing fXa inhibitors (Table 1). Firstly, the amidine group of the least polar methanesulfonamide derivative, **13** (R^2 = Me), was modified to an amidoxime moiety (**14**).

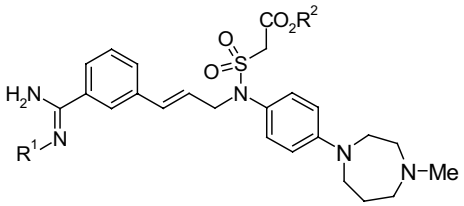
Table 1. Prodrugs of naphthamidine derivatives



Compd	R^1	R^2	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]		
					0.5 h	1.0 h	2.0 h
13	H	Me	18	1.1	1.45	NT[e]	NT[e]
14	OH	Me	10,132	>284	1.08	1.16	1.27
15	H	NH_2	17	1.3	1.18	NT[e]	NT[e]
16	OH	NH_2	1200	NT	1.09	NT[e]	NT[e]
17	H	NMe_2	19	1.8	1.01	NT[e]	NT[e]
18	OH	NMe_2	2200	NT	1.00	0.92	1.02
1	H	CH_2CO_2H	6.5	0.76	2.21	2.04	1.75
19	OH	CH_2CO_2H	890	>248	1.15	1.31	1.14
20	H	CH_2CO_2Et	12	0.77	1.85	1.80	1.47
21	OH	CH_2CO_2Et	3200	38	2.87	2.37	1.92
22	H	$NHCO_2Et$	13	1.4	1.48	NT[e]	NT[e]
23	OH	$NHCO_2Et$	990	NT	1.17	1.03	1.19

[a] Human purified enzyme were used. IC_{50} values represent the averaged of three determinations with the average standard error of the mean < 10%.
[b] Values represent the concentration required to double clotting time and represent the average of four determination with the average standard error of the mean < 10%.
[c] Prothrombin time using mice plasma.
[d] The relative prothrombin time compared with that measured using normal mice plasma at 0.5, 1.0, and 2.0 h after oral administration (100 mg/kg, $n = 3$).
[e] Not tested.

Table 2. Prodrugs of styrylamidine derivatives



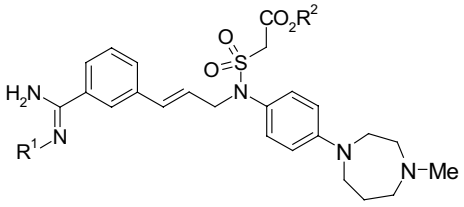
Compd	R^1	R^2	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]		
					0.5 h	1.0 h	2.0 h
28	H	H	27	1.8	1.43	NT[e]	NT[e]
30	OH	Et	7200	>252	2.27	2.17	2.10
31	OMe	Et	15,000	NT[e]	1.35	1.40	1.27
32	OAc	Et	6000	NT[e]	1.67	1.49	1.27
33	CO_2Et	Et	310	NT[e]	1.82	1.59	1.41
34	$CO_2CH_2CCl_3$	Et	600	NT[e]	1.43	1.45	1.18

[a–e]Refer to Table 1.

This, however, had an adverse effect on oral anticoagulant activity in mice compared with **13**. Similar results were obtained following the conversion of sulfonamide derivatives **15** to **16** and **17** to **18**. We next prepared the amidoxime derivative **19** of compound **1**, this latter having been reported to show good oral anticoagulant activity. However, compound **19** showed poor oral anticoagulant activity. Ethyl ester derivative **20** showed anticoagulant activity in vitro comparable to that of parent compound **1**, but did not provide a substantial increase in oral anticoagulant activity. Interestingly, masking the amidine group of compound **20** to give the prodrug **21** resulted in more potent oral anticoagulant activity, and prolonged PT 2.87-fold at 0.5 h, and 1.92-fold at 2.0 h, compared to compounds **1** and **20**. On the other hand, prodrug possessing a similar ethoxycarbonyl moiety (**23**) exhibited poor oral anticoagulant activity and prolonged PT only 1.17-fold at 0.5 h, and 1.19-fold at 2.0 h. These results strongly suggested that whether or not amidoxime derivatives would function effectively as prodrugs of their parent amidine derivatives and show potent activity after oral dosing was dependent on the nature of the substituent incorporated and that an ester moiety was a suitable substituent.

Further studies for the conversion of promoieties of amidine and alkyl groups of ethyl esters were conducted based on styrene derivative **28**. Firstly, the ester group was fixed as ethyl ester and modification of the amidine group was undertaken. Compound **30**, in which the amidine group was replaced by an amidoxime group had increased oral anticoagulant activity compared with compound **28**, and the PT was prolonged by more than 2-fold at all time points investigated after oral administration. On the other hand, modification of the amidoxime group with an alkyl or acyl group led to a decrease in oral anticoagulant activity (**30** vs **31** and **32**). The alkoxycarbonyloxyamidine derivatives (**33**, **34**) did not result in a significant increase in oral anticoagulant activity compared with **28**. These results indicated that the amidoxime derivative was the most promising prodrug for this series of monoamidine fXa inhibitors.

Table 3. Prodrugs of styrylamidine derivatives



Compd	R^1	R^2	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]		
					0.5 h	1.0 h	2.0 h
28	H	H	27	1.8	1.43	NT[e]	NT[e]
36	OH	Me	NT	NT	1.74	2.41	2.25
30	OH	Et	7200	>252	2.27	2.17	2.10
37	OH	^{n}Pr	1200	NT	2.15	NT[e]	1.91
38	OH	^{i}Pr	10,000	NT	1.95	1.68	1.79
39	OH	^{i}Bu	3800	NT	1.82	NT[e]	1.66

[a–e]Refer to Table 1.

Table 3 illustrates the results of investigations of modification of the ethyl ester moiety in compound **30**, which had good oral anticoagulant activity (Table 2). The methyl ester derivative (**36**) had oral anticoagulant activity greater than the carboxylate **28** and comparable to that of ethyl ester derivative **30**. On the contrary, replacement of the ethyl group with more bulky substitutes, such as isopropyl (**38**) or isobutyl (**39**) groups, provided less potency than other ester moieties. These results indicate that the most suitable substituents for effective prodrug function are methyl or ethyl esters.

4. Conclusion

By pursuing a prodrug approach, we were able to improve the oral anticoagulant activity of potent fXa inhibitors such as compounds **1** and **28**. In particular, amidoxime derivatives possessing an ethyl ester moiety (**21** and **30**) showed quite potent activity ex vivo after oral dosing in mice and prolonged PT about 2-fold. Interestingly, the ester moiety was found to be essential for the expression of potent oral activity in this series of prodrugs. Although the mechanistic details remain to be elucidated, these findings are expected to be useful in improving the oral anticoagulant activity of amidine compounds through use of a prodrug strategy.

4.1. Chemistry

^{1}H NMR spectra were measured with a JEOL EX90, EX400 or GX500 spectrometer; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad peak). Mass spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. ODS column chromatography was performed on YMC gel (ODS-A 120-230/70).

4.1.1. 1-Methyl-4-(4-nitrophenyl)-1,4-diazepane (3). To a stirred solution of 1-methyl-1,4-diazepane (13.67 g; 120 mmol) in DMF (120 mL) was added 4-fluoronitrobenzene (16.1 g, 114 mmol), potassium carbonate (31.5 g, 228 mmol) at 100 °C for 17 h. After the reaction mixture was cooled, the reaction mixture was diluted with ethyl acetate and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulted residue was washed with Et_2O to give **3** (19.51 g, 69%) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.88–2.08 (2H, m), 2.39 (3H, s), 2.54–2.59 (2H, m), 2.70–2.74 (2H, m), 3.56–3.68 (4H, m), 6.63 (2H, d, J = 8.8 Hz), 8.11 (2H, d, J = 8.8 Hz); FAB MS *m/e* $(M+1)^+$ 236.

4.1.2. 4-(4-Methyl-1,4-diazepan-1-yl)aniline (4). To the solution of **3** (2.41 g, 10.2 mmol) in EtOH (100 mL) was added 10% Pd–C powder (0.24 g) and stirred in hydrogen atmosphere at ambient temperature for 2 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo to give **4** (2.09 g, quant. yield) as a brown amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.93–2.02 (2H, m), 2.37 (3H, s), 2.54–2.59 (2H, m), 2.66–2.70 (2H, m), 3.38–3.44 (2H, m), 3.47–3.51 (4H, m), 6.57 (2H, d, J = 9.0 Hz), 6.65 (2H, d, J = 9.0 Hz); FAB MS *m/e* $(M+1)^+$ 206.

4.1.3. 7-({[4-(4-Methyl-1,4-diazepan-1-yl)phenyl]amino}-methyl)-2-naphthonitrile (5). To a stirred solution of **4** (2.09 g, 10.2 mmol) and 7-formyl-2-naphthonitrile (1.85 g, 10.2 mmol) in 1,2-dichloromethane (100 mL) and AcOH (6.0 mL) at ambient temperature was added sodium triacetoxyborohydride (4.2 g, 20 mmol). After 2 h, the reaction mixture was washed with 10% potassium carbonate solution and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **5** (3.77 g, quant. yield) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.93–2.06 (2H, m), 2.37 (3H, s), 2.54–2.59 (2H, m), 2.68–2.71 (2H, m), 3.36–3.43 (2H, m), 3.45–3.56 (2H, m), 4.47 (2H, s), 6.57–6.66 (4H, m), 7.26 (1H, s), 7.57 (1H, dd, J = 1.5, 8.8 Hz), 7.87–7.92 (3H, m), 8.18 (1H, s); FAB MS *m/e* $(M+1)^+$ 370.

4.1.4. *N*-[(7-Cyano-2-naphthyl)methyl]-*N*-[4-(4-methyl-1,4-diazepan-1-yl)phenyl]methanesulfonamide (6). To a stirred solution of **5** (1.35 g, 3.64 mmol) in 36 mL 1,2-dichloroethane was added pyridine (963 mg, 10.9 mmol) and methanesulfonylchloride (630 mg, 5.5 mmol) and stirred at ambient temperature. After 17 h, the reaction mixture was diluted with chloroform and washed with saturated sodium hydrogencarbonate, water, aqueous 10% citric acid, and water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residues was chromatographed on silica gel eluting with chloroform/methanol/ammonia (100:3:0.3) to give **6** (1.43 g, 87%) as a colorless amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.89–1.99 (2H, m), 2.35 (3H, s), 2.49–2.55 (2H, m), 2.61–2.66 (2H, m), 2.98 (3H, s), 3.35–3.42 (2H, m), 3.45–3.51 (2H, m), 4.94 (2H, s), 6.53 (2H, d, J = 9.0 Hz), 7.01 (2H, d, J = 9.0 Hz), 7.26 (1H, s), 7.57 (1H, dd, J = 1.8, 8.8 Hz), 7.70 (1H, dd, J = 1.8, 8.8 Hz), 7.81–7.89 (2H, m), 8.12 (1H, s); FAB MS *m/e* $(M+1)^+$ 449.

4.1.5. Ethyl ({[(7-cyano-2-naphthyl)methyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (7). Compound **7** was synthesized from **5** and ethyl (chlorosulfonyl)acetate[8] according to the same procedure as that for **6**. Compound **7** was obtained as a white amorphous powder (80% yield): ^{1}H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 6.9 Hz), 1.86–1.97 (2H, m), 2.32 (3H, s), 2.49 (2H, t, J = 4.3 Hz), 2.61 (2H, t, J = 4.3 Hz), 3.37 (2H, t, J = 4.3 Hz), 3.46 (2H, t, J = 4.3 Hz), 4.07 (2H, s), 4.34 (2H, q, J = 6.9 Hz), 5.02 (2H, s), 6.53 (2H, d, J = 8.3 Hz), 7.19 (2H, d, J = 8.3 Hz), 7.48–7.54 (1H, m), 7.62 (1H, s), 7.65–7.71 (1H, m), 7.77–7.85 (2H, m), 8.03 (1H, s); FAB Ms *m/e* $(M+H)^+$ 521.

4.1.6. *tert*-Butyl ({[(7-cyano-2-naphthyl)methyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)carbamate (8). Compound **8** was synthesized from **5** and *tert*-butyl (chlorosulfonyl)carbamate according to the same procedure as that for **6**. Compound **8** was obtained as a white amorphous powder (75% yield): ^{1}H NMR ($CDCl_3$) δ 1.59 (9H, s), 1.86–1.97 (2H, m), 2.37–2.43 (5H, m), 2.59–2.70 (2H, m), 2.74–2.83 (2H, m), 3.02–

3.10 (2H, m), 5.23 (2H, s), 6.33 (2H, d, $J = 9.0$ Hz), 7.04 (2H, d, $J = 9.0$ Hz), 7.52 (1H, dd, $J = 1.8$, 9.0 Hz), 7.64 (1H, s), 7.78–7.86 (3H, m), 8.07 (1H, s); FAB MS *m/e* $(M+1)^+$ 550.

4.1.7. *N*-[(7-Cyano-2-naphthyl)methyl]-*N*-[4-(4-methyl-1,4-diazepan-1-yl)phenyl]sulfamide (9). To a stirred solution of **8** (0.24 g, 0.44 mmol) in 4.8 mL chloroform was added 4 N hydrogen chloride in ethyl acetate (4.8 mL) and stirred at ambient temperature for 6 h. The reaction mixture was concentrated in vacuo to give **9** (0.25 g, quant. yield) as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.20–2.45 (2H, m), 2.75 (3H, s), 2.94–3.23 (2H, m), 3.30–3.39 (4H, m), 3.58–3.69 (2H, m), 4.85 (2H, s), 6.60 (2H, d, $J = 8.4$ Hz), 7.16 (2H, d, $J = 8.4$ Hz), 7.71–7.77 (2H, m), 7.90 (1H, s), 7.98 (1H, d, $J = 8.8$ Hz), 8.05 (1H, d, $J = 8.8$ Hz), 8.49 (1H, s); FAB MS *m/e* $(M+1)^+$ 450.

4.1.8. *tert*-Butyl ({[(7-cyano-2-naphthyl)methyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)methylcarbamate (10). To a stirred solution of **8** (1.3 g, 2.36 mmol) in 50 mL tetrahydrofurane was added triphenylphosphine (2.48 g, 9.44 mmol), methanol (0.38 mL; 9.44 mmol), and diethylazodicarboxylate (1.49 mL, 9.44 mmol) and stirred at ambient temperature for 4 h. The reaction mixture was concentrated, added H_2O, and extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with chloroform/methanol/ammonia (50:1:0.1) to give **10** (1.33 g, quant. yield) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.63 (9H, s), 1.90–1.99 (2H, m), 2.35 (3H, s), 2.48–2.55 (2H, m), 2.61–2.67 (2H, m), 2.94 (3H, s), 3.37–3.43 (2H, s), 3.45–3.52 (2H, m), 5.15 (2H, s), 6.51 (2H, d, $J = 8.8$ Hz), 7.01 (2H, d, $J = 8.8$ Hz), 7.56 (1H, dd, $J = 1.8$, 8.8 Hz), 7.65–7.72 (2H, m), 7.85 (2H, t, $J = 8.8$ Hz), 8.12 (1H, s); FAB MS *m/e* $(M+1)^+$ 564.

4.1.9. *N*-[(7-Cyano-2-naphthyl)methyl]-*N*′,*N*′-dimethyl-*N*-[4-(4-methyl-1,4-diazepan-1-yl)phenyl]sulfamide (11). To a stirred solution of **10** (1.43 g, 2.54 mmol) in 30 mL chloroform was added trifluoroacetic acid (6.0 mL) and stirred at ambient temperature for 5 h. The reaction mixture was diluted with chloroform and washed with saturated sodium hydrogencarbonate and water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give intermediate de-protected compound. To a stirred solution of crude de-protected compound in 30 mL tetrahydrofurane was added triphenylphosphine (1.35 g, 5.16 mmol), methanol (0.21 mL; 5.16 mmol), and diethylazodicarboxylate (0.81 mL, 5.16 mmol) and stirred at ambient temperature for 24 h. The reaction mixture was concentrated, added H_2O, and extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with chloroform/methanol/ammonia (50:1:0.1) to give **11** (520 mg, 84%) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.89–1.99 (2H, m), 2.35 (3H, s), 2.48–2.54 (2H, m), 2.61–2.66 (2H, m), 2.76 (6H, s), 3.36–3.43 (2H, m), 3.45–3.50 (2H, m), 4.89 (2H, s), 6.50 (2H, d, $J = 8.8$ Hz), 7.05 (2H, d, $J = 8.8$ Hz), 7.54–7.72 (3H, m), 7.80–7.89 (2H, m), 8.11 (1H, s); FAB MS *m/e* $(M+1)^+$ 478.

4.1.10. Ethyl ({[(7-cyano-2-naphthyl)methyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)carbamate (12). Compound **12** was synthesized from **5** and ethyl (chlorosulfonyl)carbamate according to the same procedure as that for **6**. Compound **12** was obtained as a slight green amorphous powder (91% yield): ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, t, $J = 6.8$ Hz), 1.88–2.00 (2H, m), 2.53 (3H, s), 2.77–2.89 (2H, m), 2.91–3.00 (2H, m), 3.01–3.09 (2H, m), 3.19–3.51 (2H, m), 4.03 (2H, q, $J = 6.8$ Hz), 5.10 (2H, s), 6.47 (2H, d, $J = 8.8$ Hz), 7.05 (2H, d, $J = 8.8$ Hz), 7.70 (1H, dd, $J = 1.6$, 8.0 Hz), 7.74 (1H, dd, $J = 1.6$, 8.0 Hz), 7.82 (1H, s), 7.96 (1H, d, $J = 8.8$ Hz), 8.02 (1H, d, $J = 8.8$ Hz), 8.46 (1H, s); FAB MS *m/e* $(M+1)^+$ 522.

4.1.11. 7-{[[4-(4-Methyl-1,4-diazepan-1-yl)phenyl](methylsulfonyl)amino]methyl}naphthalene-2-carboximidamide (13). HCl gas was bubbled through a solution of **6** (1.05 g, 2.34 mmol) in MeOH (12 mL) and chloroform (21 mL) under −20 °C for 20 min. The mixture was allowed to stir for 21 h at 5 °C, and then concentrated in vacuo. To the crude imidate dissolved in MeOH (12 mL) and 1,4-dioxane (12 mL) at ambient temperature was added ammonium acetate (1.8 g, 23 mmol). The reaction mixture was stirred at ambient temperature for 19 h and concentrated in vacuo. The resulted residue was chromatographed on ODS-gel eluting with MeOH/H_2O (10:90). MeOH was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **13** (629 mg, 50%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.02–2.14 (1H, m), 2.29–2.41 (1H, m), 2.70 (3H, d, $J = 4.8$ Hz), 2.98–3.05 (2H, m), 3.09 (3H, s), 3.25–3.44 (4H, m), 3.62–3.87 (2H, m), 5.00 (2H, s), 6.64 (2H, d, $J = 8.8$ Hz), 7.23 (2H, d, $J = 8.8$ Hz), 7.67 (1H, dd, $J = 1.6$, 8.4 Hz), 7.82–7.87 (1H, m), 7.90 (1H, s), 8.01 (1H, d, $J = 8.4$ Hz), 8.08 (1H, d, $J = 8.4$ Hz), 8.54 (1H, s), 9.36–9.45 (2H, br), 9.55–9.66 (2H, br); FAB MS *m/e* $(M+1)^+$ 466; Anal. Calcd for $C_{25}H_{31}N_5O_2S{\cdot}2.5HCl{\cdot}1.0H_2O$: C, 50.06; H, 5.99; N, 12.97; S, 4.95; Cl, 13.69. Found: C, 50.19; H, 6.12; N, 13.03; S, 4.93; Cl, 13.84.

4.1.12. *N*-Hydroxy-7-{[[4-(4-methyl-1,4-diazepan-1-yl)-phenyl](methylsulfonyl)amino]methyl}naphthalene-2-carboximidamide (14). To a stirred solution of **6** (350 mg, 0.78 mmol) in 15 mL MeOH was added triethylamine (202 mg; 2.00 mmol), hydroxylamine hydrochloride (65 mg, 0.94 mmol) and stirred at 90 °C for 24 h. The reaction mixture was concentrated and the resulting residue was chromatographed on silica gel eluting with chloroform/methanol/ammonia (100:10:1). The organic solvent was removed in vacuo, and the result residue was lyophilized after being acidified with 1 N HCl. Compound **14** (280 mg, 34%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.03–2.14 (1H, m), 2.24–2.39 (1H, m), 2.72 (3H, d, $J = 4.9$ Hz), 2.96–3.04 (2H, m), 3.09 (3H, s), 3.25–3.42 (4H, m), 3.59–3.75 (2H, m), 4.99 (2H, s), 6.64 (2H, d, $J = 8.8$ Hz),

7.24 (2H, d, $J = 8.8$ Hz), 7.67 (1H, dd, $J = 1.5$, 8.8 Hz), 7.72 (1H, dd, $J = 1.5$, 8.8 Hz), 7.90 (1H, s), 8.00 (1H, d, $J = 8.8$ Hz), 8.08 (1H, d, $J = 8.8$ Hz), 8.37 (1H, s), 11.02–11.16 (2H, br), 11.28–11.50 (2H, br); FAB MS *m/e* $(M+1)^+$ 482; Anal. Calcd for $C_{25}H_{31}N_5O_3S{\cdot}2.4HCl{\cdot}1.0H_2O$: C, 51.14; H, 6.08; N, 11.93; S, 5.46; Cl, 14.49. Found: C, 51.35; H, 6.21; N, 11.65; S, 5.48; Cl, 14.36.

4.1.13. 7-({[(Aminosulfonyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}methyl)naphthalene-2-carboximidamide (15). Compound **15** was synthesized from **9** according to the same procedure as that for **13**. Compound **15** was obtained as a white amorphous powder (30% yield): ^{1}H NMR (DMSO-d_6) δ 2.03–2.15 (1H, m), 2.24–2.37 (1H, m), 2.71 (3H, d, $J = 4.9$ Hz), 2.95–3.07 (2H, m), 3.23–3.45 (4H, m), 3.58–3.74 (2H, m), 4.87 (2H, s), 5.53 (2H, s), 6.61 (2H, d, $J = 8.8$ Hz), 7.17 (2H, d, $J = 8.8$ Hz), 7.73 (1H, dd, $J = 1.4$, 8.8 Hz), 7.81 (1H, dd, $J = 1.4$, 8.8 Hz), 7.92 (1H, s), 7.99 (1H, d, $J = 8.8$ Hz), 8.08 (1H, d, $J = 8.8$ Hz), 8.46 (1H, s), 9.31–9.36 (2H, br), 9.52–9.58 (2H, br); FAB MS *m/e* $(M+1)^+$ 467; Anal. Calcd for $C_{24}H_{30}N_6O_2S{\cdot}2.8HCl{\cdot}1.5H_2O$: C, 48.39; H, 6.60; N, 14.11; S, 5.38; Cl, 16.66. Found: C, 48.40; H, 6.11; N, 13.85; S, 5.07; Cl, 16.54.

4.1.14. 7-({[(Aminosulfonyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}methyl)-*N*-hydroxynaphthalene-2-carboximidamide (16). Compound **16** was synthesized from **9** according to the same procedure as that for **14**. Compound **16** was obtained as a white amorphous powder (16% yield): ^{1}H NMR (DMSO-d_6) δ 2.02–2.13 (2H, m), 2.20–2.39 (2H, m), 2.71 (3H, d, $J = 4.9$ Hz), 2.95–3.09 (2H, m), 3.25–3.41 (4H, m), 3.59–3.74 (2H, m), 4.87 (2H, s), 6.63 (2H, d, $J = 8.8$ Hz), 7.17 (2H, d, $J = 8.8$ Hz), 7.68–7.74 (2H, m), 7.93 (1H, s), 7.98 (1H, d, $J = 8.8$ Hz), 8.07 (1H, d, $J = 8.8$ Hz), 8.33 (1H, s), 8.98–9.51 (2H, br), 11.10 (1H, s), 11.25–11.50 (1H, br); FAB MS *m/e* $(M+1)^+$ 487; Anal. Calcd for $C_{24}H_{30}N_6O_3S{\cdot}3.0HCl{\cdot}1.0H_2O$: C, 46.57; H, 5.86; N, 13.58; S, 5.18; Cl, 17.18. Found: C, 46.48; H, 5.98; N, 13.50; S, 5.16; Cl, 17.48.

4.1.15. 7-({[(Dimethylamino)sulfonyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}methyl)naphthalene-2-carboximidamide (17). To the solution of **18** (850 mg, 0.137 mmol) in acetic acid (17 mL) and chloroform (17 mL) was added acetic anhydride (0.2 mL) and 10% Pd–C powder (100 mg) and stirred in hydrogen atmosphere at ambient temperature for 2 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. The resulted residue was chromatographed on ODS-gel eluting with MeOH/H_2O (10:90). MeOH was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **17** (424 mg, 51%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.02–2.18 (1H, m), 2.25–2.40 (1H, m), 2.71 (3H, d, $J = 4.8$ Hz), 2.78 (6H, s), 2.98–3.10 (2H, m), 3.26–3.45 (4H, m), 3.60–3.79 (2H, m), 5.00 (2H, s), 6.62 (2H, d, $J = 8.8$ Hz), 7.20 (2H, d, $J = 8.8$ Hz), 7.66 (1H, dd, $J = 1.2$, 8.8 Hz), 7.82 (1H, dd, $J = 1.2$, 8.8 Hz), 7.88 (1H, s), 8.00 (1H, d, $J = 8.8$ Hz), 8.09 (1H, d, $J = 8.8$ Hz), 9.30–9.40 (2H, br), 9.38–9.57 (2H, br); FAB MS *m/e* $(M+1)^+$ 495; Anal. Calcd for $C_{26}H_{34}N_6O_2S{\cdot}2.7HCl{\cdot}1.0H_2O$: C, 51.10; H, 6.38; N, 13.75; S, 5.25; Cl, 15.66. Found: C, 50.83; H, 6.59; N, 13.57; S, 5.23; Cl, 15.78.

4.1.16. 7-({[(Dimethylamino)sulfonyl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}methyl)-*N*-hydroxynaphthalene-2-carboximidamide (18). Compound **18** was synthesized from **11** according to the same procedure as that for **14**. Compound **18** was obtained as a white amorphous powder (90% yield): ^{1}H NMR (DMSO-d_6) δ 2.03–2.12 (1H, m), 2.20–2.32 (1H, m), 2.73 (2H, d, $J = 4.8$ Hz), 2.78 (6H, s), 2.99–3.10 (4H, m), 3.58–3.70 (2H, m), 4.99 (2H, s), 6.62 (2H, d, $J = 8.0$ Hz), 7.21 (2H, d, $J = 8.0$ Hz), 7.64 (1H, dd, $J = 2.0$, 8.0 Hz), 7.71 (1H, dd, $J = 2.0$, 8.0 Hz), 7.87 (1H, s), 8.00 (1H, d, $J = 8.0$ Hz), 8.07 (1H, d, $J = 8.0$ Hz), 8.35 (1H, s), 8.80–9.40 (1H, br), 10.81–10.92 (1H, br), 11.18–11.40 (1H, br); FAB MS *m/e* $(M+1)^+$ 511; Anal. Calcd for $C_{26}H_{34}N_6O_3S{\cdot}2.0HCl{\cdot}2.2H_2O$: C, 50.11; H, 6.53; N, 13.49; S, 5.15; Cl, 11.38. Found: C, 50.03; H, 6.41; N, 13.12; S, 4.99; Cl, 11.52.

4.1.17. ({({7-[(Hydroxyamino)(imino)methyl]-2-naphthyl}methyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}-sulfonyl)acetic acid (19). To a stirred solution of **21** (550 mg, 0.99 mmol) in 10 mL dioxane was added 1 N NaOHaq (2 mL, 2.00 mmol) and stirred at ambient temperature for 3 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on ODS-gel eluting with 0.001 M HCl/CH_3CN (100:5). CH_3CN was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **19** (107 mg, 19%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.03–2.14 (1H, m), 2.29–2.40 (1H, m), 2.71 (3H, d, $J = 4.9$ Hz), 2.98–3.10 (2H, m), 3.26–3.41 (4H, m), 3.62–3.77 (2H, m), 4.24 (2H, s), 5.02 (2H, s), 6.66 (2H, d, $J = 8.8$ Hz), 7.23 (2H, d, $J = 8.8$ Hz), 7.66 (1H, dd, $J = 1.5$, 8.8 Hz), 7.74 (1H, dd, $J = 1.2$, 8.8 Hz), 7.88 (1H, s), 8.02 (1H, d, $J = 8.8$ Hz), 8.07 (1H, d, $J = 8.8$ Hz), 8.36 (1H, s), 8.90–9.54 (4H, br); FAB MS *m/e* $(M+1)^+$ 526; Anal. Calcd for $C_{26}H_{31}N_5O_5S{\cdot}3.0HCl{\cdot}1.8H_2O$: C, 46.53; H, 5.66; N, 10.44; S, 4.78; Cl, 16.38. Found: C, 46.90; H, 6.04; N, 10.39; S, 4.86; Cl, 16.30.

4.1.18. Ethyl ({({7-[amino(imino)methyl]-2-naphthyl}methyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (20). Compound **20** was synthesized from **7** according to the same procedure as that for **13**. Compound **20** was obtained as a white amorphous powder (40% yield): ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, $J = 7.2$ Hz), 2.04–2.16 (1H, m), 2.28–2.40 (1H, m), 2.71 (1.5H, s), 2.72 (1.5H, s), 2.99–3.09 (2H, m), 3.26–3.42 (4H, m), 3.62–3.76 (2H, m), 4.25 (2H, q, $J = 7.2$ Hz), 4.36 (2H, s), 5.02 (2H, s), 6.67 (2H, d, $J = 8.4$ Hz), 7.22 (2H, d, $J = 8.4$ Hz), 7.67 (1H, d, $J = 8.4$ Hz), 7.83 (1H, d, $J = 8.4$ Hz), 7.90 (1H, s), 8.03 (1H, d, $J = 8.4$ Hz), 8.10 (1H, d, $J = 8.4$ Hz), 8.51 (1H, s), 9.37 (2H, s), 9.56 (2H, s), 11.21 (1H, s); FAB MS *m/e* $(M+1)^+$ 538; Anal. Calcd for $C_{28}H_{35}N_5O_4S{\cdot}2.9HCl{\cdot}1.5H_2O$: C, 50.16; H,

6.15; N, 10.45; S, 4.78; Cl, 15.34. Found: C, 50.45; H, 6.04; N, 10.50; S, 4.78; Cl, 15.15.

4.1.19. Ethyl ({({7-[(hydroxyamino)(imino)methyl]-2-naphthyl}methyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]-amino}sulfonyl)acetate (21). Compound **21** was synthesized from **7** according to the same procedure as that for **14**. Compound **21** was obtained as a white amorphous powder (12% yield): ^{1}H NMR (DMSO-d_6) δ 1.27 (3H, t, J = 7.3 Hz), 2.02–2.14 (1H, m), 2.21–2.38 (1H, m), 2.73 (3H, d, J = 4.4 Hz), 2.98–3.10 (2H, m), 3.22–3.70 (6H, m), 4.24 (2H, q, J = 7.3 Hz), 4.35 (2H, s), 5.01 (2H, s), 6.66 (2H, d, J = 8.8 Hz), 7.21 (2H, d, J = 8.8 Hz), 7.64 (1H, dd, J = 1.9, 8.8 Hz), 7.71 (1H, dd, J = 1.9, 8.8 Hz), 7.89 (1H, s), 8.00 (1H, d, J = 8.8 Hz), 8.07 (1H, d, J = 8.8 Hz), 8.35 (1H, s), 8.80–9.42 (2H, br), 10.72–10.89 (1H, br), 11.12–11.42 (1H, br); FAB MS *m/e* (M+1)$^+$ 554; Anal. Calcd for $C_{28}H_{35}N_5O_5S{\cdot}2.1HCl{\cdot}2.8H_2O$: C, 49.41; H, 6.32; N, 10.29; S, 4.71; Cl, 10.94. Found: C, 49.77; H, 6.34; N, 10.23; S, 4.61; Cl, 11.16.

4.1.20. Ethyl ({({7-[amino(imino)methyl]-2-naphthyl}-methyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)carbamate (22). Compound **22** was synthesized from **12** according to the same procedure as that for **13**. Compound **22** was obtained as a white amorphous powder (48% yield): ^{1}H NMR (DMSO-d_6) δ 1.29 (3H, t, J = 6.0 Hz), 2.06–2.16 (1H, m), 2.28–2.40 (1H, m), 2.72 (3H, d, J = 3.2 Hz), 2.96–3.11 (2H, m), 3.26–3.42 (4H, m), 3.60–3.78 (2H, m), 4.25 (2H, q, J = 6.0 Hz), 5.14 (2H, s), 6.67 (2H, d, J = 8.8 Hz), 7.10 (2H, d, J = 8.8 Hz), 7.66 (1H, dd, J = 1.6, 8.8 Hz), 7.83 (1H, dd, J = 1.6, 8.8 Hz), 7.91 (1H, s), 8.03 (1H, d, J = 8.8 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.49 (1H, s), 9.30–9.39 (2H, br), 9.48–9.59 (2H, br); FAB MS *m/e* (M+1)$^+$ 539; Anal. Calcd for $C_{27}H_{34}N_6O_2S{\cdot}2.6HCl{\cdot}1.0H_2O$: C, 51.91; H, 6.20; N, 12.11; S, 5.54; Cl, 15.94. Found: C, 52.04; H, 6.18; N, 12.49; S, 5.30; Cl, 15.90.

4.1.21. Ethyl ({({7-[(hydroxyamino)(imino)methyl]-2-naphthyl}methyl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]-amino}sulfonyl)carbamate (23). Compound **23** was synthesized from **12** according to the same procedure as that for **14**. Compound **23** was obtained as a white amorphous powder (42% yield): ^{1}H NMR (DMSO-d_6) δ 1.23 (3H, t, J = 7.4 Hz), 1.93–2.01 (2H, m), 2.55 (3H, s), 2.89–3.03 (4H, m), 3.10–3.19 (2H, m), 3.29–3.40 (2H, m), 4.07 (2H, q, J = 7.4 Hz), 5.07 (2H, s), 6.57 (2H, d, J = 8.8 Hz), 7.07 (2H, d, J = 8.8 Hz), 7.50 (1H, dd, J = 1.5, 8.8 Hz), 7.69 (1H, s), 7.77–7.83 (3H, m), 8.09 (1H, s), 9.75 (1H, s); FAB MS *m/e* (M+1)$^+$ 555; Anal. Calcd for $C_{27}H_{34}N_6O_5S{\cdot}3.0HCl{\cdot}3.8H_2O$: C, 44.27; H, 6.14; N, 11.47; S, 4.38; Cl, 14.52. Found: C, 44.00; H, 6.22; N, 11.42; S, 4.30; Cl, 14.82.

4.1.22. 3-((1*E*)-3-{[4-(4-Methyl-1,4-diazepan-1-yl)phenyl]amino}prop-1-en-1-yl)benzonitrile (25). Compound **25** was synthesized from **4** and **24** according to the same procedure as that for **5**. Compound **25** was obtained as a white amorphous powder (35% yield): ^{1}H NMR ($CDCl_3$) δ 1.95–2.07 (2H, m), 2.39 (3H, s), 2.54–2.62 (2H, m), 2.67–2.74 (2H, m), 3.36–3.45 (2H, m), 3.47–3.55 (2H, m), 4.38–4.52 (2H, m), 6.20–6.31 (1H, m), 6.42–6.63 (3H, m), 7.13–7.28 (2H, m), 7.52–7.83 (4H, m); FAB MS *m/e* (M)$^+$ 346.

4.1.23. Ethyl ({[(2*E*)-3-(3-cyanophenyl)prop-2-en-1-yl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (26). Compound **26** was synthesized from **25** and ethyl (chlorosulfonyl)acetate[8] according to the same procedure as that for **6**. Compound **26** was obtained as a white amorphous powder (44% yield): ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J = 6.9 Hz), 1.94–2.05 (2H, m), 2.37 (3H, s), 2.52–2.57 (2H, m), 2.66–2.70 (2H, m), 3.42–3.49 (2H, m), 3.52–3.58 (2H, m), 3.99 (2H, s), 4.30 (2H, q, J = 6.9 Hz), 4.45 (2H, d, J = 5.1 Hz), 6.20–6.31 (1H, m), 6.42 (1H, d, J = 16.2 Hz), 6.63 (2H, d, J = 9.0 Hz), 7.26–7.29 (2H, m), 7.38–7.59 (4H, m); FAB MS *m/e* (M+1)$^+$ 497.

4.1.24. Isopropyl ({[(2*E*)-3-(3-cyanophenyl)prop-2-en-1-yl][4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)-acetate (27). Compound **27** was synthesized from **25** and isopropyl (chlorosulfonyl)acetate[9] according to the same procedure as that for **6**. Compound **27** was obtained as a white amorphous powder (49% yield): ^{1}H NMR (CDCl3) δ 1.33 (6H, d, J = 6.3 Hz), 1.94–2.06 (2H, m), 2.38 (3H, s), 2.53–2.61 (2H, m), 2.66–2.72 (2H, m), 3.42–3.50 (2H, m), 3.52–3.58 (2H, m), 3.95 (2H, s), 4.45 (2H, d, J = 5.3 Hz), 5.10–5.19 (1H, m), 6.21–6.30 (1H, m), 6.42 (1H, d, J = 16.1 Hz), 6.63 (2H, d, J = 7.8 Hz), 7.21–7.30 (2H, m), 7.35–7.56 (4H, m); FAB MS *m/e* (M+1)$^+$ 511.

4.1.25. ({((2*E*)-3-{3-[Amino(imino)methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetic acid (28). A solution of **29** (590 mg, 1.15 mmol) in concd HCl (9 mL) was stirred at ambient temperature for 24 h. The reaction mixture was concentrated in vacuo and the residues was chromatographed on ODS-gel eluting with CH_3CN/H_2O (4:96). CH_3CN was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **28** (134 mg, 24%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 1.82–1.98 (2H, m), 2.32 (3H, s), 2.52–2.60 (2H, m), 2.64–2.72 (2H, m), 3.40–3.46 (2H, m), 3.48–3.54 (2H, m), 3.73 (2H, s), 4.43 (2H, d, J = 4.9 Hz), 6.38–6.52 (2H, m), 6.65 (2H, d, J = 9.1 Hz), 7.32 (2H, d, J = 9.1 Hz), 7.51 (1H, t, J = 7.8 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.83 (1H, s), 8.95–9.25 (2H, br), 10.54–10.82 (2H, br); FAB MS *m/e* 486 (M+1)$^+$ 486; Anal. Calcd for $C_{24}H_{31}N_5O_4S{\cdot}2.4HCl{\cdot}2.1H_2O$: C, 47.18; H, 6.20; N, 11.46; S, 5.25; Cl, 13.93. Found: C, 46.91; H, 6.23; N, 11.40; S, 5.22; Cl, 13.85.

4.1.26. Ethyl ({((2*E*)-3-{3-[amino(imino)methyl]phenyl}-prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]-amino}sulfonyl)acetate (29). Compound **29** was synthesized from **26** according to the same procedure as that for **13**. Compound **29** was obtained as a white amorphous powder (23% yield): ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.4 Hz), 2.06–2.20 (1H, m), 2.28–2.40 (1H, m), 2.76 (3H, d, J = 4.4 Hz), 3.03–3.18 (2H, m), 3.32–3.45 (4H, m), 3.65–3.83 (2H, m), 4.21 (2H, q,

J = 7.4 Hz), 4.26 (2H, s), 4.41 (2H, d, J = 5.8 Hz), 6.38–6.45 (1H, m), 6.55 (1H, d, J = 5.5 Hz), 6.75 (2H, d, J = 9.3 Hz), 7.27 (2H, d, J = 9.3 Hz), 7.52 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.80 (1H, s), 9.37 (2H, s), 9.56 (2H, s), 11.21 (1H, s); FAB MS *m/e* $(M+1)^+$ 514.

4.1.27. Ethyl ({((2*E*)-3-{3-[(hydroxyamino)(imino)methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)-phenyl]amino}sulfonyl)acetate (30). Compound **30** was synthesized from **26** according to the same procedure as that for **14**. Compound **30** was obtained as a white amorphous powder (31% yield): ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.4 Hz), 2.06–2.20 (1H, m), 2.28–2.40 (1H, m), 2.76 (3H, d, J = 4.4 Hz), 3.03–3.18 (2H, m), 3.32–3.45 (4H, m), 3.65–3.83 (2H, m), 4.21 (2H, q, J = 7.4 Hz), 4.26 (2H, s), 4.41 (2H, d, J = 5.8 Hz), 6.38–6.45 (1H, m), 6.55 (1H, d, J = 5.5 Hz), 6.75 (2H, d, J = 9.3 Hz), 7.27 (2H, d, J = 9.3 Hz), 7.52 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.80 (1H, s), 8.57–9.42 (1H, br), 10.60–11.58 (1H, br), 11.25–11.42 (1H, br); FAB MS *m/e* $(M+1)^+$ 530; Anal. Calcd for $C_{26}H_{35}N_5O_5S{\cdot}2.6HCl{\cdot}2.0H_2O$: C, 47.28; H, 6.35; N, 10.60; S, 4.85; Cl, 13.96. Found: C, 47.12; H, 6.36; N, 10.50; S, 4.91; Cl, 14.24.

4.1.28. Ethyl ({((2*E*)-3-{3-[imino(methoxyamino)methyl]-phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)-phenyl]amino}sulfonyl)acetate (31). Compound **31** was synthesized from **26** and methoxyamine instead of hydroxylamine according to the same procedure as that for **14**. Compound **31** was obtained as a white amorphous powder (28% yield): ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t, J = 7.0 Hz), 2.07–2.20 (1H, m), 2.31–2.46 (1H, m), 2.74 (3H, d, J = 4.9 Hz), 3.02–3.19 (2H, m), 3.34–3.48 (4H, m), 3.67–3.82 (2H, m), 3.87 (3H, s), 4.20 (2H, q, J = 7.0 Hz), 4.27 (3H, s), 4.41 (2H, d, J = 5.8 Hz), 6.44 (1H, dt, J = 5.8, 15.6 Hz), 6.64 (1H, d, J = 15.6 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.28 (2H, d, J = 8.8 Hz), 7.49 (1H, t, J = 8.8 Hz), 7.64 (2H, t, J = 8.8 Hz), 7.86 (1H, s), 8.50–9.47 (2H, br), 11.29 (1H, s): FAB MS *m/e* $(M+1)^+$ 544; Anal. Calcd for $C_{27}H_{37}N_5O_5S{\cdot}2.7HCl{\cdot}1.4H_2O$: C, 48.59; H, 6.42; N, 10.48; S, 4.80; Cl, 14.84. Found: C, 48.63; H, 6.70; N, 10.46; S, 4.78; Cl, 14.52.

4.1.29. Ethyl ({((2*E*)-3-{3-[[(acetyloxy)amino](imino)-methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (32). To a stirred solution of **30** (517 mg, 0.98 mmol) in DMF (5 mL) and pyridine (5 mL) was added acetic anhydrate (0.99 g, 9.7 mmol) at ambient temperature. The reaction mixture was concentrated and the resulting residue was chromatographed on silica gel eluting with chloroform/methanol/ammonia (100:10:1). Compound **32** (162 mg, 29%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 1.24 (3H, t, J = 7.0 Hz), 1.92–2.00 (2H, m), 2.15 (3H, s), 2.38 (3H, s), 2.64–2.71 (2H, m), 2.73–2.83 (2H, m), 3.21–3.35 (2H, m), 3.52–3.59 (2H, m), 4.20 (2H, q, J = 7.0 Hz), 4.26 (3H, s), 4.38 (2H, d, J = 5.9 Hz), 6.30 (1H, dt, J = 5.9, 15.6 Hz), 6.49 (1H, d, J = 15.6 Hz), 6.70 (2H, d, J = 8.8 Hz), 6.83 (2H, br), 7.22 (2H, d, J = 8.8 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.71 (1H, s): FAB MS *m/e* $(M+1)^+$ 572; Anal. Calcd for $C_{28}H_{37}N_5O_6S{\cdot}1.5H_2O$: C, 56.17; H, 6.33; N, 11.70; S, 5.36. Found: C, 56.09; H, 6.69; N, 11.76; S, 5.37.

4.1.30. Ethyl ({((2*E*)-3-{3-[[(ethoxycarbonyl)amino](imino)methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (33). To a stirred solution of **29** (530 mg, 0.90 mmol) in 30 mL chloroform was added chloroethylformate (0.26 g, 2.71 mmol), 0.1 N NaOH (27.1 mL, 2.71 mmol) at ambient temperature. After 24 h, the reaction mixture was neutralized with 1 N HCl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was chromatographed on silica gel eluting with chloroform/methanol (10:1). The result residue was lyophilized after being acidified with 1 N HCl. Compound **33** (178 mg, 34%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t, J = 7.3 Hz), 1.33 (3H, t, J = 7.3 Hz), 2.10–2.18 (1H, m), 2.29–2.38 (1H, m), 2.77 (3H, d, J = 4.8 Hz), 3.04–3.16 (2H, m), 3.34–3.50 (4H, m), 3.73–3.76 (2H, m), 4.21 (2H, q, J = 7.3 Hz), 4.26 (2H, s), 4.35 (2H, q, J = 7.3 Hz), 4.42 (2H, d, J = 5.9 Hz), 6.42 (1H, dt, J = 5.9, 15.6 Hz), 6.55 (1H, d, J = 15.6 Hz), 6.76 (2H, d, J = 8.7 Hz), 7.27 (2H, d, J = 8.7 Hz), 7.54 (1H, t, J = 7.8 Hz), 7.65 (1H, d, J = 7.8 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.87 (1H, s), 10.52–10.61 (1H, br), 10.43–11.04 (1H, br), 11.32–11.44 (1H, br): FAB MS *m/e* $(M+1)^+$ 586; Anal. Calcd for $C_{29}H_{39}N_5O_6S{\cdot}2.5HCl{\cdot}2.5H_2O$: C, 48.25; H, 6.49; N, 9.70; S, 4.44; Cl, 12.28. Found: C, 48.15; H, 6.42; N, 9.22; S, 4.56; Cl, 12.63.

4.1.31. Ethyl ({{(2*E*)-3-[3-(imino{[(trichloromethoxy)carbonyl]amino}methyl)phenyl]prop-2-en-1-yl}[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (34). Compound **34** was synthesized from **29** and 2,2,2-trichloroethylchloroformate according to the same procedure as that for **33**. Compound **34** was obtained as a white amorphous powder (28% yield): ^{1}H NMR (DMSO-d_6) δ 1.25 (3H, t, J = 7.3 Hz), 2.11–2.28 (2H, m), 2.79 (3H, d, J = 4.9 Hz), 3.06–3.18 (4H, m), 3.33–3.46 (4H, m), 3.60–3.78 (2H, m), 4.20 (2H, q, J = 7.3 Hz), 4.26 (2H, s), 4.41 (2H, d, J = 5.9 Hz), 4.97 (2H, s), 6.37 (1H, dt, J = 5.9, 16.1 Hz), 6.55 (1H, d, J = 16.1 Hz), 6.76 (2H, d, J = 9.3 Hz), 7.13 (2H, d, J = 9.3 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.84 (1H, d, J = 7.8 Hz), 7.93 (1H, s), 10.20–10.34 (3H, br): FAB MS *m/e* $(M+1)^+$ 689; Anal. Calcd for $C_{29}H_{36}N_5O_6SCl_3{\cdot}1.7HCl{\cdot}2.3H_2O$: C, 43.95; H, 5.38; N, 8.84; S, 4.05; Cl, 21.03. Found: C, 43.70; H, 5.25; N, 8.39; S, 4.07; Cl, 20.79.

4.1.32. ({((2*E*)-3-{3-[(Hydroxyamino)(imino)methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]-amino}sulfonyl)acetic acid (35). To a stirred solution of **30** (181 mg, 0.27 mmol) in 5 mL EtOH and 5 mL H_2O was added 1 N NaOHaq (2 mL, 2.00 mmol) and stirred at ambient temperature for 2 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on ODS-gel eluting with MeOH/CH_3CN (40:60). CH_3CN was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **35** (152 mg, 90%) was obtained as a

white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 1.98–2.19 (1H, m), 2.26–2.40 (1H, m), 2.76 (3H, d, J = 3.5 Hz), 3.04–3.16 (2H, m), 3.32–3.50 (4H, m), 3.63–3.85 (2H, m), 4.14 (2H, s), 4.42 (2H, d, J = 5.9 Hz), 6.41 (1H, dt, J = 5.9, 16.1 Hz), 6.53 (1H, d, J = 16.1 Hz), 6.75 (2H, d, J = 9.3 Hz), 7.27 (2H, d, J = 9.3 Hz), 7.50 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.66 (1H, d, J = 7.8 Hz), 7.78 (1H, s), 10.82–10.95 (1H, br), 10.72–11.40 (2H, br), 13.21–13.63 (1H, br); FAB MS *m/e* $(M+1)^+$ 502.

4.1.33. Methyl ({((2*E*)-3-{3-[(hydroxyamino)(imino)-methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (36). To a stirred solution of **35** (100 mg, 0.19 mmol) in 10 mL MeOH was added 4 N HCl 1,4-dioxane solution (10 mL) and stirred at ambient temperature for 12 h. The reaction mixture was concentrated in vacuo and **36** (73 mg, 64%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ 2.08–2.50 (2H, m), 2.78 (2H, d, J = 4.4 Hz), 3.08–3.17 (2H, m), 3.36–3.50 (4H, m), 3.60–3.68 (2H, m), 4.29 (3H, s), 4.40 (2H, d, J = 5.8 Hz), 6.42 (1H, dt, J = 5.8, 16.2 Hz), 6.55 (1H, d, J = 16.2 Hz), 6.75 (1H, d, J = 7.8 Hz), 7.27 (2H, d, J = 7.8 Hz), 7.56 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.68 (1H, d, J = 7.8 Hz), 7.78 (1H, s), 8.80–9.50 (1H, br), 10.32–10.48 (1H, br), 11.02–11.30 (1H, br); FAB MS *m/e* $(M+1)^+$ 516; Anal. Calcd for $C_{25}H_{33}N_5O_5S{\cdot}2.9HCl{\cdot}2.0H_2O$: C, 45.63; H, 6.12; N, 10.65; S, 4.88; Cl, 15.64. Found: C, 45.49; H, 6.06; N, 10.37; S, 5.11; Cl, 15.32.

4.1.34. Propyl ({((2*E*)-3-{3-[(hydroxyamino)(imino)-methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (37). Compound **37** was synthesized from **35** and 1-propanol according to the same procedure as that for **36**. Compound **37** was obtained as a white amorphous powder (63% yield): ^{1}H NMR (DMSO-d_6) δ 0.92 (3H, t, J = 7.3 Hz), 1.58–1.67 (2H, m), 2.08–2.34 (2H, m), 2.78 (3H, s), 3.02–3.20 (2H, m), 3.26–3.40 (4H, m), 3.64–3.82 (2H, m), 4.12 (2H, t, J = 7.3 Hz), 4.26 (2H, s), 4.40 (2H, d, J = 5.9 Hz), 6.26 (1H, dt, J = 5.9, 15.6 Hz), 6.50 (1H, d, J = 15.6 Hz), 6.75 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz), 7.44 (1H, t, J = 7.3 Hz), 7.54–7.60 (2H, m), 7.75 (1H, s), 10.40–10.83 (3H, br); FAB MS *m/e* $(M+1)^+$ 544; Anal. Calcd for $C_{27}H_{37}N_5O_5S{\cdot}1.5HCl{\cdot}2.5H_2O$: C, 50.40; H, 6.81; N, 10.88; S, 4.98; Cl, 8.27. Found: C, 50.51; H, 6.65; N, 10.57; S, 5.59; Cl, 8.37.

4.1.35. Isopropyl ({((2*E*)-3-{3-[(hydroxyamino)(imino)-methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (38). Compound **38** was synthesized from **27** according to the same procedure as that for **14**. Compound **38** was obtained as a white amorphous powder (58% yield): ^{1}H NMR (DMSO-d_6) δ 1.25 (6H, d, J = 6.3 Hz), 2.08–2.16 (1H, m), 2.25–2.34 (1H, m), 2.76 (3H, d, J = 4.9 Hz), 3.04–3.16 (2H, m), 3.35–3.44 (4H, m), 3.62–3.76 (2H, m), 4.22 (2H, s), 4.41 (2H, d, J = 5.4 Hz), 4.98–5.04 (1H, m), 6.42 (1H, dt, J = 5.4, 16.2 Hz), 6.55 (1H, d, J = 16.2 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz), 7.53 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 7.8 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.80 (1H, s), 8.90–9.21 (1H, br), 11.27–11.35 (1H, br), 11.71–11.83 (1H, br): FAB MS *m/e* $(M+1)^+$ 544; Anal. Calcd for $C_{27}H_{37}N_5O_5S{\cdot}2.5HCl{\cdot}2.3H_2O$: C, 48.22; H, 6.64; N, 10.41; S, 4.77; Cl, 12.12. Found: C, 48.60; H, 6.43; N, 10.09; S, 4.77; Cl, 12.44.

4.1.36. Isobutyl ({((2*E*)-3-{3-[(hydroxyamino)(imino)-methyl]phenyl}prop-2-en-1-yl)[4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino}sulfonyl)acetate (39). Compound **39** was synthesized from **35** and 2-methylpropanol according to the same procedure as that for **36**. Compound **39** was obtained as a white amorphous powder (70% yield): ^{1}H NMR (DMSO-d_6) δ 0.92 (6H, d, J = 6.8 Hz), 1.84–1.96 (1H, m), 2.08–2.20 (1H, m), 2.25–2.37 (1H, m), 2.77 (3H, d, J = 4.4 Hz), 3.05–3.17 (2H, m), 3.34–3.50 (4H, m), 3.65–3.74 (2H, m), 3.95 (2H, d, J = 6.8 Hz), 4.29 (2H, s), 4.41 (2H, d, J = 5.3 Hz), 6.43 (1H, dt, J = 5.3, 16.2 Hz), 6.55 (1H, d, J = 16.2 Hz), 6.76 (2H, d, J = 8.8 Hz), 7.27 (2H, d, J = 8.8 Hz), 7.53 (1H, t, J = 7.3 Hz), 7.58 (1H, d, J = 7.3 Hz), 7.70 (1H, d, J = 7.3 Hz), 7.79 (1H, s), 8.92–9.21 (1H, br), 10.68–10.80 (1H, br), 11.20–11.33 (1H, br); FAB MS *m/e* $(M+1)^+$ 558; Anal. Calcd for $C_{28}H_{39}N_5O_5S{\cdot}3.3HCl{\cdot}2.0H_2O$: C, 47.10; H, 6.54; N, 9.81; S, 4.49; Cl, 16.38. Found: C, 47.21; H, 6.72; N, 9.61; S, 4.95; Cl, 16.21.

4.2. Biology

4.2.1. Chromogenic assay. The hydrolysis rates of synthetic substrates were assayed by continuously measuring absorbance at 405 nm at 37 °C with a microplate reader (Model 3550, Bio-Rad, USA). Reaction mixtures (125 μL) were prepared in 96-well plates containing chromogenic substrates and an inhibitor in either 0.05 M Tris–HCl, pH 8.4, 0.15 M NaCl. Reactions were initiated with a 25 μL portion of the enzyme solution. Enzymes and substrates were used as follows: factor Xa and S-2222. The concentration of an inhibitor required to inhibit enzyme activity by 50% (IC_{50}) was calculated from dose–response curves in which the logit transformation of residual activity was plotted against the logarithm of inhibitor concentration.

4.2.2. Plasma clotting time assays. Citrated blood samples from mice were collected. Platelet-poor plasma was prepared by centrifugation at 3000 rpm for 10 min and stored at −40 °C until use. Plasma clotting times were performed using a KC10A coagulometer (Amelung Co., Lehbrinsweg, Germany) at 37 °C. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured using Orthobrain thromboplastin and thrombofax (Ortho Diagnostic Systems Co., Tokyo, Japan), respectively. Coagulation times for each test sample were compared with coagulation times measured using a distilled water control. The concentration required to double the clotting time (CT_2) was estimated from each individual concentration–response curve. Each measurement was performed three times, and represented as the mean value.

4.2.3. Ex vivo studies. Male mice weighing 30–37 g was used in these studies. Fasted animals for overnight for

the oral studies were used. In mice, the test drug was dissolved in saline and administered to animals orally at 100 mg/kg using a gastric tube. Citrated blood was collected from the vena cava 1 min after intravenous injection or 30 min after oral administration. Platelet-poor plasma was prepared by centrifugation for measurement of PT or APTT. All data were expressed as relative fold values, compared with the vehicle group.

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