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Synthesis and biological activity of novel 1,2-disubstituted benzene derivatives as factor Xa inhibitors

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Abstract—Factor Xa (fXa) is a serine protease that plays a pivotal role in the coagulation cascade. High-throughput screening of the Yamanouchi compound library yielded lead compound **1** with the ability to inhibit fXa at micromolar concentrations. To improve its fXa inhibitory activity and its oral anticoagulant activity, the linker between benzamidine and the central benzene ring was modified and a carboxyl group was introduced at the central benzene ring. The resulting compounds **40b** (YM-203552), **41a** (YM-202054), and **41c** (YM-203558) exhibited potent fXa inhibitory activity and oral anticoagulant activity. In particular, YM-203558 exhibited the most potent oral anticoagulant activity, prolonging PT more than 3-fold at 0.5 and 2.0 h. Additionally, these compounds showed a high degree of selectivity for other serine proteases.

1. Introduction

Thrombotic diseases such as deep vein thrombosis, stroke, and pulmonary embolism are a major cause of mortality and morbidity in the developed world. Therefore, the prevention of blood coagulation is a major target for new therapeutic agents. Factor Xa (fXa) is a trypsin-like serine protease that forms a prothrombinase complex with factor Va, Ca^{2+}, and phospholipid to produce thrombin. This key enzyme functions at the convergence of the intrinsic and extrinsic coagulation pathways in a process that involves signal amplification, one molecule of fXa activating many molecules of prothrombin to thrombin.[1] Inhibition of fXa may therefore be more effective than the inhibition of thrombin itself. The discovery of orally active, small molecule competitive fXa inhibitors as novel therapies for thromboembolic disorders has been a major focus of the pharmaceutical industry.

In the course of the search for fXa inhibitors in our laboratories, we have previously reported potent, selective, and orally active *N*-[(7-amidino-2-naphthyl)methyl]aniline-based fXa inhibitors, YM-60828 and YM-167065, respectively, containing an acetimidoylpiperidine moiety and an *N*-methyl-1,4-diazepane moiety as the P4 part.[2–4] With the hope of discovering a novel class of fXa inhibitors having novel frame structures, high-throughput screening (HTS) of the Yamanouchi compound library was conducted, leading to the identification of the 1,2-dibenzoamidobenzene derivative **1** as an fXa inhibitor (Fig. 1). Compound **1** showed rather weak inhibitory activity against fXa (IC_{50} = 6226 nM), but possessed a novel and unique structure, which resulted in different from our naphthylamidine-based fXa inhibitors.[5–9] We therefore selected **1** as a lead compound, and modified it in a search for potent and orally active fXa inhibitors.

2. Chemistry

Scheme 1 illustrates the synthesis of 1,2-dibenzamidobenzene derivatives, starting from either 1,2-phenylenediamine (**3**, **11a**, **11b**) or 2-nitroaniline (**8a**, **8b**).

Keywords: Anticoagulants; Enzyme inhibitors; Factor Xa.
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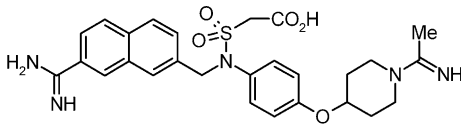
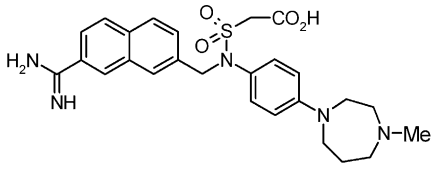


YM-60828



YM-167065

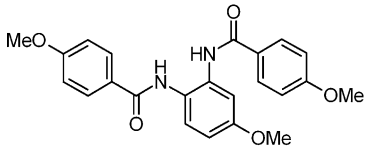


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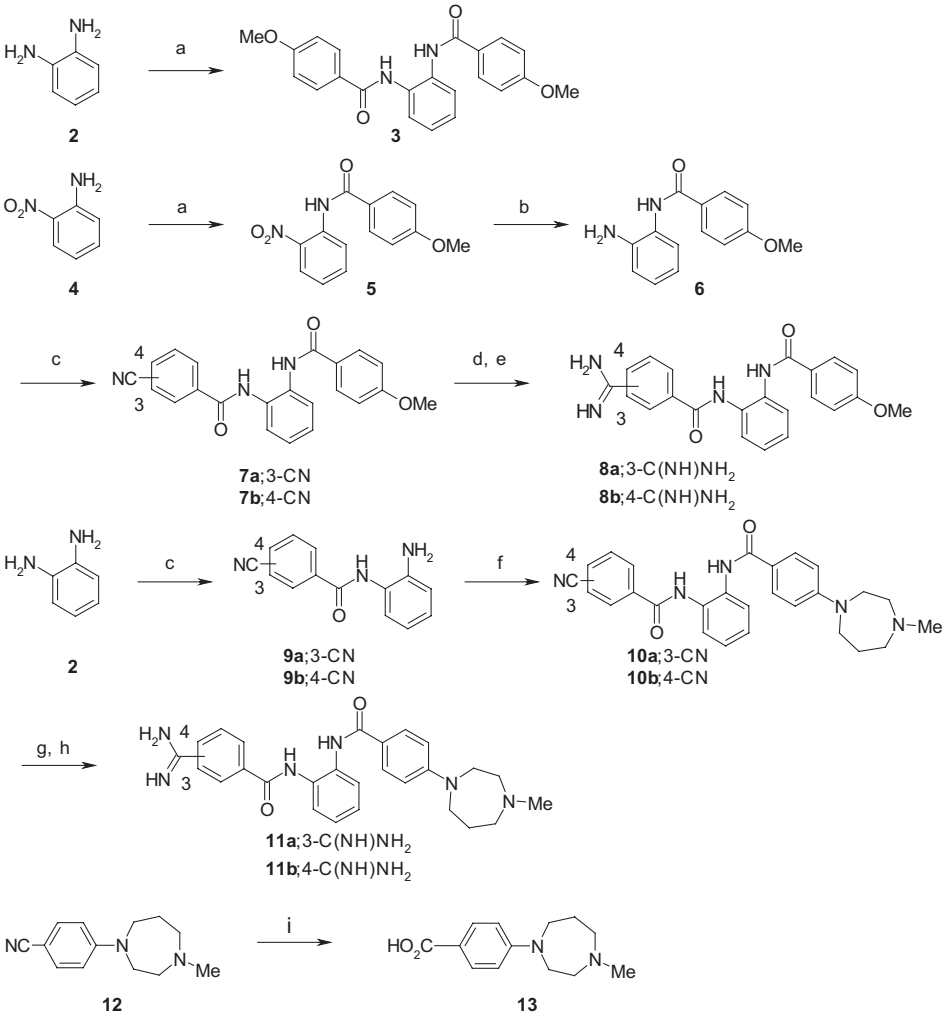
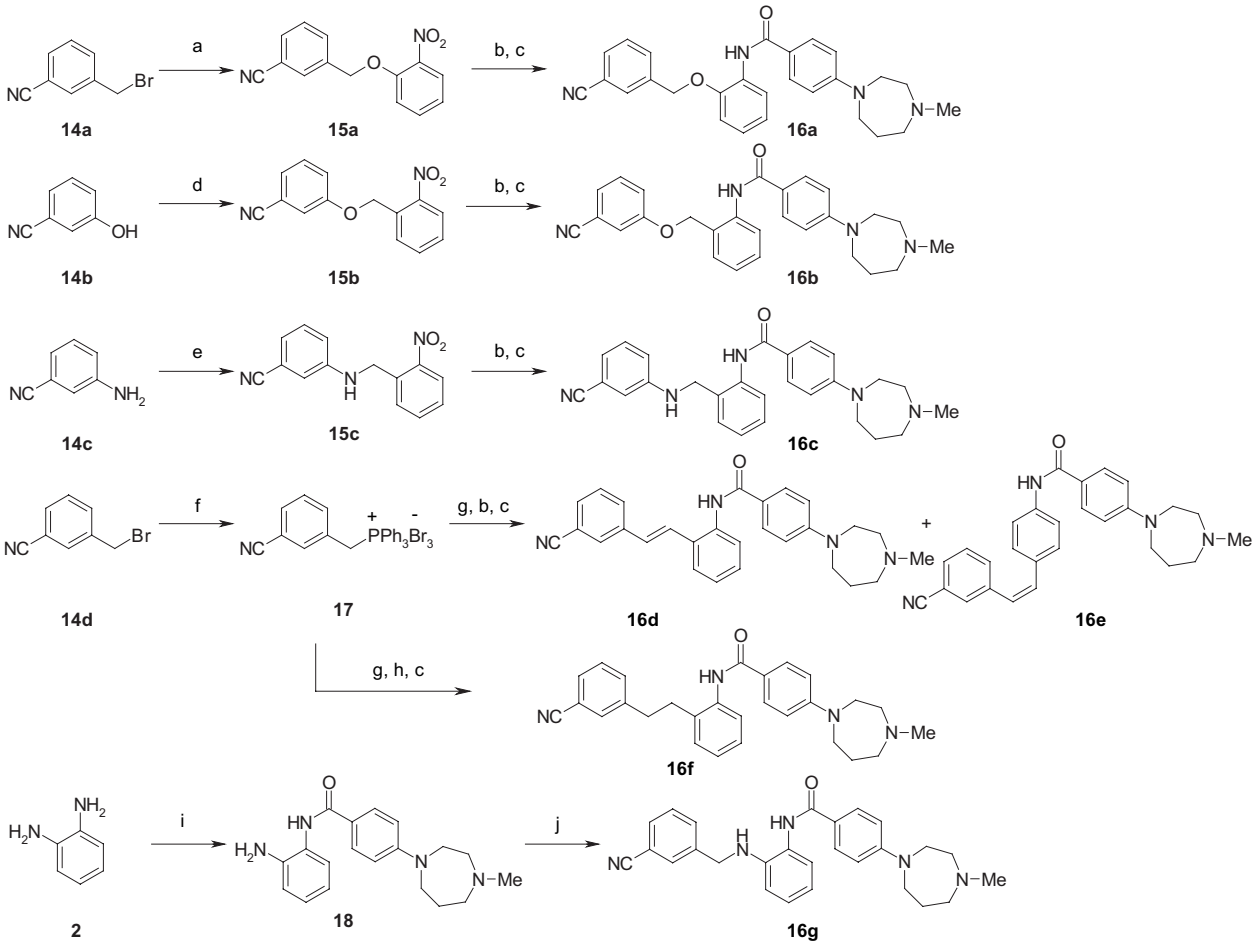
Figure 1. YM-60828 and YM-167065 and HTS hit compound **1**.

Treatment of 1,2-phenylenediamine (**2**) with 2 equiv of *p*-anisoyl chloride gave **3**. Treatment of **2** with cyanobenzoic acid followed by acylation with **13** gave intermediates **10a** and **10b**. In the 2-nitroaniline approach, the first side chain was introduced through acylation with *p*-anisoyl chloride to give compound **5**. The nitro group was then reduced by hydrogenation to aniline **6**. A second acylation with cyanobenzoic acid provided the diacylated intermediates **7a** and **7b**. Treatment of intermediates **7a**, **7b**, **10a**, and **10b** under Pinner conditions produced the imidates, which were immediately reacted with excess ammonium acetate to give the corresponding amidine derivatives **8a**, **8b**, **11a**, and **11b**. The benzoic acid derivative **13** was prepared by hydrolysis of **12**.[10]

Synthesis of intermediates **16a**–**g** is described in Scheme 2. Alkylation with phenol derivatives or reductive alkylation with benzaldehyde gave the nitrobenzene derivatives **15a**–**c**. Intermediates **16a**–**c** were prepared by reduction of the nitro group in **15a**–**c** with reduced iron, followed by acylation with **13**. Treatment of **14d** with tri-



Scheme 1. Reagents and conditions: (a) *p*-anisoylchloride, pyridine; (b) H_2, 10% Pd–C, MeOH; (c) 3-cyanobenzoic acid or 4-cyanobenzoic acid, HOBt, WSC, DMF; (d) HCl, MeOH; (e) NH_4OAc, MeOH; (f) (1) $SOCl_2$, **13**, (2) pyridine; (g) HCl, EtOH; (h) NH_4OAc, EtOH; (i) 6 N NaOH.



Scheme 2. Reagents and conditions: (a) 2-nitrophenol, K_2CO_3, DMF; (b) Fe, NH_4Cl, EtOH, H_2O; (c) (1) $SOCl_2$, **13**, (2) pyridine; (d) 2-bromomethylnitrobenzene, K_2CO_3, DMF; (e) 2-nitrobenzaldehyde, $NaB(OAc)_3H$, 1,2-dichloroethane, AcOH; (f) PPh_3, benzene; (g) 2-nitrobenzaldehyde, DBU, toluene; (h) PdO–$BaSO_4$, H_2, EtOH; (i) (1) $SOCl_2$, **13**, (2) pyridine; (j) 3-cyanobenzaldehyde, $NaB(OAc)_3H$, 1,2-dichloroethane, AcOH.

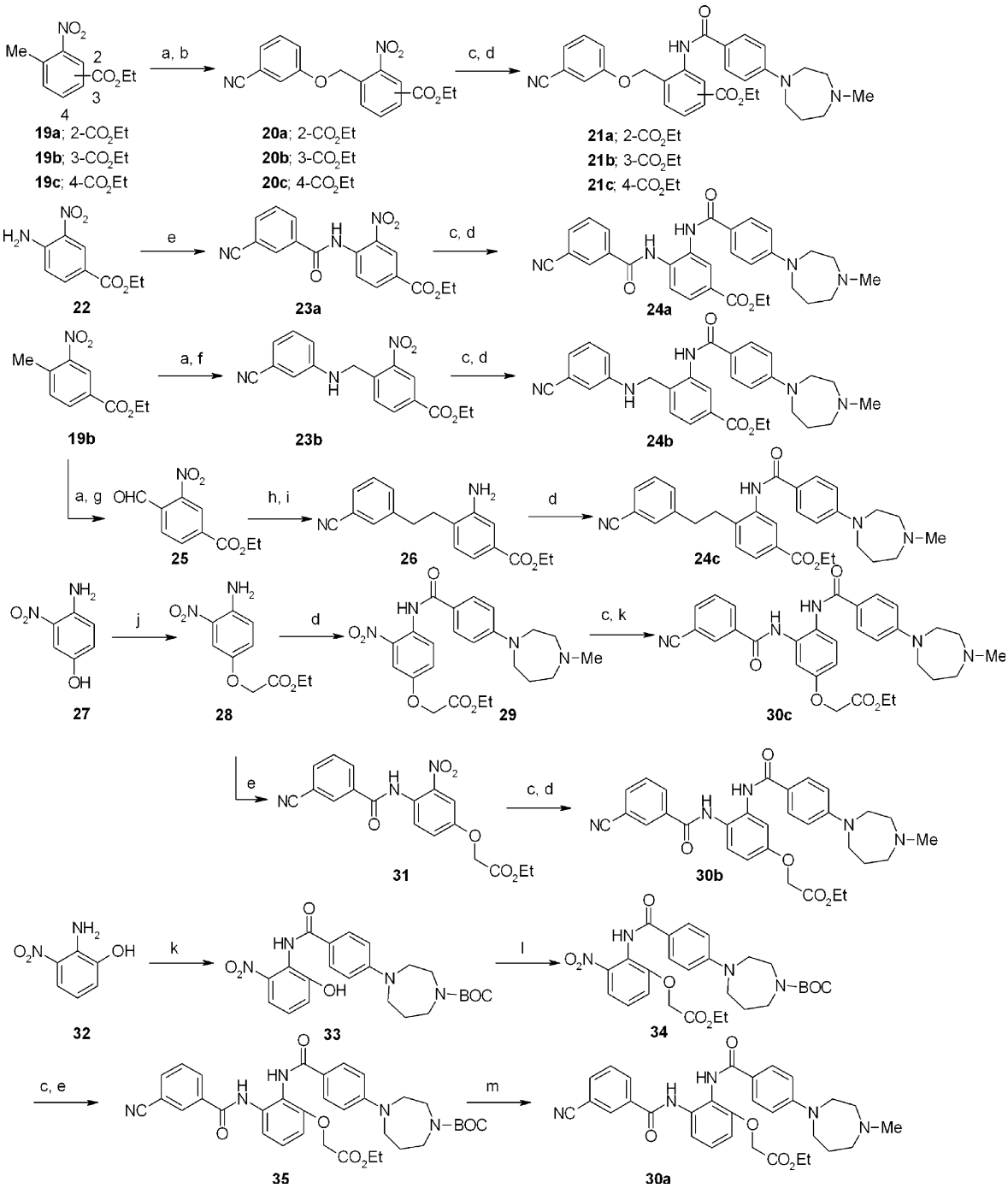
phenylphosphine gave **17**. Intermediates **16d–f** were prepared by Wittig olefination, reduction of the nitro group in **16d** and **16e** or both the nitro group and the double bond in **16f**, followed by acylation with **13**. Treatment of **2** with **13** followed by reductive alkylation with 3-cyanobenzaldehyde gave intermediate **16g**.

The synthesis of **21a–c**, **24a–c**, and **30a–c** is outlined in Scheme 3. The nitrobenzene derivatives **20a–c** and **23b** were synthesized by bromination of **19a–c** followed by reaction with phenol or aniline. Treatment of **22** with 3-cyanobenzoylchloride gave nitrobenzene derivative **23a**. Compounds **20a–c**, **23a**, and **23b** were converted to corresponding intermediates **21a–c**, **24a**, and **24b** by the same procedure applied to **16a–c** in Scheme 2. Compound **25** was prepared by bromination of **19b**, followed by oxidation with *N*-methyl morphorine-*N*-oxide. Aniline derivative **26** was prepared by a Wittig reaction involving **17** and **25** followed by reduction of the nitro group and the double bond. Compound **26** was acylated with **13** to give intermediate **24c**. Phenol derivative **27** was alkylated with ethyl glycolate under Mitsunobu conditions to give **28**. Compounds **30b** and **30c** were synthesized by the same procedure as **21a**. Treatment of **32** with 4-[4-(*tert*-butoxycarbonyl)-1,4-diazepan-1-yl]benzoic acid gave **33**. Compound **33** was alkylated with ethyl bromoacetate to give **34**. Compound **34** was converted to **35** by reduction with reduced iron followed by acylation with 3-cyanobenzoylchloride. Following the removal of the *tert*-butoxycarbonyl (BOC) protecting group from **35** under acidic conditions, the resulting 1,4-diazepane derivative was converted to the 4-methyl-1,4-diazepane derivative **30a** by reductive alkylation with formaldehyde.

The fully assembled benzonitrile intermediates were then elaborated to the amidine target molecules under the conditions described in Scheme 1, as illustrated in Scheme 4.

3. Results and discussion

Compounds were evaluated for fXa inhibitory activity according to their IC_{50} values, and for anticoagulant activity in vitro according to the CT2 values of their prothrombin times (PT). The CT2 value was defined as the concentration required to double the clotting

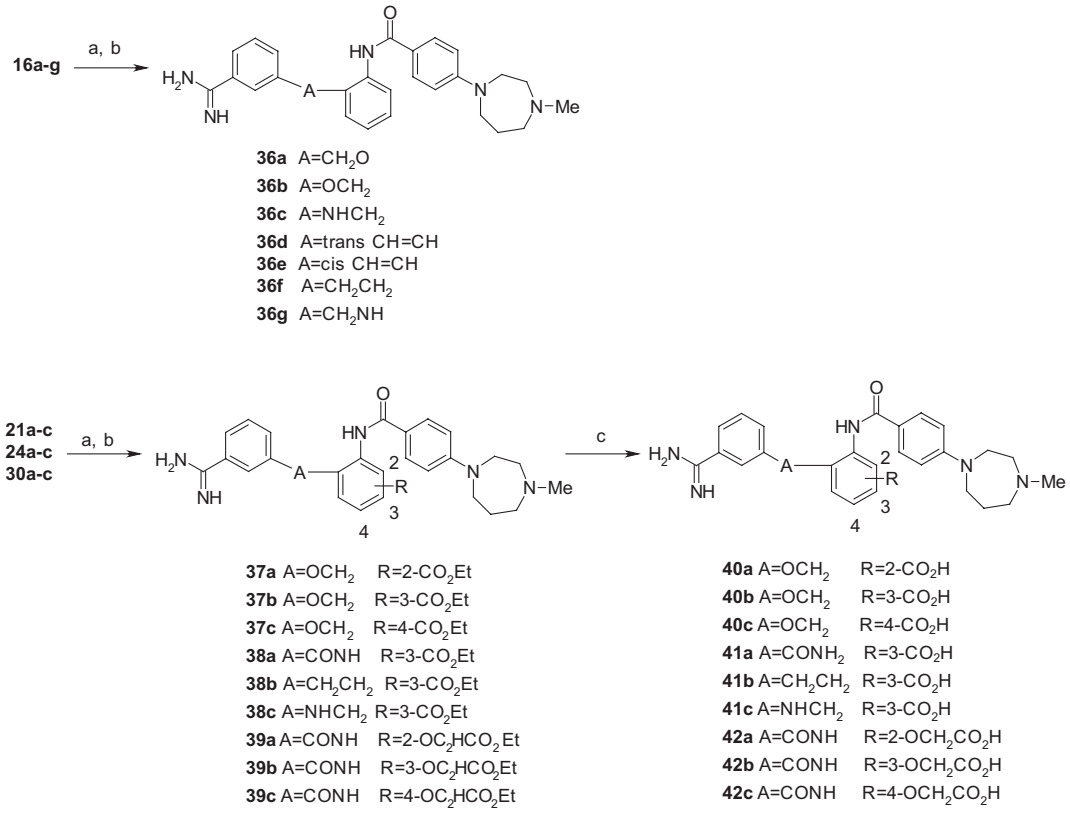


Scheme 3. Reagents and conditions: (a) NBS, AIBN, CCl_4; (b) 3-cyanophenol, K_2CO_3, DMF; (c) Fe, NH_4Cl, EtOH, H_2O; (d) (1) $SOCl_2$, **13**; (2) pyridine; (e) 3-cyanobenzoylchloride, pyridine; (f) 3-cyanoaniline, K_2CO_3, DMF; (g) *N*-methyl morphorine *N*-oxide, CH_3CN; (h) **17**, DBU, toluene; (i) PdO–$BaSO_4$, H_2, EtOH; (j) ethyl glycolate, PPh_3, DEAD, THF; (k) 4-[4-(*tert*-butoxycarbonyl)-1,4-diazepan-1-yl]benzoic acid, NBS, PPh_3, pyridine, CH_2CH_2; (l) ethyl bromoacetate, K_2CO_3, DMF; (m) (1) 4 N HCl–AcOEt, (2) HCHO, $NaB(OAc)_3H$, 1,2-dichloroethane, AcOH.

time. In addition, the oral anticoagulant activity of compounds was evaluated according to their ability to prolong PT following oral administration in mice.

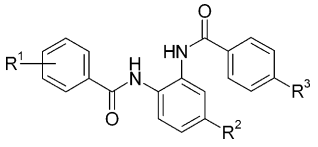
Our observations are in agreement with those of Wiley and colleagues (Table 1). Briefly, the methoxy group on the central benzene ring was not necessary for activity (**3**), and replacement of the 4-methoxy substituent on one of the side benzene rings of **3** with an amidine at the *para*- or *meta*-position produced a 10- to 30-fold increase in inhibitory activity (**8a**, **8b**).[7]

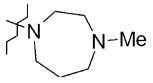
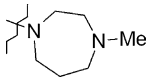
Next, the 4-methyl-1,4-diazepane,[4] which was discovered in our laboratory as a novel P4 scaffold for fXa inhibitors, was introduced to amidine derivatives **8a** and **8b**. The 4-amidine derivative **11b** showed significantly decreased inhibitory activity. However, the 3-amidine derivative **11a** showed a 20-fold increase in



Scheme 4. Reagents: (a) HCl, EtOH; (b) NH_4OAc, EtOH; (c) NaOH.

Table 1. Activity of 1,2-dibenzamidobenzenes

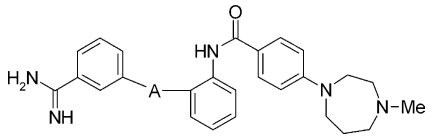


Compd	R^1	R^2	R^3	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]	
						0.5 h	2.0 h
1	4-MeO	MeO	MeO	6216	NT[e]	NT[e]	NT[e]
3	4-MeO	H	MeO	4224	NT[e]	NT[e]	NT[e]
8a	3-Am[e]	H	MeO	127	NT[e]	NT[e]	NT[e]
8b	4-Am[e]	H	MeO	364	NT[e]	NT[e]	NT[e]
11a	3-Am[e]	H		5.8	0.33	1.62	1.40
11b	4-Am[e]	H		23,779	7.2	1.07	1.02
YM-60828				6.0	0.21	2.55	1.74

[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] Am means amidine moiety.

potency compared with **8a**, and a 1000-fold increase in potency compared with lead compound **1**. Compound **11a** was further evaluated for both its in vitro anticoagulant activity and its oral anticoagulant activity. The in vitro anticoagulant activity of **11a** was comparable to that of YM-60828; however, it showed poor oral anticoagulant activity in mice at a dose of 100 mg/kg. Modification of the linker between benzamidine and

Table 2. Effects of linker between the benzamidine and the central benzene ring



Compd	A	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]	
				0.5 h	2.0 h
11a	–CONH–	5.8	0.33	1.62	1.40
36a	$–CH_2O–$	1236	9.2	1.03	1.02
36b	$–OCH_2–$	23.8	0.62	1.51	1.29
36c	$–NHCH_2–$	9.8	0.24	1.17	1.07
36d	*trans*-CH=CH–	92.0	1.2	1.00	0.97
36e	*cis*-CH=CH–	1668	NT[e]	1.01	1.01
36f	$–CH_2CH_2–$	97.1	0.93	1.12	1.04
36g	$–CH_2NH–$	903.9	NT[e]	1.13	1.04

[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.

the central benzene ring was undertaken in order to improve its oral anticoagulant activity. The results are shown in Table 2.

The fXa inhibitory activity of the *trans*-olefin derivative **36d**, which enforces geometry similar to that imposed by an amide linker, was 15 times less than that of **11a**, and that of the *cis*-olefin analogue (**36e**) was 280 times less than that of **11a**. The activity of the ethylene derivative **36f,** considered to have greater flexibility than imparted by an amide bond, was comparable to that of the *trans*-olefin derivative **36d**. Among compounds containing ether or aminomethyl linkers, **36b** and **36c**, containing a hetero atom located near the benzamidine moiety, showed favorable fXa inhibitory activity, and **36c** showed fXa inhibitory activity similar to that of amide derivative **11a**. Compounds **36a** and **36g**, in which the hetero atom was located in a different position than in **36b** and **36c**, had 50–90 times less activity than **36b** and **36c**. However, compounds **36a**–**g** all showed poor oral anticoagulant activity in mice.

Figure 2 illustrates the overlayed energy-minimized structure of the fXa active site complex of ether derivative **36b**. The analysis indicates that the benzamidine moiety occupies the S1 pocket, and that the 1,4-diazepane moiety is in close contact with the S4 pocket defined by the three aromatic amino acids. Moreover, the NH group located between the central benzene ring and the phenyl-1,4-diazepane moiety is in a position to form a hydrogen bond with the backbone carbonyl group of Gly 216. From the modeling study illustrated in Figure 2, we considered there was a possibility of introducing a substituent in the central benzene ring without markedly affecting fXa inhibitory activity, thereby changing the physiological profiles of the compounds to improve their oral efficacy by having the central benzene ring pointing into solution away from the

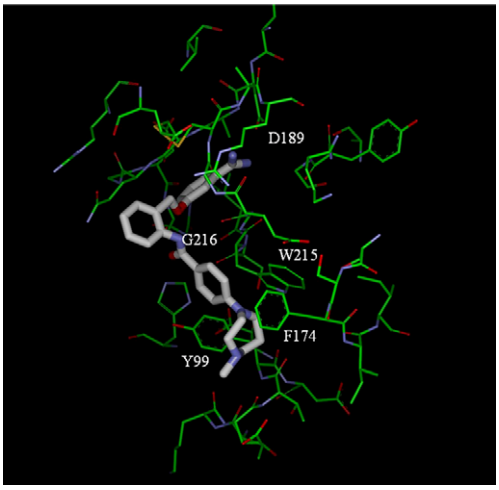


Figure 2. Binding model of compound **36b** to fXa.

enzyme. Previous studies on structure–activity relationships of YM-60828 derivatives have demonstrated that the presence of a carboxyl group resulted in potent oral anticoagulant activity in mice.[3,4] Therefore, to improve oral anticoagulant activity, a carboxyl group was introduced to the central benzene ring in ether derivative **36b**. Compounds **40a**–**c** retained or had a slightly improved fXa inhibitory activity, and showed good in vitro anticoagulant activity. Moreover, all compounds showed increased oral activity as expected. In particular, compound **40b**, containing a carboxyl group at the 3-position in the central benzene ring, showed the greatest oral activity.

Figure 3 illustrates the overlayed energy-minimized structure of the fXa active site complex of ether derivative **40b**. Molecular modeling studies indicate that the carboxyl group at the 3-position of the central benzene ring is located outside the enzyme pocket and extends

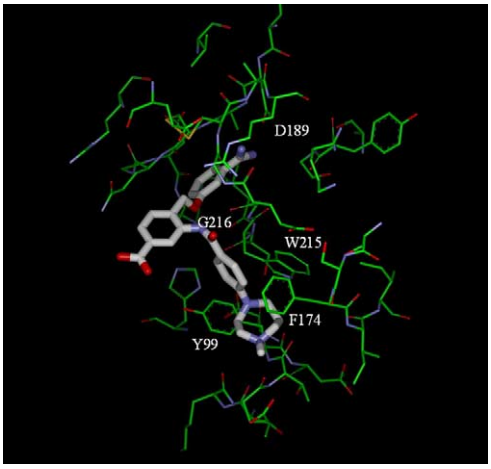


Figure 3. Binding model of compound **40b** to fXa.

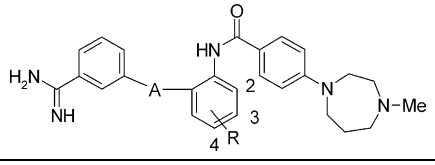
into the solvent. A possible explanation for the fact that compound **40b** has a slightly greater fXa inhibitory activity than **36b**, even though it does not seem to bind directly to the enzyme, is that the carboxyl group is better able to solvate in the aqueous environment surrounding the enzyme. In order to study other acidic residues and optimum position on the central benzene ring, an oxymethylcarboxylic acid moiety was introduce to amide derivative **11a**. Compounds **42a**–**c** showed similar properties, and the 3-subsitituted derivative **42b** had the greatest oral activity. On the other hand, the 4-subsitituted derivative **42c** showed no significant increase in oral anticoagulant activity. Therefore, the carboxyl group was fixed at the 3-position in the central benzene ring, and modification with the other linkers that showed good inhibitory activity in Table 2 was undertaken. The amide derivative, the ethylene derivative, and the aminomethyl derivative improved oral anticoagulant activity without decreasing inhibitory activity (**41a** vs **11a**, **41b** vs **36f**, and **41c** vs **36c**). In particular, compound **41c** exhibited the most potent oral activity, prolonging PT 3.25-fold at 0.5 h and 3.44-fold at 2.0 h (Table 3).

Compounds **40b** and **41a**–**c**, which exhibited good fXa inhibitory activity and oral anticoagulant activity in mice, were further evaluated in terms of enzymatic selectivity and in vitro anticoagulant activity using human plasma. All compounds showed high selectivity for fXa over trypsin (>300-fold). In particular, they showed exceptional selectivity against the related serine protease thrombin (>30,000-fold). These compounds also prolonged PT to a greater extent in human plasma than in mouse plasma (Table 4).

4. Conclusion

We have designed and synthesized fXa inhibitors based on 1,2-dibenzoamidobenzene derivatives from HTS screening to improve inhibitory activity. The series of fXa inhibitors containing a 3-benzamidine moiety as the P1 part and a 4-methyl-1,4-diazepane moiety as the P4 part exhibited potent fXa inhibitory activity. Additionally, their oral anticoagulant activity was improved by the introduction of a carboxyl group at the central benzene ring, without affecting their inhibitory activity. Compounds **40b** (YM-203552), **41a** (YM-202054), and **41c** (YM-203558) exhibited potent fXa inhibitory activity and showed a high degree of selectivity for other serine proteases, and prolonged PT in both

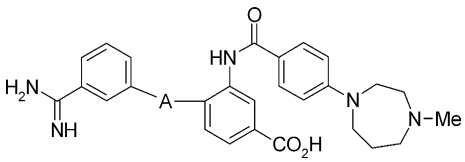
Table 3. Effects of the central benzene ring substituents



Compd	A	R	IC_{50} (nM)[a]	CT_2 (μM)[b] PT[c]	PT/control PT[d]	
					0.5 h	2.0 h
36b	$-OCH_2-$	H	23.8	0.62	1.51	1.29
40a	$-OCH_2-$	2-CO_2H	15.7	0.55	2.29	1.84
40b	$-OCH_2-$	3-CO_2H	8.6	0.29	2.58	2.39
40c	$-OCH_2-$	4-CO_2H	13.6	0.24	1.72	1.43
11a	–CONH–	H	5.8	0.33	1.62	1.40
42a	–CONH–	2-OCH_2CO_2H	2.8	0.43	1.71	1.33
42b	–CONH–	3-OCH_2CO_2H	2.4	0.27	2.41	1.60
42c	–CONH–	4-OCH_2CO_2H	6.3	0.71	1.00	1.01
41a	–CONH–	3-CO_2H	3.2	0.35	2.82	2.70
41b	$-CH_2CH_2-$	3-CO_2H	28.3	0.44	1.90	1.66
41c	$-NHCH_2-$	3-CO_2H	3.5	0.16	3.25	3.44

[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, $n = 3$).

Table 4. The in vitro anticoagulant activity and enzyme selectivity



Compd	A	IC_{50} (nM)[a]			CT_2 (μM)[b]PT[c]	
		fXa	Trypsin	Thrombin	Mice	Human
40b	$–OCH_2–$	8.6	3300	>100,000	0.29	0.11
41a	–CONH–	3.2	8600	>100,000	0.35	0.13
41b	$–CH_2CH_2–$	28.3	19,000	>100,000	0.44	0.14
41c	$–NHCH_2–$	3.5	4000	>100,000	0.16	0.093

[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.

mouse and human plasma. Additionally, these compounds exhibited excellent oral anticoagulant activity in mice. In particular, YM-203558 exhibited the most potent oral activity, prolonging PT more than 3-fold at 0.5 and 2.0 h after oral administration to mice at a dose of 100 mg/kg.

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. *N*,*N*′-1,2-Phenylenebis(4-methoxybenzamide) (3). To a stirring solution of *o*-phenylene diamine (800 mg, 7.4 mmol) in pyridine (10 mL) was added *p*-anisoyl chloride (3.1 g, 17.8 mmol). After 12 h, the solvent was removed in vacuo and the residue was partitioned between chloroform and 1 M NaOH. The organic layer was washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 2.22 g (80%) of white solid: ^{1}H NMR ($CDCl_3$) δ: 3.87 (6H, s), 6.77 (2H, d, J = 3.6, 6.0 Hz), 6.99 (4H, d, J = 9.0 Hz), 7.34 (2H, dd, J = 3.6, 6.0 Hz), 7.98 (4H, d, J = 9.0 Hz), 9.39 (2H, s); EI MS *m*/*e* $(M)^+$ 377; Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.18; H, 5.42; N, 7.36.

4.1.2. 4-Methoxy-*N*-(2-nitrophenyl)benzamide (5). To a stirring solution of 2-nitroaniline (2 g, 14.5 mmol) in pyridine (20 mL) was added *p*-anisoyl chloride (3.03 g, 17.4 mmol). After 12 h, the solvent was removed in vacuo and the residue was partitioned between chloroform and 1 M NaOH. The organic layer was washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 3.9 g (98%) of yellow solid: ^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s), 7.02 (2H, d, J = 9.2 Hz), 7.18–7.74 (1H, m), 7.67–7.74 (1H, m), 7.97 (2H, dd, J = 1.5, 8.4 Hz), 9.00 (1H, dd, J = 1.5, 8.4 Hz), 11.3 (1H, s); FAB MS *m*/*e* $(M+H)^+$ 273.

4.1.3. *N*-(2-Aminophenyl)-4-methoxybenzamide (6). To the solution of **5** (4.35 g, 16 mmol) in EtOH (30 mL) was added 10% Pd–C powder (400 mg) and stirred in hydrogen atmosphere at ambient temperature for 15 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo to give **6** (3.82 g, quant. yield) as a brown amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 3.88 (3H, s), 6.56–6.63 (1H, m), 6.78 (1H, dd, J = 1.2, 8.1 Hz), 6.93–7.00 (1H, m), 7.04 (2H, d, J = 9.0 Hz), 7.13–7.18 (1H, m), 7.97 (2H, d, J = 9.0 Hz); FAB MS *m*/*e* $(M+H)^+$ 243.

4.1.4. 3-Cyano-*N*-{2-[(4-methoxybenzoyl)amino]phenyl}-benzamide (7a). To a stirred solution of **6** (600 mg, 2.46 mmol) in DMF (20 mL) was added 3-cyanobenzoic acid (361 mg, 2.46 mmol), HOBt (450 mg, 3.72 mmol), and WSC (720 mg, 3.72 mmol) at ambient temperature for 12 h. 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 resulting residues was crystallized by EtOH (30 mL) to give **7a** (808 mg, 88%) as a white powder: ^{1}H NMR (DMSO-d_6): 3.82 (3H, s), 7.05 (2H, d, J = 8.7 Hz), 7.28–7.34 (2H, m), 7.60–7.70 (2H, m), 7.75 (1H, t, J = 7.8 Hz), 7.94 (2H, d, J = 8.7 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.23 (1H, d, J = 7.8 Hz), 8.36 (1H, s), 9.84 (1H, s), 10.24 (1H, s); FAB MS *m*/*e* $(M+H)^+$ 372.

4.1.5. 4-Cyano-*N*-{2-[(4-methoxybenzoyl)amino]phenyl}-benzamide (7b). Compound **7b** was synthesized from 4-cyanobenzoic acid and **6** according to the same procedure as that for **7a**. Compound **7b** was obtained as a white amorphous powder (87% yield): ^{1}H NMR (DMSO-d_6) δ: 3.82 (3H, s), 7.05 (2H, d, J = 8.7 Hz), 7.64–7.70 (2H, m), 7.93 (2H, d, J = 8.7 Hz), 8.02 (2H, d, J = 8.7 Hz), 8.10 (2H, d, J = 8.7 Hz), 9.89 (1H, s), 10.28 (1H, s); FAB MS *m*/*e* $(M+H)^+$ 372.

4.1.6. 3-[Amino(imino)methyl]-*N*-{2-[(4-methoxybenzoyl)amino]phenyl}benzamide (8a). HCl gas bubbled through a solution of **7a** (300 mg, 0.81 mmol) in MeOH (5 mL) and chloroform (10 mL) under −20 °C for 20 min. The mixture was allowed to stir for 24 h at 5 °C, and then concentrated in vacuo. To the crude imidate dissolved in MeOH (20 mL) at ambient temperature was added ammonium acetate (280 mg, 4.1 mmol). The reaction mixture was stirred at ambient temperature for 36 h and concentrated in vacuo. The resulting residues was chromatographed on silica gel eluting with chloroform/MeOH (5:1) to give **8a** (186 mg, 60%) as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 2.00 (3H, s), 3.82 (3H, s), 7.04 (2H, d, J = 8.7 Hz), 7.25–7.31 (2H, m), 7.64–7.71 (2H, m), 7.77 (1H, t, J = 8.7 Hz), 8.03 (3H, t, J = 8.7 Hz), 8.29 (1H, d, J = 8.7 Hz), 8.53 (1H, s), 9.28–9.64 (3H, br); FAB MS *m/e* $(M+H)^+$ 389; Anal. Calcd for $C_{22}H_{20}N_4O_3 \cdot C_2H_4O_4$: C, 64.25; H, 5.40; N, 12.20. Found: C, 64.35; H, 5.45; N, 12.02.

4.1.7. 4-[Amino(imino)methyl]-*N*-{2-[(4-methoxybenzoyl)amino]phenyl}benzamide (8b). Compound **8b** was synthesized from **7b** according to the same procedure as that for **8a**. Compound **8b** was obtained as a white amorphous powder (60 % yield): ^{1}H NMR (DMSO-d_6) δ: 2.00 (3H, s), 3.82 (3H, s), 7.04 (2H, d, J = 8.7 Hz), 7.26–7.35 (2H, m), 7.60–7.71 (2H, m), 7.94 (2H, d, J = 8.7 Hz), 8.01 (2H, d, J = 8.7 Hz), 8.17 (2H, d, J = 8.7 Hz), 9.20–9.80 (3H, br); FAB MS *m/e* $(M+H)^+$ 389; Anal. Calcd for $C_{22}H_{20}N_4O_3 \cdot C_2H_4O_4$: C, 64.25; H, 5.40; N, 12.20. Found: C, 64.28; H, 5.39; N, 12.49.

4.1.8. *N*-(2-Aminophenyl)-3-cyanobenzamide (9a). To a stirred solution of *o*-phenylene diamine (2.2 g, 20.4 mmol) in DMF (20 mL) was added 3-cyanobenzoic acid (1.5 g, 10.2 mmol), HOBt (2.1 g, 15.3 mmol), and WSC (2.9 g, 15.3 mmol) at ambient temperature for 18 h. 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 to give **9a** (2.217 g, 92%) as a brown amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 6.60 (1H, t, J = 7.7 Hz), 6.79 (1H, dd, J = 1.4, 7.7 Hz), 6.99 (1H, t, J = 7.7 Hz), 7.17 (1H, d, J = 7.7 Hz), 7.73 (1H, t, J = 7.7 Hz), 8.05 (1H, d, J = 7.7 Hz), 8.27 (1H, d, J = 7.7 Hz), 8.44 (1H, s), 9.83 (1H, s); FAB MS *m/e* $(M+H)^+$ 238.

4.1.9. *N*-(2-Aminophenyl)-4-cyanobenzamide (9b). Compound **9b** was synthesized from 4-cyanobenzoic acid and *o*-phenylene diamine according to the same procedure as that for **9a**. Compound **9b** was obtained as a white amorphous powder (48% yield): ^{1}H NMR (DMSO-d_6) δ: 6.60 (1H, t, J = 7.5 Hz), 6.77 (1H, d, J = 7.5 Hz), 6.99 (1H, t, J = 7.5 Hz), 7.16 (1H, d, J = 7.5 Hz), 8.00 (2H, d, J = 8.2 Hz), 8.13 (2H, d, J = 8.2 Hz), 9.87 (1H, s); FAB MS *m/e* $(M+H)^+$ 238.

4.1.10. 3-Cyano-*N*-(2-{[4-(4-methyl-1,4-diazepan-1-yl)-benzoyl]amino}phenyl)benzamide (10a). The solution of **13** (1.1 g, 4.1 mmol) in thionylchloride (5 mL) stirred at 60 °C for 2 h. After the reaction mixture was cooled, the reaction mixture was concentrated in vacuo. The residue was dissolved in pyridine (10 mL) and cooled to 0 °C. To this solution **9a** (900 mg, 3.79 mmol) was added and stirred at ambient temperature for 4 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with chloroform/methanol/ammonia (15:1:0.1) to give **10a** (822 mg, 48%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 2.05–2.16 (2H, m), 2.44 (3H, s), 2.63–2.69 (2H, m), 2.78–2.83 (2H, m), 3.58 (2H, t, J = 6.2 Hz), 3.66–3.72 (2H, m), 6.73 (2H, d, J = 9.0 Hz), 6.87–6.94 (2H, m), 7.31–7.35 (1H, m), 7.42–7.46 (1H, m), 7.62 (1H, t, J = 7.8 Hz), 7.79–7.84 (1H, m), 7.89 (2H, d, J = 9.0 Hz), 8.24–8.32 (2H, m), 8.92 (1H, s), 10.10 (1H, s); FAB MS *m/e* $(M+H)^+$ 454.

4.1.11. 4-Cyano-*N*-(2-{[4-(4-methyl-1,4-diazepan-1-yl)-benzoyl]amino}phenyl)benzamide (10b). Compound **10b** was synthesized from **9b** according to the same procedure as that for **10a**. Compound **10b** was obtained as a white amorphous powder (65% yield): ^{1}H NMR ($CDCl_3$) δ: 2.05–2.15 (2H, m), 2.40 (3H, s), 2.60–2.68 (2H, m), 2.79–2.84 (2H, m), 3.55 (2H, t, J = 6.0 Hz), 3.66–3.70 (2H, m), 6.74 (2H, d, J = 8.8 Hz), 6.80–6.96 (1H, m), 7.50–7.56 (1H, m), 7.77 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz), 8.12 (2H, d, J = 8.8 Hz), 8.80 (1H, s), 10.08 (1H, s); FAB MS *m/e* $(M+H)^+$ 454.

4.1.12. 3-[Amino(imino)methyl]-*N*-(2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenyl)benzamide (11a). HCl gas bubbled through a solution of **10a** (350 mg, 0.77 mmol) in EtOH (15 mL) under −20 °C for 20 min. The mixture was allowed to stir for 24 h at 5 °C, and then concentrated in vacuo. To the crude imidate dissolved in EtOH (20 mL) at ambient temperature was added ammonium acetate (595 mg, 7.70 mmol). The reaction mixture was stirred at ambient temperature for 36 h and concentrated in vacuo. The resulted residue was chromatographed on ODS-gel eluting with EtOH/H_2O (10:90). EtOH was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **11a** (190 mg, 53%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6): 2.10–2.22 (1H, m), 2.29–2.43 (1H, m), 2.77 (3H, d, J = 4.9 Hz), 3.00–3.21 (2H, m), 3.36–3.56 (4H, m), 3.70–3.82 (1H, m), 3.86–3.99 (1H, m), 6.83 (2H, d, J = 8.8 Hz), 7.22–7.32 (2H, m), 7.63 (1H, dd, J = 2.0, 7.3 Hz), 7.69 (1H, dd, J = 2.0, 7.3 Hz), 7.77 (1H, t, J = 7.8 Hz), 7.97 (3H, d, J = 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.31 (1H, d, J = 7.8 Hz), 8.53 (1H, s), 9.34 (2H, s), 9.57 (2H, s), 9.97 (1H, s), 10.97 (1H, s), 10.96 (1H, s); FAB MS *m/e* $(M+H)^+$ 471; Anal. Calcd for $C_{27}H_{30}N_6O_2 \cdot 3.1HCl \cdot 2.0H_2O$: C, 52.34; H, 6.03; N, 13.56; Cl, 17.74. Found: C, 51.99; H, 6.19; N, 13.60; Cl, 17.84.

4.1.13. 4-[Amino(imino)methyl]-*N*-(2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenyl)benzamide (11b). Compound **11b** was synthesized from **10b** according to the same procedure as that for **11a**. Compound **11b** was obtained as a white amorphous powder (26% yield): ^{1}H NMR (DMSO-d_6) δ: 2.10–2.22 (1H, m), 2.39–2.45 (1H, m), 2.77 (3H, d, J = 4.9 Hz), 3.01–3.20 (2H, m),

3.37–3.56 (4H, m), 3.79–3.83 (1H, m), 3.86–3.95 (1H, m), 6.83 (2H, d, $J = 9.2$ Hz), 7.23–7.32 (2H, m), 7.61–7.68 (2H, m), 7.92–8.01 (3H, m), 8.21 (2H, d, $J = 8.3$ Hz), 9.35 (2H, s), 9.57 (2H, s), 10.66 (1H, s), 11.20 (1H, s); FAB MS *m/e* $(M+H)^+$ 471; Anal. Calcd for $C_{27}H_{30}N_6O_2 \cdot 3.1HCl \cdot 2.0H_2O$: C, 52.34; H, 6.03; N, 13.56; Cl, 17.74. Found: C, 52.23; H, 6.29; N, 13.63; Cl, 17.64.

4.1.14. 4-(4-Methyl-1,4-diazepan-1-yl)benzoic acid (13). The solution of **12** (2.5 g, 11.6 mmol) in 6 M NaOH (20 mL) was refluxed. After 40 h, CHCl was added and concentrated in vacuo gave **13** (2.71 g, 98%): ^{1}H NMR (DMSO-d_6) δ: 2.06–2.24 (1H, m), 2.30–2.45 (1H, m), 2.77 (3H, s), 3.00–3.24 (2H, m), 3.24–3.55 (4H, m), 3.70–4.00 (2H, m), 6.81 (2H, d, $J = 9.1$ Hz), 7.78 (2H, d, $J = 9.1$ Hz), 11.06 (1H, s), 12.20 (1H, s); FAB MS *m/e* $(M+H)^+$ 235.

4.1.15. 3-[(2-Nitrophenoxy)methyl]benzonitrile (15a). To a stirred solution of 2-nitrophenol (2.39 g, 17.2 mmol) in DMF (30 mL) was added 3-cyanobenzylbromide (3.37 g, 17.2 mmol), potassium carbonate (2.61 g, 18.9 mmol) at ambient temperature for 1 h. The reaction mixture was diluted with chloroform and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residues was chromatographed on silica gel eluting with hexane/ethylacetate (1:1) to give **15a** (3.96 g, 89%) as a pale yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 5.38 (2H, s), 7.14–7.19 (1H, m), 7.44–7.46 (1H, m), 7.62–7.71 (2H, m), 7.79–7.85 (2H, m), 7.91–7.94 (2H, m); EI MS *m/e* $(M+H)^+$ 254.

4.1.16. 3-[(2-Nitrobenzyl)oxy]benzonitrile (15b). Compound **15b** was synthesized from 2-nitrobenzylbromide and 3-cyanophenol according to the same procedure as that for **15a**. Compound **15b** was obtained as a white amorphous powder (69% yield): ^{1}H NMR ($CDCl_3$) δ: 5.25 (2H, s), 7.21–7.27 (2H, m), 7.31 (1H, dt, $J = 1.3$, 7.5 Hz), 7.40–7.45 (1H, m), 7.51–7.57 (1H, m), 7.71 (1H, dt, $J = 1.3$, 7.9 Hz), 7.83 (1H, dd, $J = 1.1$, 7.9 Hz), 8.20 (1H, dd, $J = 1.3$, 8.2 Hz); EI MS *m/e* $(M+H)^+$ 254.

4.1.17. 3-[(2-Nitrobenzyl)amino]benzonitrile (15c). To a stirred solution of 2-nitro benzaldehyde (2.50 g, 16.5 mmol) and 3-cyanoaniline (1.95 g, 16.5 mmol) in 1,2-dichloromethane (50 mL) and AcOH (4.7 mL, 82.1 mmol) at ambient temperature was added sodium triacetoxyborohydride (5.26 g, 24.8 mmol). After 19 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. The resulting residues was chromatographed on silica gel eluting with hexane/ethylacetate (1:1) to give **15c** (3.75 g, 89%) as a pale yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 4.75 (2H, d, $J = 6.2$ Hz), 6.75–6.78 (2H, m), 6.98–7.01 (1H, m), 7.19–7.25 (1H, m), 7.45–7.51 (1H, m), 7.57–7.76 (2H, m), 8.11 (1H, d, $J = 7.7$ Hz); FAB MS *m/e* $(M+H)^+$ 254.

4.1.18. (3-Cyanobenzyl)(triphenyl)phosphonium bromide (17). To a stirred solution of 3-cyanobenzylbromide (3.01 g, 15.4 mmol) in benzene (100 mL) was added triphenylphosphine (4.04 g, 15.4 mmol) at 100 °C for 14 h. After the reaction mixture was cooled, the reaction mixture was filtrated to give **17** (6.28 g, 89%) as a white solid: ^{1}H NMR ($CDCl_3$) δ: 6.72–6.76, 6.99–7.05, 7.16–7.19, 7.24–7.80, 7.95–8.17 (10H, m); EI MS *m/e* $(M+H)^+$ 250.

4.1.19. *N*-(2-Aminophenyl)-4-(4-methyl-1,4-diazepan-1-yl)benzamide (18). To a stirred solution of *o*-phenylenediamide (4.2 g, 30 mmol) in DMF (120 mL) was added **13** (2.7 g, 10 mmol), HOBt (1.7 g, 15 mmol), and WSC (2.4 g, 15 mmol) at ambient temperature for 12 h. 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 resulting residues was chromatographed on silica gel eluting with chloroform/methanol/NH_4OH (7:1:0.1) to give **18** (2.87 g, 89%) as a pale brown amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.98–2.06 (2H, m), 2.38 (3H, s), 2.54–2.59 (2H, m), 2.69–2.73 (2H, m), 3.49 (2H, t, $J = 6.2$ Hz), 3.55–3.60 (2H, m), 5.45–5.54 (2H, m), 6.66–6.78 (2H, m), 7.43–7.47 (1H, m), 7.57 (1H, s); EI MS *m/e* $(M+H)^+$ 325.

4.1.20. *N*-{2-[(3-Cyanobenzyl)oxy]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16a). To the solution of **15a** (1.04 g, 4.09 mmol) in EtOH (40 mL) and H_2O (40 mL) was added Fe powder (2.28 g, 40.8 mmol) and ammonium chloride (110 mg, 2.0 mmol) and refluxed for 0.5 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. The resulting residue was diluted with chloroform and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give intermediate aniline compound. The solution of **13** (1.22 g, 4.51 mmol) in thionylchloride (40 mL) refluxed for 2 h at 60 °C. After the reaction mixture was cooled, the reaction mixture was concentrated in vacuo. The residue was dissolved in pyridine (10 mL) and cooled to 0 °C. To this solution aniline intermediate was added and stirred at ambient temperature for 20 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with chloroform/methanol (20:1) to give **16a** (1.37 g, 76%) as a pale yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 2.41–2.55 (2H, m), 2.74 (3H, s), 3.07–3.13 (2H, m), 3.17–3.25 (2H, m), 3.61 (2H, t, $J = 6.6$ Hz), 3.89–3.95 (2H, m), 5.19 (2H, s), 6.77 (2H, d, $J = 9.0$ Hz), 6.95–6.99 (1H, m), 7.03–7.09 (2H, m), 7.53 (1H, dd, $J = 7.7$ Hz), 7.60–7.68 (2H, m), 7.78 (2H, d, $J = 9.0$ Hz), 7.83–7.86 (1H, m), 8.45–8.47 (1H, m), 8.50–8.54 (1H, m); FAB MS *m/e* $(M+H)^+$ 441.

4.1.21. *N*-{2-[(3-Cyanophenoxy)methyl]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16b). Compound **16b** was synthesized from **15b** according to the same procedure as that for **16a**. Compound **16b** was obtained as a white amorphous powder (26% yield): ^{1}H NMR ($CDCl_3$) δ: 2.20–2.32 (2H, m), 2.78 (3H, s), 3.16–3.56 (4H, m), 3.75–3.93 (2H, m), 4.06–4.13 (2H, m), 5.21

(2H, s), 6.83 (2H, d, $J = 9.0$ Hz), 7.22–7.52 (8H, m), 7.87 (2H, d, $J = 9.0$ Hz), 9.73 (1H, s); FAB MS *m/e* $(M+H)^+$ 441.

4.1.22. *N*-(2-{[(3-Cyanophenyl)amino]methyl}phenyl)-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16c). Compound **16c** was synthesized from **15c** according to the same procedure as that for **16a**. Compound **16c** was obtained as a white amorphous powder (13% yield): ^{1}H NMR ($CDCl_3$) δ: 1.85–1.95 (2H, m), 2.27 (3H, s), 2.42–2.48 (2H, m), 2.60–2.65 (2H, m), 3.51 (2H, t, $J = 6.2$ Hz), 3.55–3.60 (2H, m), 4.30 (2H, d, $J = 5.7$ Hz), 6.73–6.93 (5H, m), 7.14–7.33 (4H, m), 7.45 (1H, d, $J = 7.5$ Hz), 7.81 (2H, d, $J = 8.6$ Hz), 9.66 (1H, s); FAB MS *m/e* $(M+H)^+$ 440.

4.1.23. *N*-{2-[(*E*)-2-(3-Cyanophenyl)vinyl]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16d) and *N*-{2-[(*Z*)-2-(3-cyanophenyl)vinyl]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16e). To the solution of **17** (5.5 g, 12.0 mmol) in toluene (90 mL) was added DBU (1.80 mL, 21.0 mmol) stirred at 80 °C. After 2.0 h, 2-nitrobenzaldehyde (1.65 g, 10.9 mmol) in toluene (50 mL) was added and stirred at 80 °C for 16 h. The precipitates was removed by filtration and concentrated in vacuo. To the solution of the residue in EtOH (40 mL) and H_2O (40 mL) was added Fe powder (2.23 g, 39.9 mmol) and ammonium chloride (107 mg, 2.0 mmol) refluxed for 0.5 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. The resulting residue was diluted with chloroform and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give intermediate aniline compound. The solution of **13** (1.62 g, 5.98 mmol) in thionylchloride (20 mL) stirred for 2 h at 60 °C. After the reaction mixture was cooled, the reaction mixture was concentrated in vacuo. The residue was dissolved in pyridine (10 mL) and cooled to 0 °C. To this solution aniline intermediate was added and stirred at ambient temperature for 20 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with chloroform/MeOH (15:1) to give **16d** (951 mg, 34%) as a pale brown amorphous powder and **16e** (396 mg, 14%) as a pale brown amorphous powder: **16d**; ^{1}H NMR ($CDCl_3$) δ: 1.86–1.94 (2H, m), 2.27 (3H, s), 2.43–2.48 (2H, m), 2.61–2.65 (2H, m), 3.52 (2H, t, $J = 6.2$ Hz), 3.57–3.62 (2H, m), 6.78 (2H, d, $J = 9.0$ Hz), 7.25 (1H, d, $J = 16.5$ Hz), 7.25–7.37 (2H, m), 7.40–7.44 (1H, m), 7.44 (1H, d, $J = 16.5$ Hz), 7.57 (1H, dd, $J = 7.7$, 7.9 Hz), 7.68–7.73 (1H, m), 7.78–7.90 (4H, m), 7.96–7.98 (1H, m), 9.73 (1H, s); FAB MS *m/e* $(M+H)^+$ 437. **16e**; ^{1}H NMR ($CDCl_3$) δ: 2.04–2.15 (2H, m), 2.58 (3H, s), 2.86–3.09 (4H, m), 3.52 (2H, t, $J = 6.2$ Hz), 3.69–3.76 (2H, m), 6.63 (1H, d, $J = 11.9$ Hz), 6.74 (1H, d, $J = 11.9$ Hz), 6.80 (2H, d, $J = 9.0$ Hz), 7.02–7.11 (2H, m), 7.28–7.34 (1H, m), 7.40 (1H, dd, $J = 7.5$, 7.9 Hz), 7.44–7.53 (2H, m), 7.57–7.59 (1H, m), 7.60–7.64 (1H, m), 7.79 (2H, d, $J = 9.0$ Hz), 9.58 (1H, s); FAB MS *m/e* $(M+H)^+$ 437.

4.1.24. *N*-{2-[2-(3-Cyanophenyl)ethyl]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16f). To the solution of **17** (1.62 g, 3.52 mmol) in toluene (30 mL) was added DBU (0.53 mL, 3.54 mmol) stirred at 80 °C. After 2.0 h, 2-nitrobenzaldehyde (510 mg, 3.35 mmol) in toluene (20 mL) was added and stirred at 80 °C for 16 h. The precipitates was removed by filtration and concentrated in vacuo. To the solution of the residue in EtOH (5 mL) was added PdO–$BaSO_4$ powder (100 mg) and stirred in hydrogen atmosphere at ambient temperature for 24 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo to give intermediate aniline compound. The solution of **13** (851 mg, 3.14 mmol) in thionylchloride (18 mL) stirred for 2 h at 60 °C. After the reaction mixture was cooled, the reaction mixture was concentrated in vacuo. The residue was dissolved in pyridine (10 mL) and cooled to 0 °C. To this solution aniline intermediate was added and stirred at ambient temperature for 20 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with chloroform/MeOH (9:1) to give **16f** (764 mg, 66%) as a pale brown amorphous powder. ^{1}H NMR ($CDCl_3$) δ: 2.12–2.21 (2H, m), 2.67–2.73 (2H, m), 2.88 (3H, s), 3.10–3.32 (6H, m), 3.53 (2H, t, $J = 6.2$ Hz), 3.75–3.82 (2H, m), 6.84 (2H, d, $J = 9.2$ Hz), 7.14–7.31 (4H, m), 7.40–7.49 (2H, m), 7.52–7.54 (1H, m), 7.61 (1H, dd, $J = 1.7$, 6.9 Hz), 7.91 (2H, d, $J = 9.0$ Hz), 9.62 (1H, s); FAB MS *m/e* $(M+H)^+$ 439.

4.1.25. *N*-{2-[(3-Cyanobenzyl)amino]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (16g). To a stirred solution of **18** (486 mg, 1.5 mmol) and 3-cyanobenzaldehyde (197 mg, 2.25 mmol) in 1,2-dichloromethane (5 mL) and AcOH (0.85 mL) at ambient temperature was added sodium triacetoxyborohydride (636 mg, 3.0 mmol). After 5 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. The resulted residue was chromatographed on silica gel eluting with chloroform/MeOH (9:1) to give **16g** (495 mg, 70%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.99–2.08 (2H, m), 2.39 (3H, s), 2.54–2.59 (2H, m), 2.70–2.75 (2H, m), 3.56 (2H, t, $J = 6.2$ Hz), 3.62–3.66 (2H, m), 4.43 (2H, d, $J = 5.5$ Hz), 4.84–4.90 (1H, m), 6.60–6.64 (1H, m), 6.74 (2H, d, $J = 9.0$ Hz), 6.77–6.83 (1H, m), 7.05–7.11 (1H, m), 7.42 (1H, dd, $J = 7.7$ Hz), 7.50–7.55 (1H, m), 7.64 (1H, d, $J = 7.9$ Hz), 7.69 (2H, br s), 7.80 (2H, d, $J = 9.0$ Hz); FAB MS *m/e* $(M+H)^+$ 440.

4.1.26. Ethyl 3-[(3-cyanobenzyl)oxy]-2-nitrobenzoate (20a). To the solution of ethyl 3-methyl-2-nitrobenzoate (8.4 g, 40.2 mmol) in CCl_4 (200 mL) was added NBS (8.72 g, 48.2 mmol) and catalytic AIBN (10 mg) and refluxed for 24 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. To the crude product in CH_3CN (50 mL) was added 3-cyanophenol (2.34 g, 19.7 mmol) and potassium carbonate (3.32 g, 23.6 mmol) at ambient temperature for 48 h. The reaction mixture was diluted with chloroform and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residues was chromatographed on silica gel eluting with hexane/ethylacetate (3:1) to

give **20a** (5.946 g, 93%) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.36 (3H, t, J = 7.0 Hz), 4.38 (2H, q, J = 7.0 Hz), 5.14 (2H, s), 7.14–7.22 (1H, m), 7.30 (1H, dt, J = 1.0, 7.7 Hz), 7.37 (1H, s), 7.40 (1H, s), 7.63 (1H, t, J = 7.7 Hz), 7.82 (1H, dd, J = 1.0, 7.7 Hz), 7.97 (1H, dd, J = 1.0, 7.7 Hz); FAB MS *m/e* $(M+H)^+$ 327.

4.1.27. Ethyl 4-[(3-cyanobenzyl)oxy]-3-nitrobenzoate (20b). Compound **20b** was synthesized from ethyl 4-methyl-3-nitrobenzoate according to the same procedure as that for **20a**. Compound **20b** was obtained as a yellow amorphous powder (45% yield): ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.1 Hz), 4.46 (2H, q, J = 7.1 Hz), 5.56 (2H, s), 7.24–7.35 (4H, m), 7.96 (1H, d, J = 8.2 Hz), 8.34 (1H, dd, J = 1.7, 8.4 Hz), 8.83 (1H, d, J = 1.7 Hz); FAB MS *m/e* $(M-H)^+$ 325.

4.1.28. Ethyl 3-[(3-cyanobenzyl)oxy]-4-nitrobenzoate (20c). Compound **20c** was synthesized from ethyl 5-methyl-4-nitrobenzoate according to the same procedure as that for **20a**. Compound **20c** was obtained as a yellow amorphous powder (37% yield): ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, J = 7.1 Hz), 4.32 (2H, q, J = 7.1 Hz), 5.49 (2H, s), 7.26–7.34 (4H, m), 8.15–8.22 (2H, m), 8.50 (1H, s); FAB MS *m/e* $(M-H)^+$ 325.

4.1.29. Ethyl 3-[(3-cyanobenzyl)oxy]-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (21a). Compound **21a** was synthesized from **20a** according to the same procedure as that for **16a**. Compound **21a** was obtained as a white amorphous powder (81% yield): ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H, t, J = 7.1 Hz), 2.21–2.32 (2H, m), 2.56 (3H, s), 2.77–2.84 (2H, m), 2.93–2.98 (2H, m), 3.61 (2H, t, J = 6.4 Hz), 3.80 (2H, t, J = 6.4 Hz), 4.36 (2H, q, J = 7.1 Hz), 5.13 (2H, s), 6.75 (2H, d, J = 9.1 Hz), 7.12–7.21 (3H, m), 7.24–7.34 (2H, m), 7.81–7.85 (1H, m), 7.95 (2H, d, J = 9.1 Hz), 8.02 (1H, dd, J = 1.7, 7.9 Hz), 10.73 (1H, s); FAB MS *m/e* $(M+H)^+$ 513.

4.1.30. Ethyl 4-[(3-cyanobenzyl)oxy]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (21b). Compound **21b** was synthesized from **20b** according to the same procedure as that for **16a**. Compound **21b** was obtained as a white amorphous powder (86% yield): ^{1}H NMR ($CDCl_3$) δ: 1.39 (3H, t, J = 7.1 Hz), 1.98–2.07 (2H, m), 2.39 (3H, s), 2.54–2.59 (2H, m), 2.70–2.74 (2H, m), 3.55 (2H, t, J = 6.2 Hz), 3.61–3.66 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 5.21 (2H, s), 6.69 (2H, d, J = 9.2 Hz), 7.22–7.33 (3H, m), 7.39–7.42 (1H, m), 7.45–7.48 (1H, m), 7.74 (2H, d, J = 9.2 Hz), 7.86 (1H, dd, J = 1.7, 7.9 Hz), 8.55 (1H, s), 8.70 (1H, d, J = 1.7 Hz); FAB MS *m/e* $(M+H)^+$ 513.

4.1.31. Ethyl 3-[(3-cyanobenzyl)oxy]-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (21c). Compound **21c** was synthesized from **20c** according to the same procedure as that for **16a**. Compound **21c** was obtained as a white amorphous powder (52% yield): ^{1}H NMR ($CDCl_3$) δ: 1.39 (3H, t, J = 7.1 Hz), 1.98–2.07 (2H, m), 2.39 (3H, s), 2.54–2.59 (2H, m), 2.70–2.74 (2H, m), 3.55 (2H, t, J = 6.2 Hz), 3.61–3.66 (2H, m), 4.39 (2H, q, J = 7.1 Hz), 5.21 (2H, s), 6.69 (2H, d, J = 9.2 H), 7.22–7.33 (3H, m), 7.39–7.42 (1H, m), 7.45–7.48 (1H, m), 7.74 (2H, d, J = 9.2 Hz), 7.86 (1H, dd, J = 1.7, 7.9 Hz), 8.55 (1H, d, J = 8.6 Hz), 8.70 (1H, d, J = 1.7 Hz); FAB MS *m/e* $(M+H)^+$ 513.

4.1.32. Ethyl 4-[(3-cyanobenzoyl)amino]-3-nitrobenzoate (23a). To a stirring solution of ethyl 4-amino-3-nitrobenzoate (6.02 g, 28.6 mmol) in 1,2-dichloroethane (30 mL) was added pyridine (3.34 g, 43 mmol) and 3-cyanobenzoylchloride (3.1 g, 17.8 mmol). After 12 h, the solvent was removed in vacuo and the residue was washed EtOH to give **23a** (10.59 g, 47%) as a yellow powder: ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7.1 Hz), 4.45 (2H, q, J =7.1 Hz), 7.72 (1H, dd, J = 7.7, 7.9 Hz), 7.92 (1H, dt, J = 1.3, 7.7 Hz), 8.17–8.22 (1H, m), 8.31–8.33 (1H, m), 8.38 (1H, dd, J = 2.0, 8.8 Hz), 8.97 (1H, d, J = 2.0 Hz), 9.08 (1H, d, J = 8.8 Hz), 11.6 (1H, br s); FAB MS *m/e* $(M+H)^+$ 338.

4.1.33. Ethyl 4-{[(3-cyanophenyl)amino]methyl}-3-nitrobenzoate (23b). To the solution of ethyl 4-methyl-3-nitrobenzoate (20.3 g, 97 mmol) in CCl_4 (145 mL) was added NBS (19 g, 107 mmol) and catalytic AIBN (50 mg) and refluxed for 24 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. To the crude product in CH_3CN (90 mL) was added 3-cyanoaniline (7.97 g, 67.5 mmol) and potassium carbonate (12.44 g, 90 mmol), and stirring at 70 °C for 3 h. The reaction mixture was filtrated and concentrated in vacuo and the resulted residue was chromatographed on silica gel eluting with hexane/ethylacetate (3:1) to give **23b** (12.63 g, 39% yield) as a brown amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, J = 7.2 Hz), 4.43 (2H, q, J = 7.2 Hz), 4.63 (1H, t, J = 5.7 Hz), 4.81 (2H, d, J = 6.0 Hz), 6.72–6.78 (2H, m), 7.01 (1H, dt, J = 1.3, 7.7 Hz), 7.19–7.27 (1H, m), 7.69 (1H, d, J = 8.0 Hz), 8.24 (1H, dd, J = 1.7, 8.0 Hz), 8.73 (1H, d, J = 1.7 Hz); FAB MS *m/e* $(M+H)^+$ 295.

4.1.34. Ethyl 4-formyl-3-nitrobenzoate (25). To the solution of ethyl 4-methyl-3-nitrobenzoate (35.6 g, 170.3 mmol) in CCl_4 (500 mL) was added NBS (34 g, 188 mmol) and catalytic AIBN (10 mg) and refluxed for 24 h. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. To the crude product in CH_3CN (500 mL) was added *N*-methyl morphorine *N*-oxide (20.0 g, 170.3 mmol) at ambient temperature for 1.0 h. The reaction mixture was concentrated in vacuo and the residue was diluted with chloroform and washed with H_2O and saturated saline. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting residues was chromatographed on silica gel eluting with hexane/ethylacetate (4:1) to give **25** (10.723 g, 28%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, t, J = 7.2 Hz), 4.48 (2H, q, J = 7.2 Hz), 8.00 (1H, d, J = 8.0 Hz), 8.42 (1H, d, J = 8.0 Hz), 8.75 (1H, s), 10.46 (1H, s); GC MS *m/e* $(M)^+$ 224.

4.1.35. Ethyl 3-amino-4-[2-(3-cyanophenyl)ethyl]benzoate (26). Compound **26** was synthesized from **17** and **25** according to the same procedure as that for **16f**. Compound **26** was obtained as a brown amorphous powder

(83% yield): ^{1}H NMR ($CDCl_3$) δ: 1.38 (3H, t, J = 7.1 Hz), 2.82 (2H, t, J = 8.4 Hz), 2.96 (2H, t, J = 8.4 Hz), 4.34 (2H, q, J = 7.1 Hz), 6.97 (1H, d, J = 8.4 Hz), 7.33–7.41 (4H, m), 7.44–7.52 (2H, m); FAB MS *m/e* $(M+H)^+$ 295.

4.1.36. Ethyl 4-[(3-cyanobenzoyl)amino]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (24a). Compound **24a** was synthesized from **23a** according to the same procedure as that for **16a**. Compound **24a** was obtained as a white amorphous powder (55% yield): ^{1}H NMR ($CDCl_3$) δ: 1.40 (3H, t, J = 7.1 Hz), 2.00–2.10 (2H, m), 2.41 (3H, br s), 2.57–2.62 (2H, m), 2.73–2.77 (2H, m), 3.62 (2H, t, J = 6.3 Hz), 3.67–3.72 (2H, m), 4.40 (2H, q, J = 7.1 Hz), 6.76 (2H, d, J = 9.2 Hz), 7.57 (1H, t, dd, J = 7.5, 7.9 Hz), 7.72 (1H, dt, J =1.5, 7.9 Hz), 7.85 (1H, d, J = 9.0 Hz), 8.0–8.08 (4H, m), 8.30–8.35 (1H, m), 8.40–8.42 (1H, m); FAB MS *m/e* $(M+H)^+$ 525.

4.1.37. Ethyl 4-{[(3-cyanophenyl)amino]methyl}-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (24b). Compound **24b** was synthesized from **23b** according to the same procedure as that for **16a**. Compound **24b** was obtained as a white amorphous powder (67% yield): ^{1}H NMR ($CDCl_3$) δ: 1.39 (3H, t, J = 7.4 Hz), 1.97–2.06 (2H, m), 2.38 (3H, s), 2.53–2.59 (2H, m), 2.68–2.73 (2H, m), 3.51 (2H, t, J = 6.4 Hz), 3.57–3.63 (2H, m), 4.34–4.42 (5H, m), 6.58 (2H, d, J = 8.8 Hz), 6.96–7.01 (2H, m), 7.12 (1H, d, J = 7.8 Hz), 7.31 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 7.81 (1H, dd, J = 1.5, 7.8 Hz), 8.67 (1H, d, J = 2.0 Hz), 8.85 (1H, s); FAB MS *m/e* $(M+H)^+$ 512.

4.1.38. Ethyl 4-[2-(3-cyanophenyl)ethyl]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (24c). The solution of **13** (2.94 g, 9.59 mmol) in thionylchloride (10 mL) stirred for 2 h at 60 °C. After the reaction mixture was cooled, the reaction mixture was concentrated in vacuo. The residue was dissolved in pyridine (10 mL) and cooled to 0 °C. To this solution 25 (2.35 g, 7.79 mmol) was added and stirred at ambient temperature for 20 h. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with chloroform/methanol (20:1) to give **24c** (3.681 g, 90%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.37 (3H, t, J = 7.2 Hz), 2.42–2.53 (2H, m), 2.76 (3H, s), 2.94 (4H, s), 3.14–3.21 (2H, m), 3.24–3.29 (2H, m), 3.60 (2H, t, J = 6.4 Hz), 3.88–3.95 (2H, m), 4.34 (2H, q, J = 7.2 Hz), 6.73 (2H, d, J = 9.0 Hz), 7.18–7.22 (1H, m), 7.28–7.35 (3H, m), 7.39–7.44 (1H, m), 7.69–7.72 (1H, m), 7.75 (2H, d, J = 9.0 Hz), 7.86 (1H, dd, J = 1.7, 8.0 Hz), 8.24 (1H, d, J = 1.5 Hz); FAB MS *m/e* $(M+H)^+$ 511.

4.1.39. Ethyl (4-amino-3-nitrophenoxy)acetate (28). To a stirring solution of 4-amino-3-nitrophenol (1.54 g, 10.0 mmol) in tetrahydofuran (20 mL) was added glycolic acid ethyl ester (0.95 mL, 10 mmol), triphenylphosphine (2.89 g, 11 mmol), and DEAD (1.7 mL, 11 mmol). After 24 h, the reaction mixture was concentrated in vacuo and the residue was chromatographed on silica gel eluting with hexane/ethylacetate (2:1) to give **28** (1.37 g, 57%) as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 1.20 (3H, t, J = 6.9 Hz), 3.31 (2H, s), 4.16 (2H, q, J = 6.9 Hz), 7.00 (1H, d, J = 9.2 Hz), 7.21 (1H, dd, J = 3.1, 9.2 Hz), 7.27 (2H, s), 7.36 (1H, d, J = 3.1 Hz); FAB MS *m/e* $(M+H)^+$ 240.

4.1.40. Ethyl (4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]-amino}-3-nitrophenoxy)acetate (29). Compound **29** was synthesized from **28** according to the same procedure as that for **24c**. Compound **29** was obtained as a white amorphous powder (95% yield): ^{1}H NMR ($CDCl_3$) δ: 1.32 (3H, t, J = 7.1 Hz), 2.33 (3H, s), 2.73–2.80 (4H, m), 3.02–3.41 (2H, m), 3.57–3.67 (2H, m), 3.89–4.03 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 4.68 (2H, s), 6.76 (2H, d, J = 8.9 Hz), 7.24–7.36 (1H, m), 7.72 (1H, d, J = 2.9 Hz), 7.89 (2H, d, J = 8.9 Hz), 8.95 (1H, d, J = 9.1 Hz), 11.06 (1H, s); FAB MS *m/e* $(M+H)^+$ 457.

4.1.41. Ethyl {4-[(3-cyanobenzoyl)amino]-3-nitrophenoxy}acetate (31). Compound **31** was synthesized from **28** according to the same procedure as that for **23a**. Compound **31** was obtained as a white amorphous powder (43% yield): ^{1}H NMR ($CDCl_3$) δ: 1.33 (3H, t, J = 7.1 Hz), 4.31 (2H, q, J = 7.1 Hz), 4.71 (2H, s), 7.37 (1H, dd, J = 2.9, 9.3 Hz), 7.68 (1H, t, J = 7.8 Hz), 7.77 (1H, d J = 2.9 Hz), 7.86–7.91 (1H, m), 8.14–8.19 (1H, m), 8.27–8.30 (1H, m), 8.88 (1H, d, J = 9.3 Hz); FAB MS *m/e* $(M+H)^+$ 370.

4.1.42. Ethyl (3-[(3-cyanobenzoyl)amino]-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (30c). Compound **30c** was synthesized from **29** according to the same procedure as that for **16a** using 3-cyanobenzoic acid instead of **13**. Compound **30c** was obtained as a white amorphous powder (50% yield): ^{1}H NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.1 Hz), 1.98–2.08 (2H, m), 2.34 (3H, s), 2.54–2.60 (2H, m), 2.68–2.76 (2H, m), 3.56 (2H, t, J = 6.2 Hz), 3.61–3.67 (2H, m), 4.23 (2H, q, J = 7.1 Hz), 4.34 (2H, s), 6.59 (1H, dd, J = 2.9, 9.0 Hz), 6.73 (2H, d, J = 9.0 Hz), 7.15–7.21 (2H, m), 7.26 (1H, s), 7.60 (1H, t, J = 7.7 Hz), 7.80 (1H, dt, J = 1.3, 7.7 Hz), 7.86 (2H, d, J = 9.0 Hz), 8.21–8.26 (1H, m), 8.33 (1H, t, J = 1.3 Hz), 8.57 (1H, s), 10.16 (1H, s); FAB MS *m/e* $(M+H)^+$ 556.

4.1.43. Ethyl (4-[(3-cyanobenzoyl)amino]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (30b). Compound **30b** was synthesized from **31** according to the same procedure as that for **16a**. Compound **30b** was obtained as a white amorphous powder (57% yield): ^{1}H NMR ($CDCl_3$) δ: 1.27 (3H, t, J = 6.9 Hz), 1.97–2.05 (2H, m), 2.33 (3H, s), 2.50–2.57 (2H, m), 2.62–2.76 (2H, m), 3.55 (2H, t, J = 6.1 Hz), 3.62–3.68 (2H, m), 4.22 (2H, q, J = 6.9 Hz), 4.44 (2H, s), 6.57–6.61 (1H, m), 6.72 (2H, d, J = 9.0 Hz), 7.12–7.20 (2H, m), 7.22 (1H, s), 7.60 (1H, t, J = 7.6 Hz), 7.73–7.82 (1H, m), 7.86 (2H, d, J = 9.0 Hz), 8.22–8.25 (1H, m), 8.90 (1H, t, J = 1.3 Hz), 8.56 (1H, s), 10.20 (1H, s); FAB MS *m/e* $(M+H)^+$ 556.

4.1.44. *tert*-Butyl 4-(4-{[(2-hydroxy-6-nitrophenyl)-amino]carbonyl}phenyl)-1,4-diazepane-1-carboxylate (33). To the solution of *tert*-butyl 4-(4-carboxyphenyl)-1,4-diazepane-1-carboxylate (5.11 g, 16 mmol) in methylenechloride (50 mL) was added triphenylphosphine (4.31 g,

16.4 mmol) and NBS (3.2 g, 18 mmol) at 0 °C and stirred at ambient temperature. After 5 min, 2-amino-3-nitroohenol (2.47 g, 16 mmol) and pyridine (1.6 mL, 19.8 mmol) in methylenechloride (20 mL) was added and stirred 12 h. The reaction mixture was concentrated in vacuo and the resulted residue was chromatographed on silica gel eluting with chloroform/MeOH (90:1) to give **33** (1.867 g, 25% yield) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.39 (4H, s), 1.43 (5H, s), 1.94–2.06 (2H, m), 3.24–3.40 (4H, m), 3.56–3.74 (4H, m), 6.70 (2H, d, J = 8.9 Hz), 7.10–7.26 (2H, m), 7.56–7.62 (1H, m), 7.91 (2H, d, J = 8.9 Hz), 8.97 (1H, s); FAB MS *m/e* $(M+H)^+$ 457.

4.1.45. *tert*-Butyl 4-[4-({[2-(2-ethoxy-2-oxoethoxy)-6-nitrophenyl]amino}carbonyl)phenyl]-1,4-diazepane-1-carboxylate (34). To a stirred solution of **33** (1.86 g, 4.08 mmol) in CH_3CN (50 mL) was added ethyl bromoacetate (0.57 mL, 5.12 mmol), potassium carbonate (733 mg, 5.12 mmol), and stirring at ambient temperature for 48 h. The reaction mixture was filtrated and concentrated in vacuo and the resulted residue was chromatographed on silica gel eluting with chloroform/MeOH (100:1) to give **34** (1.995 g, 91% yield) as a yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7.1 Hz), 1.38 (4H, s), 1.44 (5H, s), 3.17–3.25 (2H, m), 3.28–3.36 (2H, m), 3.54–3.67 (4H, m), 4.27 (2H, q, J = 7.1 Hz), 4.74 (2H, s), 6.74 (2H, d, J = 9.0 Hz), 7.11–7.25 (2H, m), 7.62 (1H, dd, J = 1.4, 8.2 Hz), 7.90 (2H, d, J = 9.0 Hz), 8.97 (1H, s); FAB MS *m/e* $(M+H)^+$ 541.

4.1.46. *tert*-Butyl 4-[4-({[2-[(3-cyanobenzoyl)amino]-6-(2-ethoxy-2-oxoethoxy)phenyl]amino}carbonyl)phenyl]-1,4-diazepane-1-carboxylate (35). Compound **35** was synthesized from **34** according to the same procedure as that for **16a** using 3-cyanobenzoic acid instead of **13**. Compound **35** was obtained as a white amorphous powder (quant yield): ^{1}H NMR ($CDCl_3$) δ: 1.31 (3H, t, J = 7.0 Hz), 1.35 (4H, s), 1.43 (5H, s), 1.92–2.02 (2H, m), 3.16–3.35 (4H, m), 3.54–3.70 (4H, m), 4.29 (2H, q, J = 7.0 Hz), 4.77 (2H, s), 6.76 (2H, d, J = 9.1 Hz), 6.83 (1H, dd, 1.2, 8.0 Hz), 7.26–7.35 (1H, m), 7.54–7.60 (1H, m), 7.75–7.80 (2H, m), 8.20 (2H, d, J = 9.1 Hz), 8.25–8.26 (1H, m), 8.30–8.45 (1H, m), 9.52 (1H, s), 10.77 (1H, s); FAB MS *m/e* $(M+H)^+$ 642.

4.1.47. Ethyl (3-[(3-cyanobenzoyl)amino]-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (30a). To a solution of **35** (3.48 mg, 5.43 mmol) in ethyl acetate (20 mL) at ambient temperature was added 4 M HCl ethyl acetate solution (5 mL). After stirring at ambient temperature for 2 h, the reaction mixture was concentrated in vacuo. The resulting residue was dissolved in chloroform and washed with 10% aquarius potassium carbonate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. To a stirred solution of the deprotected intermediate in 1,2-dichloromethane (10 mL) at ambient temperature was added acetic acid (1.53 mL, 54.3 mmol), 35% aquarius formaldehyde (1.53 mL, 54.3 mmol) and sodium triacetoxyborohydride (1.8 g, 8.15 mmol). After 2 h, the reaction mixture was washed with 10% aqueous potassium carbonate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulted residue was chromatographed on silica gel eluting with chloroform/MeOH (20:1) to give **30a** (2.508 g, 82%) as a white amorphous powder: ^{1}H NMR ($CDCl_3$) δ: 1.31 (3H, t, J = 7.1 Hz), 1.98–2.08 (2H, m), 2.38 (3H, s), 2.53–2.57 (2H, m), 2.69–2.75 (2H, m), 3.57 (2H, t, J = 6.2 Hz), 3.61–3.67 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 4.76 (2H, s), 6.75 (2H, d, J = 8.9 Hz), 6.83 (1H, dd, J = 1.0, 8.2 Hz), 7.24–7.31 (1H, m), 7.57 (1H, t, J = 7.7 Hz), 7.74–7.81 (2H, m), 8.02 (2H, d, J = 8.9 Hz), 8.22–8.28 (1H, m), 8.32–8.36 (1H, m), 9.48 (1H, s), 10.80 (1H, s); FAB MS *m/e* $(M+H)^+$ 556.

4.1.48. *N*-[2-({3-[Amino(imino)methyl]benzyl}oxy)phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36a). HCl gas bubbled through a solution of **16a** (307 mg, 0.70 mmol) in EtOH (10 mL) and chloroform (10 mL) under −20 °C for 20 min. The mixture was allowed to stir for 24 h at 5 °C, and then concentrated in vacuo. To the crude imidate dissolved in EtOH (10 mL) at ambient temperature was added ammonium acetate (270 mg, 3.50 mmol). The reaction mixture was stirred at ambient temperature for 36 h and concentrated in vacuo. The resulted residue was chromatographed on ODS-gel eluting with EtOH/H_2O (2:98). EtOH was removed in vacuo, and the aqueous solution was lyophilized after being acidified with 1 N HCl. Compound **36a** (101 mg, 25%) was obtained as a pale yellow amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 2.12–2.22 (1H, m), 2.31–2.45 (1H, m), 2.78 (3H, d, J = 4.3 Hz), 3.02–3.20 (2H, m), 3.39–3.55 (4H, m), 3.74–3.82 (1H, m), 3.93 (1H, dd, J = 2.9, 16.6 Hz), 5.26 (2H, s), 6.83 (2H, d, J = 8.8 Hz), 7.24–7.32 (2H, m), 7.34–7.42 (2H, m), 7.45–7.53 (4H, m), 7.90 (2H, d, J = 8.8 Hz), 9.23, 9.40 (each 2H, 2s), 9.82 (1H, s), 11.1 (1H, br s); FAB MS *m/e* $(M+H)^+$ 458; Anal. Calcd for $C_{27}H_{31}N_5O_2 \cdot 2.2HCl \cdot 2.2H_2O$: C, 56.16; H, 6.56; N, 12.13; Cl, 13.51. Found: C, 56.04; H, 6.59; N, 12.14; Cl, 13.41.

4.1.49. *N*-[2-({3-[Amino(imino)methyl]phenoxy}methyl)-phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36b). Compound **36b** was synthesized from **16b** according to the same procedure as that for **36a**. Compound **36b** was obtained as a pale yellow amorphous powder (46% yield): ^{1}H NMR (DMSO-d_6) δ: 2.14–2.23 (1H, m), 2.32–2.45 (1H, m), 2.80 (3H, d, J = 4.4 Hz), 3.06–3.23 (2H, m), 3.42–3.58 (4H, m), 3.79 (1H, dd, J = 9.6, 16.4 Hz), 3.97 (1H, dd, J = 2.9, 16.1 Hz), 5.28 (2H, s), 6.84 (2H, d, J = 9.1 Hz), 6.97–7.02 (1H, m), 7.12–7.19 (2H, m), 7.63 (1H, t, J = 7.8 Hz), 7.78–7.87 (3H, m), 7.86 (2H, d, J = 9.1 Hz), 8.13 (1H, s), 9.24 (1H, s), 9.41, 9.48 (each 2H, 2s) 11.08 (1H, s); FAB MS *m/e* $(M+H)^+$ 458; Anal. Calcd for $C_{27}H_{31}N_5O_2 \cdot 2.2HCl \cdot 3.0H_2O$: C, 54.80; H, 6.68; N, 11.83; Cl, 13.18. Found: C, 54.61; H, 6.42; N, 11.86; Cl, 13.16.

4.1.50. *N*-{2-[({3-[Amino(imino)methyl]phenyl}amino)-methyl]phenyl}-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36c). Compound **36c** was synthesized from **16c** according to the same procedure as that for **36a**. Compound **36c** was obtained as a pale yellow amorphous powder

(43% yield): ^{1}H NMR (DMSO-d_6) δ: 2.12–2.22 (1H, m), 2.35–2.46 (1H, m), 2.77 (3H, d, J = 4.4 Hz), 3.03–3.20 (2H, m), 3.38–3.56 (4H, m), 3.80 (1H, dd, J = 10.0, 16.0 Hz), 3.95 (1H, dd, J = 3.0, 6.6 Hz), 4.40 (2H, s), 6.84 (2H, d, J = 9.0 Hz), 6.98 (1H, dd, J = 1.0, 8.3 Hz), 7.05 (1H, d, J = 7.8 Hz), 7.14 (1H, s), 7.19 (1H, dt, J = 1.0, 7.3 Hz), 7.25–7.33 (2H, m), 7.37 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 6.8 Hz), 7.97 (2H, d, J = 9.0 Hz), 9.21, 9.34 (each 2H, 2s), 9.96 (1H, s), 11.4 (1H, br s); FAB MS *m/e* (M+H)$^+$ 457; Anal. Calcd for $C_{27}H_{32}N_6O{\cdot}4.6HCl{\cdot}3.0H_2O$: C, 47.81; H, 6.33; N, 12.39; Cl, 24.04. Found: C, 47.74; H, 6.57; N, 12.43; Cl, 24.30.

4.1.51. *N*-[2-((*E*)-2-{3-[Amino(imino)methyl]phenyl}vinyl)-phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36d). Compound **36d** was synthesized from **16d** according to the same procedure as that for **36a**. Compound **36d** was obtained as a pale yellow amorphous powder (51% yield): ^{1}H NMR (DMSO-d_6) δ: 2.14–2.23 (1H, m), 2.36–2.47 (1H, m), 2.79 (3H, d, J = 4.9 Hz), 3.05–3.21 (2H, m), 3.40–3.57 (4H, m), 3.77–3.85 (1H, m), 3.92–3.99 (1H, m), 6.86 (2H, d, J = 9.1 Hz), 7.29 (1H, d, J = 16.4 Hz), 7.28–7.37 (1H, m), 7.41 (1H, 1.0, 7.8 Hz), 7.50 (1H, d, J = 16.4 Hz), 7.60 (1H, t, J = 7.8 Hz), 7.71 (1H, d, J = 7.8 Hz), 7.84 (1H, t, J = 7.3 Hz), 7.98 (2H, d, J = 9.1 Hz), 7.99 (1H, s), 9.35, 9.50 (each 2H, 2s), 9.90 (1H, s), 11.3 (1H, br s); FAB MS *m/e* (M+H)$^+$ 454; Anal. Calcd for $C_{28}H_{31}N_5O{\cdot}2.5HCl{\cdot}2.5H_2O$: C, 57.02; H, 6.58; N, 11.87; Cl, 15.03. Found: C, 57.35; H, 6.91; N, 11.82; Cl, 15.43.

4.1.52. *N*-[2-((*Z*)-2-{3-[Amino(imino)methyl]phenyl}vinyl)-phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36e). Compound **36e** was synthesized from **16e** according to the same procedure as that for **36a**. Compound **36e** was obtained as a pale yellow amorphous powder (46% yield): ^{1}H NMR (DMSO-d_6) δ: 2.12–2.22 (1H, m), 2.34–2.47 (1H, m), 2.77 (3H, d, J = 4.9 Hz), 3.03–3.20 (2H, m), 3.38–3.55 (4H, m), 3.73–3.83 (1H, m), 3.89–3.97 (1H, m), 6.67 (1H, d, J = 12.2 Hz), 6.77 (1H, d, J = 12.2 Hz), 6.82 (2H, d, J = 9.1 Hz), 7.06–7.11 (2H, m), 7.29–7.34 (2H, m), 7.37 (1H, dd, J = 7.3, 7.8 Hz), 7.45 –7.50 (2H, m), 7.62 (1H, d, J = 7.8 Hz), 7.66 (1H, s), 7.83 (2H, d, J = 9.1 Hz), 9.27, 9.36 (each 2H, 2s), 9.71 (1H, s), 11.3 (1H, br s); FAB MS *m/e* (M+H)$^+$ 454; Anal. Calcd for $C_{28}H_{31}N_5O{\cdot}2.3HCl{\cdot}3.0H_2O$: C, 56.86; H, 6.70; N, 11.84; Cl, 13.79. Found: C, 57.02; H, 6.58; N, 11.55; Cl, 13.56.

4.1.53. *N*-[2-(2-{3-[Amino(imino)methyl]phenyl}ethyl)-phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36f). Compound **36f** was synthesized from **16f** according to the same procedure as that for **36a**. Compound **36f** was obtained as a pale yellow amorphous powder (28% yield): ^{1}H NMR (DMSO-d_6) δ: 2.14–2.22 (1H, m), 2.35–2.49 (1H, m), 2.78 (3H, d, J = 4.8 Hz), 2.92 (4H, s), 3.05–3.21 (2H, m), 3.39–3.57 (4H, m), 3.80 (1H, dd, J = 10.0, 15.9 Hz), 3.95 (1H, dd, J = 2.7, 16.4 Hz), 6.85 (2H, d, J = 9.1 Hz), 7.18 (1H, dt, J = 1.5, 7.3 Hz), 7.24 (1H, dt, J =1.5, 7.3 Hz), 7.26–7.31 (2H, m), 7.45–7.48 (2H, m), 7.61–7.65 (1H, m), 7.72 (1H, s), 7.96 (2H, d, J = 9.1 Hz), 9.32, 9.42 (each 2H, 2s), 9.74 (1H, s), 11.3 (1H, br s); FAB MS *m/e* (M+H)$^+$ 456; Anal. Calcd for $C_{28}H_{33}N_5O{\cdot}2.6HCl{\cdot}2.0H_2O$: C, 57.35; H, 6.81; N, 11.94; Cl, 15.72. Found: C, 57.29; H, 7.09; N, 11.90; Cl, 15.68.

4.1.54. *N*-[2-({3-[Amino(imino)methyl]benzyl}amino)-phenyl]-4-(4-methyl-1,4-diazepan-1-yl)benzamide (36g). Compound **36g** was synthesized from **16g** according to the same procedure as that for **36a**. Compound **36g** was obtained as a pale yellow amorphous powder (28% yield): ^{1}H NMR (DMSO-d_6) δ: 2.13–2.24 (1H, m), 2.29–2.38 (1H, m), 2.79 (3H, d, J = 4.9 Hz), 3.03–3.21 (2H, m), 3.39 –3.57 (4H, m), 3.77 (1H, dd, J = 9.8, 16.2 Hz), 3.90–3.98 (1H, m), 4.44 (2H, s), 5.76–5.86 (1H, br), 6.53 (1H, d, J = 8.3 Hz), 6.61 (1H, t, J = 7.3 Hz), 6.85 (2H, d, J = 8.8 Hz), 6.96–6.99 (1H, m), 7.10–7.13 (1H, m), 7.55 (1H, dd, J = 7.3, 7.8 Hz), 7.68 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J =7.8 Hz), 7.92 (1H, br s), 7.96 (2H, d, J = 8.8 Hz), 9.15, 9.37 (each 2H, 2s), 9.61 (1H, s), 10.90–11.00 (1H, br); FAB MS *m/e* (M+H)$^+$ 457; Anal. Calcd for $C_{27}H_{32}N_6O{\cdot}2.0HCl{\cdot}2.2H_2O$: C, 56.98; H, 6.80; N, 14.77; Cl, 12.46. Found: C, 57.07; H, 6.68; N, 14.49; Cl, 12.19.

4.1.55. Ethyl 3-({3-[amino(imino)methyl]phenoxy}methyl)-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (37a). Compound **37a** was synthesized from **21a** according to the same procedure as that for **36a**. Compound **37a** was obtained as a white amorphous powder (19% yield): ^{1}H NMR (DMSO-d_6) δ: 1.12 (3H, t, J = 7.4 Hz), 2.09–2.25 (2H, m), 2.64 (3H, s), 2.96–3.43 (4H, m), 3.52 (2H, t, J = 5.8 Hz), 3.73–3.86 (2H, m), 4.13 (2H, q, J = 7.4 Hz), 5.27 (2H, s), 6.83 (2H, d, J = 9.3 Hz), 7.28 (2H, dd, J = 2.4, 7.8 Hz), 7.37–7.53 (4H, m), 7.74 (1H, d, J = 7.8 Hz), 7.81 (1H, dd, J = 1.0, 7.8 Hz), 7.90 (2H, d, J = 8.8 Hz), 9.24 (2H, s), 9.40 (2H, s), 9.95 (1H, s); FAB MS *m/e* (M+H)$^+$ 530.

4.1.56. Ethyl 4-({3-[amino(imino)methyl]phenoxy}methyl)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (37b). Compound **37b** was synthesized from **21b** according to the same procedure as that for **36a**. Compound **37b** was obtained as a white amorphous powder (19% yield): ^{1}H NMR (DMSO-d_6) δ: 1.32 (3H, t, J = 7.4 Hz), 2.04–2.22 (2H, m), 2.62 (3H, s), 2.89–3.14 (4H, m), 3.54 (2H, t, J = 6.3 Hz), 3.72–3.83 (2H, m), 4.34 (2H, q, J = 7.4 Hz), 5.34 (2H, s), 6.83 (2H, d, J = 8.9 Hz), 7.31 (1H, dd, J = 2.0, 7.8 Hz), 7.41 (1H, d, J = 7.8 Hz), 7.48–7.54 (2H, m), 7.66 (1H, d, J = 8.9 Hz), 7.84 (1H, dd, J = 2.0, 7.8 Hz), 7.92 (2H, d, J = 8.9 Hz), 8.06 (1H, d, J = 2.0 Hz), 9.20 (2H, s), 9.40 (2H, s); FAB MS *m/e* (M+H)$^+$ 530.

4.1.57. Ethyl 3-({3-[amino(imino)methyl]phenoxy}methyl)-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (37c). Compound **37c** was synthesized from **21c** according to the same procedure as that for **36a**. Compound **37c** was obtained as a white amorphous powder (21% yield): ^{1}H NMR (DMSO-d_6) δ: 1.32 (3H, t, J = 7.4 Hz), 2.21–2.21 (1H, m), 2.30–2.45 (1H, m), 2,78

(3H, d, J = 3.4 Hz), 3.03–3.20 (2H, m), 3.35–3.57 (4H, m), 3.73–3.97 (2H, m), 4.32 (2H, q, J = 7.4 Hz), 5.36 (2H, s), 6.84 (2H, d, J = 9.1 Hz), 7.34 (1H, dd, J = 2.0, 7.8 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.49–7.54 (2H, m), 7.77 (1H, d, J = 9.1 Hz), 7.97 (1H, dd, J = 2.0, 9.1 Hz), 8.13 (1H, d, J = 2.0 Hz), 9.22 (2H, s), 9.40 (2H, s); FAB MS *m/e* $(M+H)^+$ 530.

4.1.58. Ethyl 4-({3-[amino(imino)methyl]benzoyl}amino)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (38a). Compound **38a** was synthesized from **24a** according to the same procedure as that for **36a**. Compound **38a** was obtained as a white amorphous powder (54% yield): ^{1}H NMR (DMSO-d_6) δ: 1.34 (3H, t, J = 7.3 Hz), 2.10–2.21 (1H, m), 2.26–2.40 (1H, m), 2.78 (3H, s), 3.04–3.22 (2H, m), 3.40–3.56 (2H, m), 3.68–3.80 (1H, m), 3.88–3.97 (1H, m), 4.35 (2H, q, J = 7.3 Hz), 6.85 (2H, d, J = 9.2 Hz), 7.78 (1H, t, J = 7.8 Hz), 7.86 (2H, s), 7.98–8.05 (3H, m), 8.27 (1H, s), 8.31 (1H, d, J = 8.3 Hz), 8.52 (1H, s), 9.27 (2H, s), 9.51 (2H, s), 10.21 (1H, s), 10.86 (1H, s); FAB MS *m/e* $(M+H)^+$ 543.

4.1.59. Ethyl 4-(2-{3-[amino(imino)methyl]phenyl}ethyl)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (38b). Compound **38b** was synthesized from **24b** according to the same procedure as that for **36a**. Compound **38b** was obtained as a white amorphous powder (84% yield): ^{1}H NMR (DMSO-d_6) δ: 1.33 (3H, t, J = 6.9 Hz), 2.09–2.26 (2H, m), 2.65 (3H, s), 2.92–3.42 (8H, m), 3.54 (2H, t, J = 6.4 Hz), 3.73–3.78 (2H, m), 4.32 (2H, q, J = 6.9 Hz), 6.84 (2H, d, J = 8.8 Hz), 7.41–7.49 (3H, m), 7.58–7.64 (1H, m), 7.72 (1H, s), 7.76 (1H, dd, J = 1.0, 7.8 Hz), 7.90 (1H, d, J = 1.9 Hz), 7.95 (1H, d, J = 8.8 Hz), 9.22 (2H, s), 9.37 (2H, s), 9.86 (1H, s); FAB MS *m/e* $(M+H)^+$ 528.

4.1.60. Ethyl 4-[({3-[amino(imino)methyl]phenyl}amino)methyl]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoate (38c). Compound **38c** was synthesized from **24c** according to the same procedure as that for **36a**. Compound **38c** was obtained as a white amorphous powder (73% yield): ^{1}H NMR (DMSO-d_6) δ: 1.31 (3H, t, J = 7.3 Hz), 2.14–2.30 (2H, m), 2.65–2.78 (2H, m), 3.54 (2H, t, J = 5.8 Hz), 3.75–3.80 (4H, m), 4.31 (2H, q, J = 7.3 Hz), 4.42 (2H, d, J = 5.8 Hz), 6.77–6.87 (4H, m), 6.90–6.97 (2H, m), 7.26 (1H, t, J = 7.9 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.77 (1H, dd, J = 2.0, 8.3 Hz), 7.92 (2H, d, J = 8.3 Hz), 8.00 (1H, d, J = 2.0 Hz), 8.89 (2H, s), 9.17 (2H, s), 9.98 (1H, s), 10.60 (1H, s); FAB MS *m/e* $(M+H)^+$ 529.

4.1.61. Ethyl (3-({3-[amino(imino)methyl]benzoyl}amino)-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (39a). Compound **39a** was synthesized from **30a** according to the same procedure as that for **36a**. Compound **39a** was obtained as a white amorphous powder (79% yield): ^{1}H NMR (DMSO-d_6) δ: 1.20 (3H, t, J = 7.3 Hz), 2.10–2.21 (1H, m), 2.26–2.37 (1H, m), 2.79 (3H, d, J = 4.8 Hz), 3.20–3.23 (2H, m), 3.38–3.57 (4H, m), 3.70–3.81 (1H, m), 3.88–4.00 (1H, m), 4.16 (2H, q, J = 7.3 Hz), 4.82 (2H, s), 6.84 (2H, d, J = 8.3 Hz), 6.95 (1H, d, J = 8.3 Hz), 7.30 (1H, t, J = 8.3 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.76 (1H, t, J = 7.8 Hz), 7.94 (2H, d, J = 8.8 Hz), 7.99 (2H, d, J = 8.8 Hz), 8.19 (1H, d, J = 8.3 Hz), 8.37 (1H, s), 9.50 (2H, s), 9.61 (1H, s), 10.31 (1H, s), 10.62–10.78 (1H, br s); FAB MS *m/e* $(M+H)^+$ 573.

4.1.62. Ethyl (4-({3-[amino(imino)methyl]benzoyl}amino)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (39b). Compound **39b** was synthesized from **30b** according to the same procedure as that for **36a**. Compound **39b** was obtained as a white amorphous powder (52% yield): ^{1}H NMR (DMSO-d_6) δ: 1.22 (3H, t, J = 7.4 Hz), 2.10–2.22 (1H, m), 2.26–2.40 (1H, m), 2.79 (3H, s), 3.01–3.20 (2H, m), 3.35–3.49 (4H, m), 2.59–3.78 (1H, m), 3.82–3.98 (1H, m), 4.20 (2H, q, J = 7.4 Hz), 4.80 (2H, s), 6.80–6.89 (3H, m), 7.36 (1H, d, J = 2.9 Hz), 7.47 (1H, d, J = 8.8 Hz), 7.74–7.81 (1H, m), 7.91 (2H, d, J = 8.8 Hz), 8.02 (1H, d, J 7.8 Hz), 8.29 (1H, d, J = 7.8 Hz), 8.49 (1H, s), 9.23 (2H, s), 9.51 (2H, s), 9.82 (1H, s), 10.52 (1H, s), 10.54–10.60 (1H, br s); FAB MS *m/e* $(M+H)^+$ 573.

4.1.63. Ethyl (3-({3-[amino(imino)methyl]benzoyl}amino)-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetate (39c). Compound **39c** was synthesized from **30c** according to the same procedure as that for **36a**. Compound **39c** was obtained as a white amorphous powder (49% yield): ^{1}H NMR (DMSO-d_6) δ: 1.23 (3H, t, J = 6.9 Hz), 2.11–2.20 (1H, m), 2.30–2.39 (1H, m), 2.77 (3H, d, J = 4.9 Hz), 3.02–3.20 (4H, m), 3.88–4.05 (2H, m), 4.20 (2H, q, J = 6.9 Hz), 4.80 (2H, s), 6.80–6.89 (3H, m), 7.29 (1H, d, J = 2.9 Hz), 7.51 (1H, d, J = 8.0 Hz), 7.77 (1H, t, J = 7.8 Hz), 7.94–8.05 (3H, m), 8.28 (1H, d, J = 7.8 Hz), 8.53 (1H, s), 9.37 (2H, s), 9.56 (2H, s), 9.89 (1H, s), 10.70 (1H, s), 10.97 (1H, s); FAB MS *m/e* $(M+H)^+$ 573.

4.1.64. 3-({3-[Amino(imino)methyl]phenoxy}methyl)-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (40a). To a stirred solution of **37a** (896 mg, 1.69 mmol) in 20 mL EtOH was added 1 N NaOHaq (6.8 mL, 6.80 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 0.002 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 **40a** (872 mg, 98%) was obtained as a white amorphous powder: ^{1}H NMR (DMSO-d_6) δ: 2.12–2.22 (1H, m), 2.36–2.48 (1H, m), 2.77 (3H, d, J = 4.4 Hz), 3.03–3.21 (2H, m), 3.39–3.58 (4H, m), 3.80 (1H, dd, J = 10.2, 16.1 Hz), 3.90–4.00 (1H, m), 5.23 (2H, s), 6.85 (2H, d, J = 8.8 Hz), 7.26 (1H, dd, J = 2.2, 7.8 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.41 (1H, d, J = 7.8 Hz), 7.48 (1H, d, J = 2.0 Hz), 7.51 (1H, d, J = 7.8 Hz), 7.72 (1H, d, J = 7.1 Hz), 7.85 (1H, d, J = 7.1 Hz), 7.91 (2H, d, J = 8.8 Hz), 9.33, 9.45 (each 2H, 2s), 10.09 (1H s), 11.37 (1H, br s); FAB MS *m/e* $(M+H)^+$ 502; Anal. Calcd for $C_{28}H_{31}N_5O_4 \cdot 2.7HCl \cdot 2.3H_2O$: C, 52.43; H, 6.02; N, 10.92; Cl, 14.92. Found: C, 52.89; H, 6.44; N, 11.09; Cl, 15.28.

4.1.65. 4-({3-[Amino(imino)methyl]phenoxy}methyl)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (40b). Compound **40b** was synthesized from **37b** according to the same procedure as that for **40a**. Compound **40b** was obtained as a white amorphous powder (60% yield): ^{1}H NMR (DMSO-d_6) δ: 2.02–2.10 (2H, m), 2.75–2.84 (2H, m), 2.88–2.98 (2H, m), 3.20–3.48 (3H, br), 3.53 (2H, t, J = 6.1 Hz), 3.67–3.74 (2H, m), 5.31 (2H, s), 6.81 (2H, d, J = 8.8 Hz), 7.31 (1H, dd, J = 2.4, 8.3 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.46–7.48 (1H, m), 7.52 (1H, dd, J = 7.8, 8.3 Hz), 7.62 (1H, d, J = 8.3 Hz), 7.82 (1H, dd, J = 2.0, 8.3 Hz), 7.89 (2H, d, J = 8.8 Hz), 8.03 (1H, d, J = 1.4 Hz), 9.26–9.39 (4H, br), 9.90(1H, s); FAB MS *m/e* (M+H)$^+$ 502; Anal. Calcd for $C_{28}H_{31}N_5O_4$·1.4HCl·2.5H_2O: C, 56.27; H, 6.30; N, 11.72; Cl, 8.30. Found: C, 56.14; H, 6.51; N, 11.74; Cl, 8.17.

4.1.66. 3-({3-[Amino(imino)methyl]phenoxy}methyl)-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (40c). Compound **40c** was synthesized from **37c** according to the same procedure as that for **40a**. Compound **40c** was obtained as a white amorphous powder (63% yield): ^{1}H NMR (DMSO-d_6) δ: 2.12–2.24 (1H, m), 2.30–2.45 (1H, m), 2.79 (3H, s), 3.05–3.22 (2H, m), 3.52–3.57 (4H, m), 3.73–3.98 (2H, m), 5.34 (2H, s), 6.85 (2H, d, J = 8.8 Hz), 7.33 (1H, dd, J = 2.2, 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.49–7.52 (1H, m), 7.54 (1H, t, J = 7.8 Hz), 7.72 (1H, d, J = 7.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 7.92–7.96 (1H, m), 8.12 (1H, d, J = 2.0 Hz), 9.17, 9.38 (each 2H, 2s), 9.94 (1H, s), 10.98 (1H, br s), 12.94 (1H, br s); FAB MS *m/e* (M+H)$^+$ 502; Anal. Calcd for $C_{28}H_{31}N_5O_4$·2.1HCl·2.6-H_2O: C, 53.81; H, 6.18; N, 11.21; Cl, 11.91. Found: C, 53.78; H, 6.19; N, 11.18; Cl, 11.63.

4.1.67. 4-({3-[Amino(imino)methyl]benzoyl}amino)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (41a). Compound **41a** was synthesized from **38a** according to the same procedure as that for **40a**. Compound **41a** was obtained as a white amorphous powder (63% yield): ^{1}H NMR (DMSO-d_6) δ: 1.94–2.06 (2H, m), 2.44 (3H, br s), 2.65–2.93 (4H, m), 3.51 (2H, t, J = 6.1 Hz), 3.62–3.69 (2H, m), 6.80 (2H, d, J = 9.0 Hz), 7.79 (1H, t, J = 7.8 Hz), 7.83 (2H, s), 7.91 (2H, d, J = 9.0 Hz), 8.01 (1H, d, J = 7.8 Hz), 8.23 (1H, s), 8.28 (1H, d, J = 7.8 Hz), 8.45 (1H, s), 9.16–9.56 (3H, br), 10.00 (1H, s), 10.69 (1H, s); FAB MS *m/e* (M+H)$^+$ 515; Anal. Calcd for $C_{28}H_{30}N_6O_4$·1.4HCl·3.2H_2O: C, 53.96; H, 6.11; N, 13.48; Cl, 7.96. Found: C, 53.98; H, 6.22; N, 13.78; Cl, 7.93.

4.1.68. 4-(2-{3-[Amino(imino)methyl]phenyl}ethyl)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (41b). Compound **41b** was synthesized from **38b** according to the same procedure as that for **40a**. Compound **41b** was obtained as a white amorphous powder (23% yield): ^{1}H NMR (DMSO-d_6) δ: 2.14–2.24 (1H, m), 2.37–2.50 (1H, m), 2.78 (3H, d, J = 4.9 Hz), 2.92–2.99 (2H, m), 3.01–3.23 (4H, m), 3.40–3.58 (4H, m), 3.81 (1H, dd, J = 9.8, 16.1 Hz), 3.97 (1H, dd, J = 2.7, 16.1 Hz), 6.86 (2H, d, J = 9.3 Hz), 7.41 (1H, d, J = 8.3 Hz), 7.45–7.48 (2H, m), 7.62–7.67 (1H, m), 7.73–7.79 (2H, m), 7.88 (1H, d, J = 1.4 Hz), 7.99 (2H, d, J = 9.3 Hz), 9.35, 9.45 (each 2H, 2s), 9.91 (1H, s), 11.38 (1H, br s); FAB MS *m/e* (M+H)$^+$ 500; Anal. Calcd for $C_{29}H_{33}N_5O_3$·3.0HCl·2.1H_2O: C, 53.85; H, 6.26; N, 10.83; Cl, 16.44. Found: C, 54.15; H, 6.67; N, 10.89; Cl, 16.51.

4.1.69. 4-[({3-[Amino(imino)methyl]phenyl}amino)methyl]-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}benzoic acid (41c). Compound **41c** was synthesized from **38c** according to the same procedure as that for **40a**. Compound **41c** was obtained as a white amorphous powder (93% yield): ^{1}H NMR (DMSO-d_6) δ: 2.13–2.23 (2H, m), 2.67 (3H, s), 3.00–3.22 (4H, m), 3.53 (2H, t, J = 6.1 Hz), 3.77–3.83 (2H, m), 4.44 (2H, d, J = 5.3 Hz), 6.82–6.86 (4H, m), 6.94 (1H, d, J = 7.3 Hz), 6.98 (1H, br s), 7.26 (1H, t, J = 8.1 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.75 (1H, dd, J = 1.9, 8.1 Hz), 7.94 (2H, d, J = 9.2 Hz), 7.98 (1H, d, J = 1.9 Hz), 9.07, 9.22 (each 2H, 2s), 9.98 (1H, s); FAB MS *m/e* (M+H)$^+$ 501; Anal. Calcd for $C_{28}H_{32}N_6O_3$·1.8HCl·1.4H_2O: C, 56.86; H, 6.24; N, 14.21; Cl, 10.79. Found: C, 56.93; H, 6.52; N, 14.26; Cl, 10.43.

4.1.70. (3-({3-[Amino(imino)methyl]benzoyl}amino)-2-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetic acid (42a). Compound **42a** was synthesized from **39a** according to the same procedure as that for **40a**. Compound **42a** was obtained as a pale yellow amorphous powder (67% yield): ^{1}H NMR (DMSO-d_6) δ: 1.90–2.04 (2H, m), 2.42 (3H, s), 2.62–2.73 (2H, m), 2.82–2.90 (2H, m), 3.38–3.46 (2H, m), 3.57–3.68 (2H, m), 4.50 (2H, s), 6.76 (2H, d, J = 8.8 Hz), 7.10 (1H, d, J = 7.8 Hz), 7.27 (1H, t, J = 8.3 Hz), 7.60 (1H, d, J = 7.8 Hz), 7.75 (1H, t, J = 7.8 Hz), 7.96 (1H, d, J = 7.8 Hz), 8.03 (2H, d, J = 8.8 Hz), 8.14 (1H, d, J = 7.8 Hz), 8.27 (1H, s), 9.18–9.56 (2H, br), 10.04–10.46 (1H, br), 10.55 (1H, s), 12.10 (1H, s); FAB MS *m/e* (M+H)$^+$ 545; Anal. Calcd for $C_{29}H_{32}N_6O_3$·0.6HCl·4.2-H_2O: C, 54.24; H, 6.44; N, 13.09; Cl, 3.31. Found: C, 54.08; H, 6.22; N, 12.98; Cl, 3.51.

4.1.71. (4-({3-[Amino(imino)methyl]benzoyl}amino)-3-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetic acid (42b). Compound **42b** was synthesized from **39b** according to the same procedure as that for **40a**. Compound **42b** was obtained as a pale yellow amorphous powder (75% yield): ^{1}H NMR (DMSO-d_6) δ: 2.10–2.22 (1H, m), 2.31–2.44 (1H, m), 2.51 (3H, d, J = 4.9 Hz), 3.02–3.19 (2H, m), 3.36–3.55 (4H, m), 3.69–3.73 (2H, m), 4.70 (2H, s), 6.79–6.86 (3H, m), 7.35 (1H, d, J = 3.0 Hz), 7.47 (1H, d, J = 8.3 Hz), 7.76 (1H, d, J = 7.8 Hz), 7.97 (2H, d, J = 8.8 Hz), 8.04 (1H, d, J = 7.8 Hz), 8.31 (1H, d, J = 7.8 Hz), 8.60 (1H, s), 9.42 (2H, s), 9.59 (2H, s), 9.91 (1H, s), 9.71 (1H, s), 10.71 (1H, s), 10.04–11.05 (1H, br); FAB MS *m/e* (M+H)$^+$ 545; Anal. Calcd for $C_{29}H_{32}N_6O_3$·2.3HCl·3.1H_2O: C, 50.90; H, 5.97; N, 12.28; Cl, 11.92. Found: C, 50.61; H, 5.93; N, 12.08; Cl, 11.98.

4.1.72. (3-({3-[Amino(imino)methyl]benzoyl}amino)-4-{[4-(4-methyl-1,4-diazepan-1-yl)benzoyl]amino}phenoxy)acetic acid (42c). Compound **42c** was synthesized from **39c** according to the same procedure as that for **40a**. Compound **42c** was obtained as a pale yellow amorphous powder (87% yield): ^{1}H NMR (DMSO-d_6) δ: 1.13–1.16 (2H, m), 2.69 (3H, s), 3.07–3.40 (4H, m), 3.51 (2H, t, J = 6.3 Hz), 3.75–3.84 (2H, m), 4.66 (2H, s), 6.78–6.87 (3H, m), 7.27 (1H, d, J = 3.0 Hz), 7.48 (1H, d, J = 8.8 Hz), 7.77 (1H, t, J = 8.8 Hz), 7.92–8.04 (3H, m), 8.27 (1H, d, J = 8.8 Hz), 8.52 (1H, s), 9.53 (3H, s), 9.87 (1H, s), 10.66 (1H, s); FAB MS *m/e* $(M+H)^+$ 573; Anal. Calcd for $C_{29}H_{32}N_6O_3{\cdot}2.5HCl{\cdot}3.0H_2O$: C, 52.95; H, 6.21; N, 12.78; Cl, 13.47. Found: C, 53.03; H, 6.18; N, 12.65; Cl, 13.62.

4.2. Docking simulation

We choose the Crystal structure of Human factor Xa/ZK-807834 complex (PDB code 1FJS)[11] for docking simulation among many structure of factor Xa/ligand complex available today because of its high resolutive experiment and chemically similar feature of ZK-807834 to our compounds. Initially, all but HOH605 water molecules and ZK-807834 were removed from 1FJS ligand-binding site and hydrogen atoms were build and relaxed by a minimization protocol using TRIPOS force field in SYBYL program package.[12] As HOH605 is considered to be important for ligand binding, this water molecule and atoms within 12 Å of the ligand-binding site were used to calculate the docking interaction energy. The program GOLD[13] was then used to perform a docking simulation of compounds **36b** and **40b**. In the genetic algorithm dockings, an initial population size of 100 individuals with nich size of 2 on each 5 islands, a maximum number of 1.0×10^5 genetic operations (crossover, migration, mutation), a cross-over weight of 95, a migration weight of 10, a mutate weight of 95, and a selection pressure of 1.1 were employed. Though all protein atoms except for terminating NH and OH group were fixed during docking simulations, resulted conformations of the ligands were well converged to ZK-807834 binding region and much the same interaction as ZK-807834 were formed between our compounds and factor Xa.

4.3. Biology

4.3.1. 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; thrombin and S-2238; trypsin 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.

4.3.2. Plasma clotting time assays. Citrated blood samples from mice was 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.

4.3.3. Ex vivo studies. Male mice weighing 30–37 g was used in these studies. In mice, the test drug was dissolved in saline and administered to animals intravenously at 1 mg/kg via tail vein or 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 baseline value the vehicle group in mice.

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