

Figure 2. Prototype of *meta*-oriented antagonists.

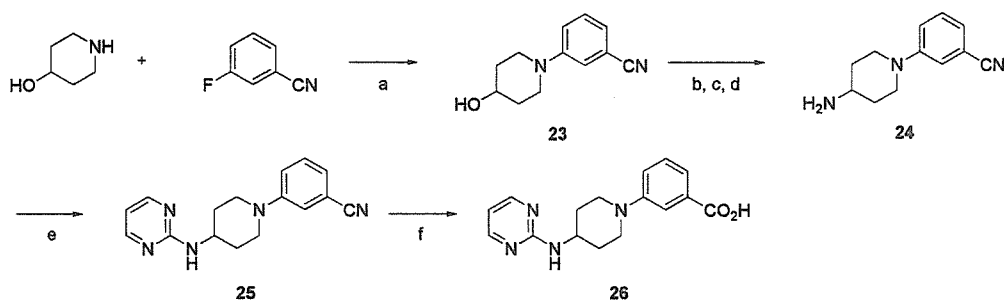
benzoate **27** could be synthesized using 1,5-dichloropentan-3-one.^{10,11} The tricyclic benzoic acid **26** was coupled with the amine **18** to construct the full framework of an

antagonist, **30**, which was treated with trifluoroacetic acid and then finally hydrogenated to furnish the desired antagonist **22** (Scheme 3).

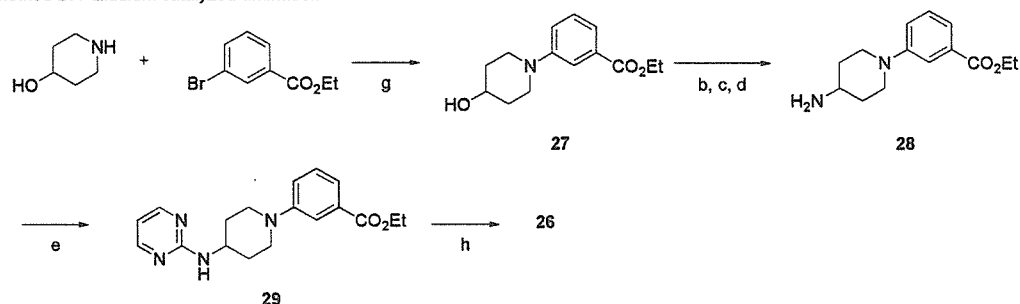
The selectivity for $\alpha_v\beta_3$ over $\alpha_{11b}\beta_3$ of the *meta*-oriented antagonists **21** and **22** was improved in comparison with those of *para*-oriented **1** and **2** (Table 3) as expected. Compound **22** not only exhibited antagonistic activity in a receptor-binding assay, but also showed moderate inhibitory activity in a cell adhesion assay. Then, optimization of **22** by chemical modification was started.

First, the heterocyclic moiety of the lead compound (**22**) was altered (Table 4 and Scheme 4). A stereoisomer **34** possessing a 3-aminopiperidine^{12,13} moiety and two substituted pyrrolidine derivatives (**36** and **37**) were as potent as **22** in an $\alpha_v\beta_3$ -binding inhibition assay. We

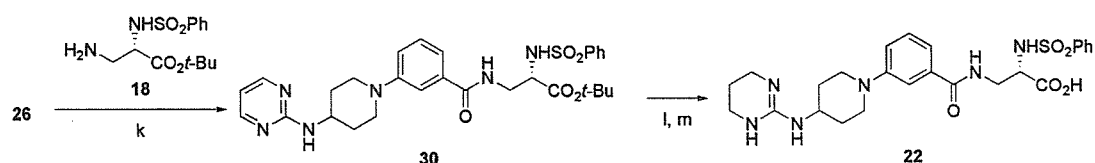
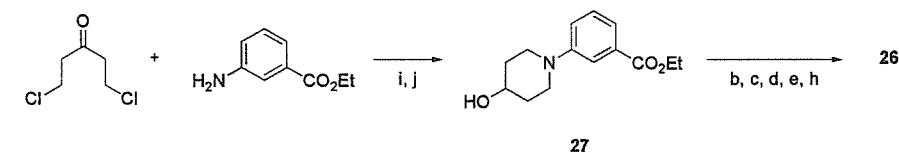
Method A: Nucleophilic substitution



Method B: Palladium catalyzed amination



Method C: Hetero ring cyclization

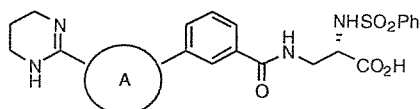


Scheme 3. Reagents and conditions: (a) NaHCO_3 , NMP, 100 °C, 5 h; (b) MsCl , Et_3N , CH_2Cl_2 , rt, 10 min; (c) NaN_3 , DMF, 80 °C, 14 h; (d) H_2 , Pd/C, 1,4-dioxane/ H_2O , rt, 10 h; (e) 2-bromopyrimidine, DIPEA, DMSO, 120 °C, 6 h; (f) 50% $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$, 80 °C, 4 h; (g) (*R*)-(+)-BINAP, CsCO_3 , Pd(OAc)₂, toluene, 90 °C, 5 h then 100 °C, 2 h; (h) NaOH, THF/ $\text{MeOH}/\text{H}_2\text{O}$, 45 °C, 16 h; (i) i-TsOH, MeOH, 65 °C, 7 h; ii-HCO₂H/ H_2O , rt, 2 h; (j) NaBH_4 , THF, rt, 3.5 h; (k) BOP, DIPEA, DMF, rt, 16 h; (l) TFA, CH_2Cl_2 , rt, 8 h; (m) H_2 , Pd/C, 1,4-dioxane/ H_2O , rt, 6 h.

Table 3. Inhibitory activity of *meta*-oriented antagonists in receptor-binding assay and cell adhesion assay

Compound	IC ₅₀ (nM)			$\alpha_v\beta_3/\alpha_{IIb}\beta_3$
	$\alpha_v\beta_3$	$\alpha_{IIb}\beta_3$	VSMC ^a	
1	160	0.73	NT	0.0046
2	1.3	3.1	190	2.4
21	2.2	6.4	NT	2.9
22	6.6	70	1090	11

^a $\alpha_v\beta_3$ -Mediated cell adhesion assay: vascular smooth muscle cells—vitronectin.

Table 4. Effect of replacement of hetero ring on inhibitory activity in receptor-binding assay

Compound	A	IC ₅₀ (nM)		$\alpha_v\beta_3/\alpha_{IIb}\beta_3$	Synthetic method ^a
		$\alpha_v\beta_3$	$\alpha_{IIb}\beta_3$		
22		6.6	70	11	A, B, C
31		1500	61	0.041	A
32		32	89	2.8	D
33		180	80	0.44	D
34		2.6	11	4.2	A
35		560	39	0.070	A
36		3.9	1.8	0.46	D
37		3.5	5.0	1.4	D

^a Methods. A: nucleophilic substitution; B: palladium-catalyzed amination; C: hetero ring cyclization; and D: see Scheme 4.

selected 4-aminopiperidine as the heterocycle next to the central benzene ring for further study because of its relatively remarkable $\alpha_v\beta_3$ selectivity.

Next, modification of the *C*-terminal substituent was examined (Table 5). Unfortunately, modification of the benzenesulfonyl group decreased the $\alpha_v\beta_3$ -binding activity. Exceptionally, the *p*-methoxybenzenesulfonyl derivative (**40**) retained its $\alpha_v\beta_3$ activity, but the $\alpha_v\beta_3$ selectivity disappeared.

Finally, optimization of the central benzene ring was performed, as shown in Table 6. When substitution effects were investigated using fluorine, substitution at the *C*-5 position was found to be very effective for improvement of the selectivity. Thus, a trifluoromethyl group was introduced at the *C*-5 position to obtain **47**. Compound **47** exhibited marked selectivity for $\alpha_v\beta_3$ over $\alpha_{IIb}\beta_3$ in a receptor-binding assay and showed moderate inhibitory activity in an $\alpha_v\beta_3$ -mediated cell adhesion assay, without antiplatelet aggregation activity (hPRP: >10,000 nM). Thus, we obtained an $\alpha_v\beta_3$ -selective antagonist containing our tricyclic pharmacophore. As noted in the introduction, this will be useful for control purposes in *in vivo* studies of dual antagonists, even though more potent and more $\alpha_v\beta_3$ -selective antagonists have already been reported.¹⁴

5. Conclusion

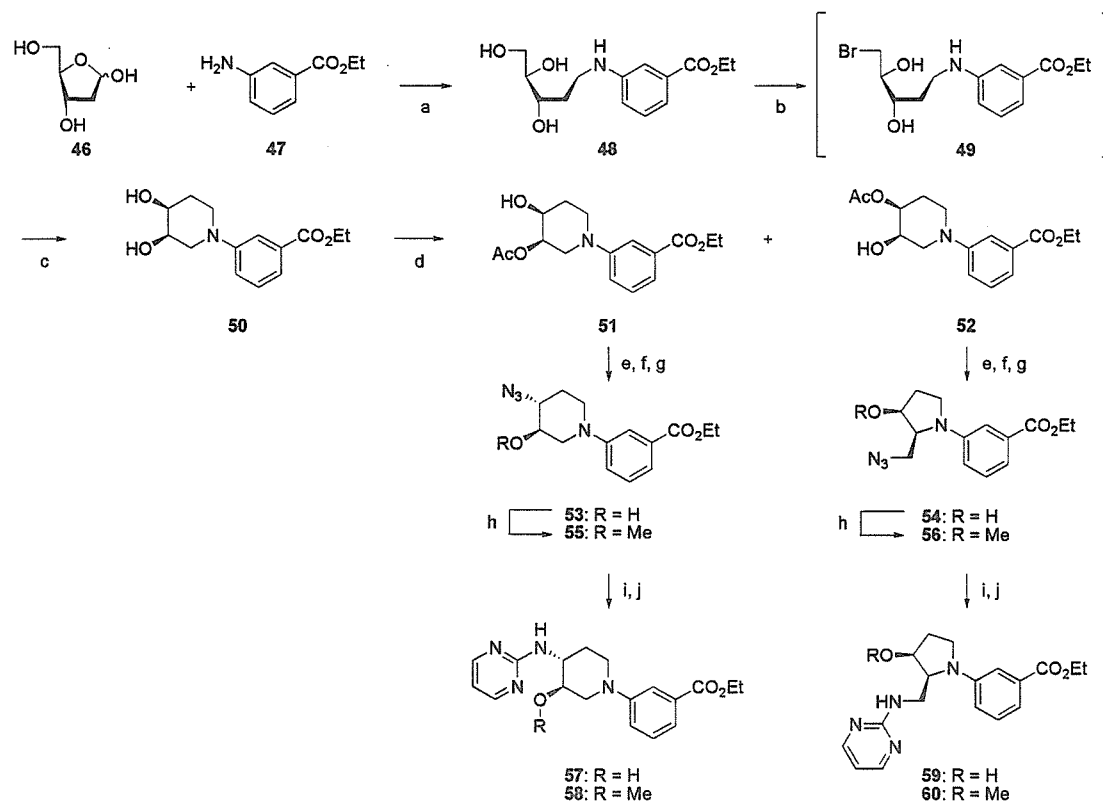
In order to prepare an $\alpha_v\beta_3$ -selective antagonist possessing the tricyclic pharmacophore, we tried three approaches. Dimerization dramatically decreased the $\alpha_{IIb}\beta_3$ -antagonistic activity, but also suppressed $\alpha_v\beta_3$ activity. Second, a novel heterocycle was introduced in place of piperazine or piperidine, in order to alter the dihedral angle between the central benzene ring and adjacent heterocycle. However, the antagonistic activity balance was not markedly altered. Finally, we altered the distance between the *N*-terminus and the *C*-terminus. Several *meta*-oriented molecules with a shorter inter-terminal distance were designed and synthesized. The prototype molecule **22** exhibited an acceptable $\alpha_v\beta_3$ activity and showed weak selectivity for $\alpha_v\beta_3$ over $\alpha_{IIb}\beta_3$. Further optimization afforded the selective antagonist, **47**, which was found to show inhibitory activity in an $\alpha_v\beta_3$ -mediated cell adhesion assay without antiplatelet aggregation activity. This molecule should be useful as a control $\alpha_v\beta_3$ -selective antagonist for *in vivo* studies of our dual antagonists possessing the tricyclic pharmacophore.¹⁵

6. Experimental

¹H NMR spectra were recorded on JNM-LA400 spectrometers with chemical shifts in parts per million with the internal tetramethylsilane as a standard. Electron ionization (EI) mass spectra were recorded on a Hitachi M-80B instrument. Fast-atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 instrument. Thermospray (TSP) mass spectra were recorded on a Hewlett-Packard 5989A instrument. Atmospheric pressure chemical ionization (APCI) mass spectra were recorded on a Hewlett-Packard 5989A instrument. High-resolution mass spectra (HRMS) were recorded under FAB conditions. Optical rotations were obtained on a JASCO DIP-370 polarimeter.

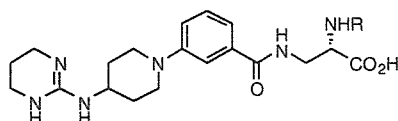
6.1. Preparation of compound 8

6.1.1. Compound 4. DMF (0.58 ml) was added to 1,6-dibromohexane (6.2 mg, 0.025 mmol) to prepare a solution and compound **3**⁴ (29 mg, 0.050 mmol) and DBU



Scheme 4. Reagents and conditions: (a) MeOH, rt, 16 h then NaBCNH₃, AcOH, rt, 4 h; (b) CBr₄, PPh₃, THF, 0 °C to rt, 1 h; (c) rt, 2 h; (d) TsOH, CH₃C(OCH₃)₃, rt, 3 h; (e) MsCl, Et₃N, CH₂Cl₂, rt, 5 min; (f) NaN₃, DMF, 90 °C, 10 h; (g) NaOEt, THF, 30 °C, 3.5 h; (h) NaH, MeI, THF, rt, 4 h; (i) H₂, Pd/C, 1,4-dioxane/H₂O, rt, 3 h; (j) 2-bromopyrimidine, DIPEA, DMSO, 120 °C, 14 h.

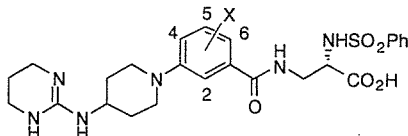
Table 5. Effect of replacement of the C-terminus on inhibitory activity in receptor-binding assay

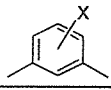


Compound	R	IC ₅₀ (nM)		α _v β ₃ /α _{IIb} β ₃	Synthetic method ^a
		α _v β ₃	α _{IIb} β ₃		
22		6.6	70	11	A, B, C
38		17,000	1700	0.10	A
39		17,000	1300	0.076	A
40		7.6	3.9	0.51	A
41		47	370	7.9	A
42		15	11	0.73	A

^a Methods. A: nucleophilic substitution; B: palladium-catalyzed amination; and C: hetero ring cyclization.

Table 6. Effect of substitution of the central aromatic ring on inhibitory activity in receptor-binding assay and cell adhesion assay



Compound		IC ₅₀ (nM)			α _v β ₃ /α _{11b} β ₃	Synthetic method ^b
		α _v β ₃	α _{11b} β ₃	VSMC ^a		
22	Unsubstitutional	6.6	70	1300	11	A, B, C
43	2-F	6.9	31	310	4.5	B
44	4-F	87	120	NT	1.4	B
45	5-F	14	710	1200	51	B
46	6-F	330	130	NT	0.39	B
47	5-CF ₃	18	2000	500	110	C

^a α_vβ₃-Mediated cell adhesion assay: vascular smooth muscle cells—vitronectin.

^b Methods. A: nucleophilic substitution; B: palladium-catalyzed amination; C: hetero ring cyclization.

(15.5 mg, 0.10 mmol) were added to the solution. The mixture was stirred at room temperature for 12 days. After addition of ethyl acetate (12 ml), the organic layer was washed with water and brine. Then the organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (ethyl acetate/*n*-hexane, 4:1) to prepare compound 4 (3.6 mg, 5.8%) as a colorless powder with accompanies with the recovered starting material (15 mg); ¹H NMR (400 MHz, CD₃OD/CDCl₃, 9:1) δ: 1.18 (4H, m, CH₂), 1.35 (18H, s, *t*-Bu), 1.48–1.64 (4H, m, CH₂), 3.14, 3.68, 3.88 (6H, m, CH₂CHNCH₂), 3.39 (8H, br dd, piperazine), 3.95 (8H, br dd, piperazine), 6.61 (2H, t, pyrimidine), 6.96 (4H, br dd, C₆H₄), 7.48 (4H, m, C₆H₅), 7.57 (2H, m, C₆H₅), 7.71 (4H, d, C₆H₄), 7.87 (4H, m, C₆H₅), 8.34 (4H, d, pyrimidine); TSPMS *m/z* 1215 (M+H)⁺.

6.1.2. Compound 8. CH₂Cl₂ (0.50 ml) was added to compound 4 (3.4 mg, 2.8 μmol) to prepare a solution. Trifluoroacetic acid (0.50 ml) and anisole (0.040 ml) were added to the solution, and stirred at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure to afford a residue, which was twice co-evaporated by toluene for azeotrope, and then dried in vacuo. This material was finally washed with isopropyl ether twice to prepare compound 8 (3.0 mg, 97%) as a colorless powder; FAB-HRMS (M+H)⁺ calcd for C₅₄H₆₂N₁₂O₁₀S₂: 1103.4232. Found: 1103.4211.

6.2. Preparation of compound 10

6.2.1. Compound 6. DMF (1.6 ml) was added to 12-bromo-1-dodecanol (190 mg, 0.72 mmol) to prepare a solution, and compound 3 (80 mg, 0.14 mmol) and DBU (130 mg, 0.85 mmol) were added to the solution. The mixture was stirred at room temperature for 16 h and then evaporated. After addition of ethyl acetate, the organic layer was washed with water and brine. Then the organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography twice (ethyl acetate/*n*-hexane, 9:1 and then benzene/MeOH/ethyl acetate, 10:1:2) to prepare compound 6

(61 mg, 56%) as a colorless powder; ¹H NMR (400 MHz, CDCl₃) δ: 1.15–1.25 (16H, m, CH₂), 1.35 (9H, s, *t*-Bu), 1.50–1.70 (4H, m, CH₂), 3.11, 3.33, 3.74, 3.95, 4.47 (5H, m, CH₂CHNCH₂), 3.39 (4H, br dd, piperazine), 3.63 (2H, t, CH₂OH), 3.99 (4H, br dd, piperazine), 6.54 (1H, t, pyrimidine), 6.95 (2H, d, C₆H₄), 7.51 (2H, m, C₆H₅), 7.58 (1H, m, C₆H₅), 7.76 (2H, d, C₆H₄), 7.91 (2H, m, C₆H₅), 8.34 (2H, d, pyrimidine); TSPMS *m/z* 751 (M+H)⁺.

6.2.2. Compound 7. CH₂Cl₂ (1.2 ml) was added to compound 6 (61 mg, 0.081 mmol) to prepare a solution. DMAP (0.50 mg, 0.0041 mmol), TEA (11 mg, 0.11 mmol) and methanesulfonyl chloride (11 mg, 0.096 mmol) were subsequently added to the solution. The mixture was stirred at room temperature for 16 h, and it was directly purified by preparative thin-layer chromatography (ethyl acetate/*n*-hexane, 3:2) to prepare the corresponding mesylate (47 mg, 64%). Acetone (4.6 ml) was added to the mesylate (47 mg, 0.057 mmol) to prepare a solution, and then NaI (42 mg, 0.28 mmol) was added thereto. The mixture was stirred at 40 °C for 40 h and then evaporated. After addition of ethyl acetate, the organic layer was washed with water, aqueous Na₂S₂O₃ solution, and brine. Then the organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (ethyl acetate/*n*-hexane, 3:2) to prepare compound 7 (40 mg, 84%) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ: 1.15–1.25 (16H, m, CH₂), 1.35 (9H, s, *t*-Bu), 1.45–1.65 (2H, m, CH₂), 1.81 (2H, ddd, CH₂), 3.10, 3.33, 3.75, 3.97, 4.47 (5H, m, CH₂CHNCH₂), 3.18 (2H, t, CH₂I), 3.39 (4H, br dd, piperazine), 3.99 (4H, br dd, piperazine), 6.54 (1H, t, pyrimidine), 6.95 (2H, d, C₆H₄), 7.51 (2H, m, C₆H₅), 7.58 (1H, m, C₆H₅), 7.76 (2H, d, C₆H₄), 7.91 (2H, m, C₆H₅), 8.34 (2H, d, pyrimidine); TSPMS *m/z* 861 (M+H)⁺.

6.2.3. Compound 5. DMF (0.58 ml) was added to compound 3 and compound 7 to prepare a solution, and DBU (9.4 mg, 0.062 mmol) was added to the solution. The mixture was stirred at room temperature for 3 days and then evaporated. After addition of ethyl acetate, the organic layer was washed with water, aqueous Na₂S₂O₃

solution, and brine. Then the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (benzene/MeOH/ethyl acetate, 10:1:2) to prepare compound **5** (24 mg, 60%) as a colorless powder; ^1H NMR (400 MHz, CDCl_3) δ : 1.14 (16H, br s, CH_2), 1.35 (18H, s, *t*-Bu), 1.45–1.65 (4H, m, CH_2), 3.10, 3.32, 3.75, 3.96, 4.47 (10H, m, $\text{CH}_2\text{CHNCH}_2$), 3.38 (8H, br dd, piperazine), 3.98 (8H, br dd, piperazine), 6.53 (2H, t, pyrimidine), 6.94 (4H, br dd, C_6H_4), 7.51 (4H, m, C_6H_5), 7.57 (2H, m, C_6H_5), 7.75 (4H, d, C_6H_4), 7.91 (4H, m, C_6H_5), 8.34 (4H, d, pyrimidine); TSPMS m/z 1299 ($\text{M}+\text{H}$) $^+$.

6.2.4. Compound 9. CH_2Cl_2 (0.50 ml) was added to compound **5** (45 mg, 0.035 mmol) to prepare a solution. Trifluoroacetic acid (0.50 ml) and anisole (0.040 ml) were added to the solution at 0 °C and stirred at 4 °C for 10 h. The reaction mixture was concentrated under reduced pressure to afford a residue, which was twice co-evaporated by 1,4-dioxane and toluene for azeotrope, and then dried in vacuo to prepare a crude bis-carboxylic acid (53 mg). A part of this crude acid (12 mg) was finally purified by preparative thin-layer chromatography ($\text{CHCl}_3/\text{MeOH}/\text{concd NH}_4\text{OH}$, 90:20:1) to prepare compound **9** (5.6 mg) as a colorless powder; ^1H NMR (400 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$, 1:1) δ : 1.16 (16H, br s, CH_2), 1.50–1.70 (4H, m, CH_2), 3.23, 3.33, 3.80, 4.54 (8H, m, $\text{CH}_2\text{CHNCH}_2$), 3.41 (8H, br dd, piperazine), 3.98 (8H, br dd, piperazine), 6.61 (2H, t, pyrimidine), 6.98 (4H, br dd, C_6H_4), 7.48 (4H, m, C_6H_5), 7.55 (2H, m, C_6H_5), 7.75 (4H, d, C_6H_4), 7.91 (4H, m, C_6H_5), 8.35 (4H, d, pyrimidine); FAB-HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{60}\text{H}_{74}\text{N}_{12}\text{O}_{10}\text{S}_2$: 1187.5171. Found: 1187.5166.

6.2.5. Compound 10. Acetic acid (4.0 ml) and concentrated hydrochloric acid (0.36 ml) were added to crude compound **9** mentioned above (41 mg) to prepare a solution. 10% Pd/C (36 mg) was added to the solution, and the mixture was vigorously shaken at room temperature for 3.0 h under a hydrogen pressure of 3 atm. The insolubles were filtered, and then washed twice with water. The filtrate was combined with the washings, followed by concentration under reduced pressure. The residue was purified by preparative thin-layer chromatography ($\text{CHCl}_3/\text{EtOH}/\text{H}_2\text{O}/\text{concd NH}_4\text{OH}$, 15:10:1:1) and Sephadex LH-20 chromatography ($\text{CHCl}_3/\text{MeOH}/\text{concd NH}_4\text{OH}$, 2:10:1) to prepare compound **10** (20 mg, 48% (two steps)) as a colorless solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 0.91–1.04 (16H, m, $8\times\text{CH}_2$), 1.35–1.55 (4H, m, $2\times\text{CH}_2$), 3.13, 3.60, 4.28 (6H, m, $\text{CH}_2\text{CHNCH}_2$), 3.26 (8H, br dd, piperazine), 3.49 (8H, br dd, piperazine), 6.91 (4H, br dd, C_6H_4), 7.46 (4H, m, C_6H_5), 7.53 (2H, m, C_6H_5), 7.64 (4H, m, C_6H_5), 7.93 (4H, d, C_6H_4); FAB-HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{60}\text{H}_{82}\text{N}_{12}\text{O}_{10}\text{S}_2$: 1195.5797. Found: 1195.5791.

6.3. Preparation of compound 20 (Experimental works were performed by Dr. Taku Yamada.)

6.3.1. Compound 15. CH_2Cl_2 (180 ml) was added to ethyl α -L-oleandroside¹⁶ (3.8 g, 18 mmol) to prepare a solution, which was then ice cooled. TEA (4.00 ml,

28.9 mmol) and methanesulfonyl chloride (19 ml, 24 mmol) were added to the solution, and the mixture was stirred at 0 °C for 2 h. Ice was added to the reaction solution, and the mixture was extracted once with CHCl_3 . The organic layer was washed with water, was dried over anhydrous MgSO_4 , and was then concentrated under reduced pressure to give a methanesulfonyl compound (5.9 g, 100%).

DMF (100 ml) was added to the crude methanesulfonyl compound (18 mmol) to prepare a solution. Sodium azide (1.4 g, 22 mmol) was added to the solution, and the mixture was stirred at 80 °C for 18 h. Water was added to the reaction solution, and the mixture was extracted once with ethyl acetate. The organic layer was dried over anhydrous MgSO_4 and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1) to give compound **13** (5.2 g, 99%).

1,4-Dioxane (50 ml) was added to the azide compound (2.1 g, 9.6 mmol) to prepare a solution, and 50 ml of 1 N hydrochloric acid was added to the solution. The mixture was stirred at 60 °C for 3 h and was then ice cooled. The mixture was adjusted to pH 8 by the addition of a 5 N NaOH and was then extracted three times with CHCl_3 . The organic layers were combined, and the combined organic layers were dried over anhydrous Na_2SO_4 and were then concentrated under reduced pressure to give compound **14** (1.6 g, 86%).

CH_2Cl_2 (35 ml) and MeOH (35 ml) were added to the crude hemiacetal compound (1.4 g, 7.2 mmol) to prepare a solution. Ethyl 4-aminobenzoate (900 mg, 5.4 mmol), acetic acid (1.5 ml, 26 mmol), and sodium cyanoborohydride (990 mg, 16 mmol) were added to the solution, and the mixture was stirred at room temperature for 24 h. Ethyl 4-aminobenzoate (230 mg, 1.4 mmol), acetic acid (1.3 ml, 22 mmol), and sodium cyanoborohydride (850 mg, 14 mmol) were added again, and the mixture was stirred at room temperature for 18 h. Water was added to the reaction solution, and the mixture was extracted twice with CHCl_3 . The extract was dried over anhydrous MgSO_4 and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate/concd NH_4OH , 5:5:0.3) to prepare compound **15** (1.58 g, 65%); ^1H NMR (400 MHz, CDCl_3) δ : 1.27 (3H, d, H-6'), 1.36 (3H, t, Et), 1.93 (2H, m, H-2'), 3.35 (2H, m, H-1' and H-4'), 3.48 (3H, s, OCH_3), 3.55 (1H, dt, H-3'), 3.94 (1H, br, H-5'), 4.32 (2H, q, Et), 6.56 (2H, m, C_6H_4), 7.88 (2H, m, C_6H_4); TSPMS m/z 337 ($\text{M}+\text{H}$) $^+$; $[\alpha]_D^{27} +0.40$ (*c* 1.3, CHCl_3).

6.3.2. Compound 16. CH_2Cl_2 (50 ml) was added to compound **15** (1.6 g, 4.8 mmol) to prepare a solution, which was then ice cooled. TEA (2.0 ml, 14 mmol) and methanesulfonyl chloride (0.56 ml, 7.2 mmol) were added to the cooled solution. The temperature of the mixture was raised to room temperature, and the mixture was stirred for 2.0 h. Ice was added to the reaction solution, and the mixture was extracted once with CHCl_3 . The organic layer was washed with water, was dried over

anhydrous MgSO_4 , and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate/concd NH_4OH , 5:5:0.3) to give ethyl 4-{(4*R*)-azido-(5*R*)-methanesulfonyloxy-(3*S*)-methoxyhexylamino}benzoate (1.68 g, 84%).

Toluene (45 ml) was added to ethyl 4-{(4*R*)-azido-(5*R*)-methanesulfonyloxy-(3*S*)-methoxyhexylamino}benzoate (1.9 g, 4.5 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (1.6 ml, 9.2 mmol) was added to the solution, and the mixture was stirred under reflux for 18 h. The reaction solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate/concd NH_4OH , 5:5:0.3) to prepare compound 16 (1.16 g, 81%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.14 (3H, d, CH_3), 1.36 (3H, t, Et), 2.01 (2H, m, piperidine), 3.04 (1H, m, piperidine), 3.46 (3H, s, OCH_3), 3.70 (2H, m, piperidine), 3.92 (1H, m, piperidine), 4.32 (1H, m, piperidine), 4.32 (2H, q, Et), 6.85 (2H, m, C_6H_4), 7.91 (2H, m, C_6H_4); FABMS m/z 319 ($\text{M}+\text{H}^+$); $[\alpha]_{\text{D}}^{28} +62$ (*c* 1.2, CHCl_3).

6.3.3. Compound 17. EtOH (24 ml) was added to compound 16 (860 mg, 2.7 mmol) to prepare a solution. To the solution was added 10% Pd/C (77 mg). The mixture was vigorously stirred under a hydrogen pressure of 1 atm at room temperature for 18 h. The insolubles were filtered and were then washed with EtOH. The filtrate and the washings were combined, and the combined solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/concd NH_4OH , 10:0.3) to give ethyl 4-{(3*R*)-amino-(4*S*)-methoxy-(2*R*)-methylpiperidin-1-yl}benzoate (850 mg, 100%).

N-Methylpyrrolidone (32 ml) was added to ethyl 4-{(3*R*)-amino-(4*S*)-methoxy-(2*R*)-methylpiperidin-1-yl}benzoate (920 mg, 3.2 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (2.8 ml, 16 mmol) and 2-bromopyrimidine (510 mg, 3.2 mmol) were added to the solution, and the mixture was stirred at 120 °C for 18 h. Water was added to the reaction solution, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, and the combined organic layers were dried over anhydrous MgSO_4 and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to give ethyl 4-{(4*S*)-methoxy-(2*R*)-methyl-(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate (500 mg, 43%).

MeOH (4.0 ml) and water (2.8 ml) were added to ethyl 4-{(4*S*)-methoxy-(2*R*)-methyl-(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate (490 mg, 1.3 mmol) to prepare a suspension, to which a 1 N NaOH (1.3 ml) was added. The mixture was stirred at 50 °C for 6 h and was then ice cooled. The reaction solution was adjusted to pH 4 by the addition of 5 N hydrochloric acid. The precipitated solid was collected by filtration, was washed twice with water, and was then dried to prepare compound 17 (280 mg, 61%); $^1\text{H NMR}$ (400 MHz, CDCl_3)

δ : 1.25 (3H, d, CH_3), 2.03 (1H, m, piperidine), 2.14 (1H, dddd, piperidine), 3.18 (1H, ddd, piperidine), 3.42 (3H, s, OCH_3), 3.79 (1H, ddd, piperidine), 3.87 (1H, m, piperidine), 4.37 (1H, m, piperidine), 4.72 (1H, m, piperidine), 6.54 (1H, t, pyrimidine), 6.65 (2H, br d, C_6H_4), 7.32 (1H, br d, NH), 7.56 (2H, br d, C_6H_4), 8.27 (2H, br, pyrimidine); EIMS m/z 342 (M^+); $[\alpha]_{\text{D}}^{26} +191$ (*c* 1.1, CHCl_3).

6.3.4. Compound 19. DMF (4.0 ml) was added to compound 17 (150 mg, 440 μmol) to prepare a solution, and compound 18 (150 mg, 493 μmol) was added to the solution. Further, benzotriazol-1-ylxytri(dimethylamino)phosphonium hexafluorophosphate (BOP) (240 mg, 550 μmol) and *N,N*-diisopropylethylamine (0.092 ml, 0.53 mmol) were added thereto, and the mixture was stirred at room temperature for 18 h. Water and an aqueous NaHCO_3 solution were added to the reaction solution, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, and the combined organic layers were washed with a mixed solution composed of brine and water, were dried over anhydrous Na_2SO_4 , and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 7:1) to prepare compound 19 (250 mg, 91%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.18 (3H, d, CH_3), 1.26 (9H, s, *t*-Bu), 1.89 (1H, m, piperidine), 2.00 (1H, m, piperidine), 3.11 (1H, ddd, piperidine), 3.39 (3H, s, OCH_3), 3.58 (2H, m, piperidine), 3.78 (1H, ddd, CONHCH_2CH), 3.85 (1H, ddd, CONHCH_2CH), 3.92 (1H, ddd, CONHCH_2CH), 4.49 (2H, m, piperidine), 5.72 (1H, d, NH), 5.98 (1H, d, NH), 6.54 (1H, t, pyrimidine), 6.58 (1H, dd, NH), 6.81 (2H, m, C_6H_4), 7.46 (2H, m, C_6H_5), 7.55 (1H, m, C_6H_5), 7.62 (2H, m, C_6H_4), 7.85 (2H, m, C_6H_5), 8.29 (2H, d, pyrimidine); FABMS m/z 625 ($\text{M}+\text{H}^+$); $[\alpha]_{\text{D}}^{27} +46$ (*c* 0.99, CHCl_3).

6.3.5. Compound 20. CH_2Cl_2 (3.0 ml) was added to compound 19 (100 mg, 0.17 mmol) to prepare a solution. Trifluoroacetic acid (3.0 ml) was added to the solution, and the mixture was stirred at room temperature for 3 h. The reaction solution was concentrated under reduced pressure to give a trifluoroacetate of (2*S*)-benzenesulfonylamino-3-[4-{(4*S*)-methoxy-(2*R*)-methyl-(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid.

1,4-Dioxane (3.0 ml) and water (0.30 ml) were added to the trifluoroacetate of crude (2*S*)-benzenesulfonylamino-3-[4-{(4*S*)-methoxy-(2*R*)-methyl-(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid (0.17 mmol) to prepare a solution. To the solution was added 10% Pd/C (18 mg). The mixture was vigorously stirred under a hydrogen pressure of 1 atm at room temperature for 18 h. The insolubles were filtered and were then washed with EtOH. The filtrate and the washings were combined, and the combined solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3/\text{MeOH}/\text{concd NH}_4\text{OH}$, 9:3:0.3) and was then purified by Sephadex LH-20 (MeOH) to prepare compound 20 (63 mg, 66%); $^1\text{H NMR}$ (400 MHz, CD_3OD) δ : 1.18

(3H, d, CH₃), 1.26 (9H, s, *t*-Bu), 1.89 (1H, m, piperidine), 2.00 (1H, m, piperidine), 3.11 (1H, ddd, piperidine), 3.39 (3H, s, OCH₃), 3.58 (2H, m, piperidine), 3.78 (1H, ddd, CONHCH₂CH), 3.85 (1H, ddd, CONHCH₂CH), 3.92 (1H, ddd, CONHCH₂CH), 4.49 (2H, m, piperidine), 5.72 (1H, d, NH), 5.98 (1H, d, NH), 6.54 (1H, t, pyrimidine), 6.58 (1H, dd, NH), 6.81 (2H, m, C₆H₄), 7.46 (2H, m, C₆H₅), 7.55 (1H, m, C₆H₅), 7.62 (2H, m, C₆H₄), 7.85 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); FAB-HRMS (M+H)⁺ calcd for C₂₇H₃₆N₆O₆S: 573.2495. Found: 573.2499; [α]_D²⁵ +136 (c 0.15, MeOH).

6.4. Preparation of compound 21

6.4.1. Ethyl 3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoate. DMF (11 ml) was added to ethyl 3-(piperazin-1-yl)benzoate (WO2000061556) (264 mg, 1.1 mmol), and 2-bromopyrimidine (269 mg, 1.7 mmol) and *N,N*-diisopropylethylamine (1.0 ml) were then successively added thereto. The mixture was stirred at 120 °C for 12 h. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was then added dropwise to 250 ml of water followed by stirring at room temperature for 1 h. The insolubles were collected by filtration, and were then washed twice with water (20 ml). The solid was dried under reduced pressure in the presence of diphosphorus pentoxide at 50 °C, and was then purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 100:2) to prepare the title compound (317 mg, 92%) as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ: 1.40 (3H, t, Et), 3.30 (4H, m, piperazine), 4.00 (4H, m, piperazine), 4.38 (2H, q, Et), 6.53 (1H, t, pyrimidine), 7.15 (1H, br ddd, C₆H₄), 7.34 (1H, t, C₆H₄), 7.56 (1H, br ddd, C₆H₄), 7.64 (1H, br dd, C₆H₄), 8.34 (2H, d, pyrimidine); EIMS *m/z* 312.

6.4.2. 3-{4-(Pyrimidin-2-yl)piperazin-1-yl}benzoic acid. THF (27 ml) and MeOH (9.0 ml) were added to ethyl 3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoate (300 mg, 0.96 mmol) to prepare a solution. NaOH, 1 N (9.0 ml) was added to the solution. The reaction mixture was stirred at 45 °C for 7 h. The reaction solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 90:10) to prepare the title compound (264 mg, 96%) as a colorless solid; ¹H NMR (400 MHz, CDCl₃/CD₃OD, 1:1) δ: 3.32 (4H, m, piperazine), 3.99 (4H, m, piperazine), 6.61 (1H, t, pyrimidine), 7.22 (1H, br dd, C₆H₄), 7.36 (1H, t, C₆H₄), 7.57 (1H, br ddd, C₆H₄), 7.67 (1H, br dd, C₆H₄), 8.35 (2H, d, pyrimidine); TSPMS *m/z* 285 (M+H)⁺.

6.4.3. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoylamino]propionate. DMF (6.5 ml) and CH₂Cl₂ (6.5 ml) were added to 3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoic acid (256 mg, 0.90 mmol) and BOP (597 mg, 1.3 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (0.24 ml) was added to the solution, and a reaction was allowed to proceed at room temperature for 2 h. Separately, CH₂Cl₂ (6.5 ml) was added to compound 18 (325 mg, 1.1 mmol)

to prepare a solution. This solution was added to the above active ester solution at 0 °C. *N,N*-Diisopropylethylamine (0.12 ml) was added thereto, and a reaction was allowed to proceed at room temperature for 16 h. The reaction solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate, followed by washing with an aqueous NaHCO₃ and saturated brine in that order. The extract was then dried over anhydrous Na₂SO₄. The organic layer was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (acetone/*n*-hexane, 6:4) to prepare the title compound (482 mg, 94%) as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (9H, s, *t*-Bu), 3.33 (4H, m, piperazine), 3.57 (1H, ddd, CONHCH₂), 3.93 (2H, m, CONHCH₂CH), 3.99 (4H, m, piperazine), 6.53 (1H, t, pyrimidine), 7.10 (1H, br dd, C₆H₄), 7.22 (1H, br d, C₆H₄), 7.34 (1H, t, C₆H₄), 7.46 (1H, br dd, C₆H₄), 7.50 (2H, m, Ph), 7.58 (1H, m, Ph), 7.86 (2H, m, Ph), 8.34 (2H, d, pyrimidine); FABMS *m/z* 567 (M+H)⁺; [α]_D²⁵ +45 (c 1.0, CHCl₃).

6.4.4. (2*S*)-Benzenesulfonylamino-3-[3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoylamino]propionic acid. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 8 as a colorless solid. Yield: (67 mg, 87%); ¹H NMR (400 MHz, CD₃OD) δ: 3.30 (4H, m, piperazine), 3.54 (1H, dd, CONHCH₂), 3.71 (1H, dd, CONHCH₂), 3.83 (1H, dd, CONHCH₂CH), 3.96 (4H, m, piperazine), 6.60 (1H, t, pyrimidine), 7.18 (1H, br dd, C₆H₄), 7.26 (1H, br d, C₆H₄), 7.33 (1H, t, C₆H₄), 7.46 (3H, m, 1H of C₆H₄ and 2H of Ph), 7.52 (1H, m, Ph), 7.86 (2H, m, Ph), 8.34 (2H, d, pyrimidine); TSPMS *m/z* 511 (M+H)⁺; [α]_D²⁵ +60 (c 1.0, MeOH).

6.4.5. Compound 21. The title compound was prepared from (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-yl)piperazin-1-yl}benzoylamino]propionic acid by the same procedure as employed for compound 10 as a colorless syrup. Yield: (31 mg, 50%); ¹H NMR (400 MHz, CD₃OD) δ: 1.94 (2H, quintet, tetrahydropyrimidine), 3.28 (4H, m, piperazine), 3.38 (4H, t, tetrahydropyrimidine), 3.51 (4H, m, piperazine), 3.54 (1H, dd, CONHCH₂), 3.69 (1H, dd, CONHCH₂), 3.76 (1H, dd, CONHCH₂CH), 7.10 (1H, br d, C₆H₄), 7.30 (2H, m, C₆H₄), 7.41 (1H, br s, C₆H₄), 7.47 (2H, m, Ph), 7.53 (1H, m, Ph), 7.85 (2H, m, Ph); FAB-HRMS (M+H)⁺ calcd for C₂₄H₃₀N₆O₅S: 515.2077. Found: 515.2083; [α]_D²⁵ +69 (c 1.0, MeOH).

6.5. General procedure for preparation of compound 26

6.5.1. Method A

6.5.1.1. Compound 23. DMSO (20 ml) was added to 3-fluorobenzonitrile (6.1 g, 60 mmol) and 4-hydroxypiperidine (6.1 g, 50 mmol). The mixture was heated at 100 °C for 5 h. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was then added dropwise to water (500 ml). The mixture was extracted twice with ethyl acetate (300 ml). The ethyl acetate layer was washed twice with water (200 ml) and brine (300 ml). The organic layer was extracted six times

with 1 N hydrochloric acid (150 ml), and then the aqueous layer was adjusted to pH 10 by the addition of NaHCO₃. The mixture was extracted twice with ethyl acetate (300 ml). The organic layer was dried over anhydrous Na₂SO₄ and was then concentrated under reduced pressure to prepare compound **23** (1.9 g, 19%); ¹H NMR (400 MHz, CDCl₃) δ: 1.62–1.73 (2H, m, piperidine), 1.97–2.04 (2H, m, piperidine), 2.97–3.05 (2H, dd, piperidine), 3.54–3.61 (2H, m, piperidine), 3.91 (1H, tt, piperidine), 7.04–7.08 (1H, m, C₆H₄), 7.10–7.14 (2H, m, C₆H₄), 7.27–7.33 (1H, m, C₆H₄); TSPMS *m/z* 203 (M+H)⁺.

6.5.1.2. Compound 24. CH₂Cl₂ (40 ml) was added to compound **23** (1.9 g, 9.4 mmol) to prepare a solution. Methanesulfonyl chloride (0.94 ml, 12 mmol) and TEA (2.8 ml, 20 mmol) were added to the solution, and a reaction was allowed to proceed at room temperature for 10 min. H₂O (400 ml) was added to stop the reaction and extracted twice with CH₂Cl₂ (300 ml). The methylene chloride layer was dried over anhydrous Na₂SO₄ and was then concentrated under reduced pressure to give crude 3-{4-(methanesulfonyloxy)piperidin-1-yl}benzotrile (2.6 g).

DMF (50 ml) was added to this crude 3-{4-(methanesulfonyloxy)piperidin-1-yl}benzotrile to prepare a solution. Sodium azide (1.2 g, 19 mmol) was added to the solution, and the mixture was stirred with heating at 80 °C for 14 h. The temperature of the reaction mixture was returned to room temperature, and then poured into H₂O. The reaction mixture was extracted twice with ethyl acetate (300 ml), followed by washing twice with water (200 ml) and brine (200 ml). The washed organic layer was dried over anhydrous Na₂SO₄ and was then concentrated under reduced pressure to prepare 3-(4-azidopiperidin-1-yl) benzotrile (2.0 g).

1,4-Dioxane (20 ml) and water (10 ml) were added to 3-(4-azidopiperidin-1-yl)benzotrile to prepare a solution. To the solution was added 10% Pd/C (270 mg), and the mixture was stirred in a hydrogen atmosphere at room temperature for 10 h. The insolubles were filtered and washed twice with a solvent (4.0 ml) having the same composition as the mixed solvent used in the reaction. The filtrate and the washings were combined, followed by concentration under reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH/concd NH₄OH, 10:1:0.1) to prepare compound **24** (410 mg, 43%); ¹H NMR (400 MHz, CDCl₃) δ: 1.41–1.53 (2H, m, piperidine), 1.90–1.98 (2H, m, piperidine), 2.80–2.96 (3H, m, piperidine), 3.63–3.72 (2H, m, piperidine), 7.06 (1H, dt, C₆H₄), 7.09–7.14 (2H, m, C₆H₄), 7.27–7.32 (1H, m, C₆H₄); EIMS *m/z* 201 (M)⁺.

6.5.1.3. Compound 25. DMSO (10 ml) was added to compound **24** (410 mg, 2.0 mmol). Next, 2-bromopyrimidine (340 mg, 2.1 mmol) and *N,N*-diisopropylethylamine (2.0 ml, 11 mmol) were added thereto, and the mixture was heated at 120 °C for 6 h. The temperature of the reaction mixture was returned to room temperature and the reaction mixture was then added dropwise to water (600 ml). The temperature of the reaction mixture

was returned to room temperature and then poured into H₂O. The reaction mixture was extracted twice with ethyl acetate (300 ml), followed by washing twice with water (200 ml) and brine (300 ml). The washed organic layer was dried over anhydrous Na₂SO₄ and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane, 2:1) to prepare compound **25** (380 mg, 67%); ¹H NMR (400 MHz, CDCl₃) δ: 1.62–1.72 (2 H, m, piperidine), 2.15–2.23 (2H, m, piperidine), 2.96–3.05 (2H, m, piperidine), 3.65–3.72 (2H, m, piperidine), 4.00–4.11 (1H, m, piperidine), 6.58 (1H, t, pyrimidine), 7.07–7.10 (1H, m, C₆H₄), 7.12–7.15 (2H, m, C₆H₄), 7.29–7.34 (1H, m, C₆H₄), 8.30 (2H, d, pyrimidine); EIMS *m/z* 279 (M)⁺.

6.5.1.4. Compound 26. 50% H₂SO₄ aqueous solution (20 ml) was added to compound **25** (380 mg, 1.4 mmol) to prepare a solution, and a reaction was allowed to proceed at 80 °C for 4 h. The temperature of the reaction solution was returned to room temperature, and the reaction solution was adjusted to pH 7 by the addition of NaHCO₃. The precipitated insolubles were then collected by filtration and were washed twice with water (6.0 ml). The solid was dried under reduced pressure to prepare compound **26** (250 mg, 63%). ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.58 (2H, br dq, piperidine), 1.94 (2H, br d, piperidine), 2.85 (2H, br t, piperidine), 3.74 (2H, br d, piperidine), 3.90 (1H, m, piperidine), 6.55 (1H, t, pyrimidine), 7.21 (1H, dt, C₆H₄), 7.31 (1H, t, C₆H₄), 7.33 (1H, m, C₆H₄), 7.47 (1H, br s, C₆H₄), 8.27 (2H, d, pyrimidine); TSPMS *m/z* 299 (M+H)⁺.

6.5.2. Method B

6.5.2.1. Compound 27. Toluene (200 ml) was added to ethyl 3-bromobenzoate (5.0 g, 22 mmol) to prepare a solution. The solution was added to 4-hydroxypiperidine (2.7 g, 26 mmol). Further, anhydrous cesium carbonate (10 g, 31 mmol), palladium(II) acetate (74 mg, 0.33 mmol), and (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (200 mg, 0.32 mmol) were added thereto, and the mixture was stirred with heating at 90 °C for 5 h and then at 100 °C for 2 h. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was then added dropwise to an aqueous ammonium chloride solution (400 ml), followed by extraction with ethyl acetate (200 ml). The ethyl acetate layer was dried over anhydrous Na₂SO₄ and was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane, 2:1) to prepare compound **27** (490 mg, 8.9%); ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.70 (2H, m, piperidine), 2.02 (2H, m, piperidine), 2.97 (2H, ddd, piperidine), 3.61 (2H, m, piperidine), 3.87 (1H, m, piperidine), 4.37 (2H, q, Et), 7.12 (1H, br ddd, C₆H₄), 7.30 (1H, t, C₆H₄), 7.50 (1H, br ddd, C₆H₄), 7.61 (1H, br dd, C₆H₄); TSPMS *m/z* 250 (M+H)⁺.

6.5.2.2. Compound 28. The title compound was prepared from compound **27** by the same procedure as employed for compound **24**. Yield: (720 mg, 72%); ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.50 (2H, m, piperidine), 1.94 and 2.04 (2H, each br d, piperidine),

2.83 (3H, m, piperidine), 3.71 (2H, m, piperidine), 4.36 (2H, q, Et), 7.12 (1H, br dd, C₆H₄), 7.29 (1H, t, C₆H₄), 7.49 (1H, br ddd, C₆H₄), 7.61 (1H, br dd, C₆H₄); TSPMS *m/z* 249 (M+H)⁺.

6.5.2.3. Compound 29. The title compound was prepared from compound 28 by the same procedure as employed for compound 25. Yield: (530 mg, 56%); ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.66 (2H, br dq, piperidine), 2.19 (2H, br d, piperidine), 2.99 (2H, m, piperidine), 3.71 (2H, br d, piperidine), 4.02 (1H, m, piperidine), 4.37 (2H, q, Et), 6.54 (1H, t, pyrimidine), 7.13 (1H, br ddd, C₆H₄), 7.31 (1H, t, C₆H₄), 7.52 (1H, br ddd, C₆H₄), 7.63 (1H, br dd, C₆H₄), 8.28 (2H, d, pyrimidine); TSPMS *m/z* 327 (M+H)⁺.

6.5.2.4. Compound 26. THF (45 ml), MeOH (15 ml), and 1 N NaOH (15 ml) were successively added to compound 29 (530 mg, 1.6 mmol) to prepare a solution, and a reaction was allowed to proceed at 45 °C for 16 h. The temperature of the reaction solution was returned to room temperature, and the reaction solution was then concentrated to dryness. The residue was dissolved in water (16 ml). The solution was adjusted to pH 3 by the addition of 5 N hydrochloric acid (2.5 ml) and 1 N hydrochloric acid (2.0 ml). The precipitated insolubles were then collected by filtration and were washed twice with water (6.0 ml). The solid was dried under reduced pressure in the presence of diphosphorus pentoxide at 60 °C for 3 h to prepare compound 26 (470 mg, 97%). Compound 26 synthesized by method B was identified with that prepared by method A with 400 MHz ¹H NMR and TSP mass spectrum.

6.5.3. Method C

6.5.3.1. Compound 27. Ethyl 3-aminobenzoate (3.3 g, 20 mmol) was added to 1,5-dichloropentan-3-one,¹⁰ and the mixture was dissolved in 200 ml of MeOH. *p*-Toluenesulfonic acid monohydrate (4.6 g, 24 mmol) was added to the solution, and a reaction was allowed to proceed at 65 °C for 7 h, and the reaction mixture was then concentrated under reduced pressure. An aqueous NaHCO₃ solution (300 ml) was added to the residue, and the mixture was extracted twice with CH₂Cl₂ (200 ml). The combined organic layers were washed with an aqueous NaHCO₃ solution (300 ml), were dried over anhydrous MgSO₄, and were then concentrated under reduced pressure. Immediately, formic acid (70 ml) and water (7.0 ml) were added to the residue to prepare a solution. A reaction was allowed to proceed at room temperature for 2 h, and the reaction mixture was then concentrated under reduced pressure. An aqueous NaHCO₃ solution (200 ml) was added to the residue, and the mixture was extracted twice with ethyl acetate (200 ml). The combined organic layers were washed with an aqueous NaHCO₃ solution (200 ml), were dried over anhydrous MgSO₄, and were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 2:1) to prepare ethyl 3-(4-oxopiperidin-1-yl)benzoate.

THF (150 ml) was added to ethyl 3-(4-oxopiperidin-1-yl)benzoate to prepare a solution. Sodium borohydride

(601 mg, 16 mmol) was added to the solution at room temperature, and the mixture was stirred for 3.5 h. Water (300 ml) was added thereto, and the mixture was extracted with ethyl acetate (300 ml), followed by washing with saturated brine (100 ml). The extract was dried over anhydrous MgSO₄ and was concentrated under reduced pressure to prepare compound 27 (3.6 g, 72%); compound 27 synthesized by method C was identified with that prepared by method B with 400 MHz ¹H NMR and TSP mass spectrum.

6.5.3.2. Compound 26. The title compound was prepared by the same procedure as method B.

6.6. Preparation of compound 22

6.6.1. Compound 30. DMF (5.4 ml) and CH₂Cl₂ (5.4 ml) were added to compound 26 (93 mg, 0.31 mmol) and 207 mg of benzotriazol-1-yloxytri(dimethylamino)phosphonium hexafluorophosphate (210 mg, 0.47 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (0.082 ml, 0.47 mmol) was added to the solution, and a reaction was allowed to proceed at room temperature for 2 h. Separately, CH₂Cl₂ (5.4 ml) was added to *tert*-butyl (2*S*)-*N*-benzenesulfonyl-2,3-diaminopropionate (110 mg, 0.38 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (0.041 ml, 0.24 mmol) was added to the solution. The above active ester solution was added to this mixture at 0 °C, and a reaction was allowed to proceed at room temperature for 16 h. The reaction solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (40 ml), followed by washing with an aqueous NaHCO₃ solution and saturated brine. The extract was then dried over anhydrous Na₂SO₄. The ethyl acetate layer was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (CHCl₃/MeOH/concd NH₄OH, 30:1:0.03) to prepare compound 30 (180 mg, 100%); ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (9H, s, *t*-Bu), 1.64 (2H, br q, piperidine), 2.17 (2H, m, piperidine), 2.99 (2H, br t, piperidine), 3.60 (1H, ddd, CONHCH₂), 3.73 (1H, br d, piperidine), 3.89 (1H, ddd, CONHCH₂), 3.93–4.05 (2H, m, CONHCH₂CH and piperidine), 6.53 (1H, t, pyrimidine), 7.07 (1H, br dd, C₆H₄), 7.15 (1H, br d, C₆H₄), 7.29 (1H, t, C₆H₄), 7.42 (1H, br dd, C₆H₄), 7.49 (2H, m, C₆H₅), 7.57 (1H, m, C₆H₅), 7.86 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); TSPMS *m/z* 581 (M+H)⁺; [α]_D²⁵ +46 (*c* 0.70, CHCl₃).

6.6.2. Compound 22. CH₂Cl₂ (4.0 ml) and anisole (0.20 ml) were added to compound 30 (170 mg, 0.29 mmol) to prepare a solution, and the solution was cooled to 0 °C. Trifluoroacetic acid (4.0 ml) was added thereto, and a reaction was allowed to proceed at room temperature for 8 h. The reaction solution was concentrated under reduced pressure, and the residue was subjected to azeotropic distillation twice with toluene (4.0 ml). The product obtained by the azeotropic distillation was then washed twice with isopropyl ether (4.0 ml), and the residue was purified by column chromatography on silica gel (CHCl₃/MeOH/concd NH₄OH, 9:2:0.2) to prepare (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid.

1,4-Dioxane (10.5 ml), water (3.0 ml), and 1 N hydrochloric acid (1.5 ml) were successively added to (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid (160 mg) to prepare a solution. To the solution was added 10% Pd/C (40 mg). The mixture was stirred in a hydrogen atmosphere at room temperature for 6 h. The insolubles were filtered and were washed twice with 4.0 ml of a solvent having the same composition as the mixed solvent used in the reaction. The filtrate and the washings were combined, followed by concentration under reduced pressure. The residue was purified by preparative thin-layer chromatography (CHCl₃:EtOH:H₂O:concd NH₄OH, 8:8:1:1) to prepare the title compound as crude. Finally, the crude compound was purified by Sephadex LH-20 (10% concd NH₄OH/MeOH) to prepare compound **22** (120 mg, 78%); ¹H NMR (400 MHz, 10% ND₄OD/CD₃OD) δ: 1.63 (2H, m, piperidine), 1.94 (2H, quintet, tetrahydropyrimidine), 2.00 (2H, br d, piperidine), 2.90 (2H, m, piperidine), 3.35 (4H, t, tetrahydropyrimidine), 3.49 (1H, m, piperidine), 3.52 (1H, dd, CONHCH₂), 3.70 (1H, dd, CONHCH₂), 3.72 (2H, br d, piperidine), 3.78 (1H, dd, CONHCH₂CH), 7.13 (1H, br dd, C₆H₄), 7.24 (1H, br d, C₆H₄), 7.32 (1H, t, C₆H₄), 7.42 (1H, br s, C₆H₄), 7.48 (2H, m, C₆H₅), 7.55 (1H, m, C₆H₅), 7.85 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₂N₆O₅S: 529.2233. Found: 529.2223; [α]_D²⁵ +65 (c 1.0, 10% concd NH₄OH/MeOH).

6.7. Preparation of the compounds displayed in Table 4

6.7.1. Preparation of compound 31 (method A)

6.7.1.1. 3-{4-(Aminomethyl)piperidin-1-yl}benzoxonitrile. The title compound was prepared from 4-aminopiperidine by the same procedure as employed for compound **23**. Yield: (40 mg, 38%); ¹H NMR (400 MHz, CDCl₃) δ: 1.33 (2H, ddd, piperidine), 1.43–1.55 (1H, m, piperidine), 1.85 (2H, br d, piperidine), 2.64 (2H, d, NHCH₂), 2.77 (2H, ddd, piperidine), 3.73 (2H, br d, piperidine), 7.05 (1H, ddd, C₆H₄), 7.09–7.14 (2H, m, C₆H₄), 7.29 (1H, dd, C₆H₄); TSPMS *m/z* 216 (M+H)⁺.

6.7.1.2. 3-{4-(Pyrimidin-2-ylaminomethyl)piperidin-1-yl}benzoxonitrile. The title compound was prepared from 3-{4-(aminomethyl)piperidin-1-yl}benzoxonitrile by the same procedure as employed for compound **25**. Yield: (160 mg, 54%); ¹H NMR (400 MHz, CDCl₃) δ: 1.41 (2H, dddd, piperidine), 1.76–1.87 (1H, m, piperidine), 1.86–1.94 (2H, m, piperidine), 2.78 (2H, ddd, piperidine), 3.38 (2H, dd, NHCH₂), 3.69–3.76 (2H, m, piperidine), 6.54 (1H, t, pyrimidine), 7.05 (1H, ddd, C₆H₄), 7.09–7.13 (2H, m, C₆H₄), 7.29 (1H, m, C₆H₄), 8.28 (1H, d, pyrimidine); TSPMS *m/z* 294 (M+H)⁺.

6.7.1.3. 3-{4-(Pyrimidin-2-ylaminomethyl)piperidin-1-yl}benzoic acid. The title compound was prepared from 3-{4-(aminomethyl)piperidin-1-yl}benzoxonitrile by the same procedure as employed for compound **26**. Yield: (44 mg, 80%); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.20–1.30 (2H, m, piperidine), 1.74–1.83 (3H, m, piperidine), 2.67 (2H, br dd, piperidine), 3.38 (2H, m, NHCH₂), 3.72 (2H, br d, piperidine), 6.52

(1H, t, pyrimidine), 7.15–7.25 (2H, m, C₆H₄), 7.29 (1H, dd, C₆H₄), 7.44 (1H, br s, C₆H₄), 8.24 (1H, d, pyrimidine); TSPMS *m/z* 313 (M+H)⁺.

6.7.1.4. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-ylaminomethyl)piperidin-1-yl}benzoylamino]propionate. The title compound was prepared from 3-{4-(aminomethyl)piperidin-1-yl}benzoic acid by the same procedure as employed for compound **30**. Yield: (43 mg, 52%); ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (9H, s, *t*-Bu), 1.37–1.50 (2H, m, piperidine), 1.73–1.85 (1H, m, piperidine), 1.90 (2H, br d, piperidine), 2.77 (2H, br dd, piperidine), 3.37 (2H, dd, NHCH₂), 3.53–3.62 (1H, m, CONHCH₂), 3.78 (2H, br d, piperidine), 3.85–3.95 (2H, m, CONHCH₂CH), 6.52 (1H, t, pyrimidine), 7.05 (1H, d, C₆H₄), 7.14 (1H, d, C₆H₄), 7.28 (1H, dd, C₆H₄), 7.40 (1H, br s, C₆H₄), 7.46–7.60 (3H, m, C₆H₅), 7.83–7.88 (2H, m, C₆H₅), 8.27 (2H, d, pyrimidine); TSPMS *m/z* 595 (M+H)⁺.

6.7.1.5. Compound 31. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(aminomethyl)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (17 mg, 58%); ¹H NMR (400 MHz, CD₃OD) δ: 1.37 (2H, ddd, piperidine), 1.65–1.76 (1H, m, piperidine), 1.81 (2H, br d, piperidine), 1.94 (2H, dddd, tetrahydropyrimidine), 2.75 (2H, ddd, piperidine), 3.03 (2H, d, NHCH₂), 3.36 (4H, br t, tetrahydropyrimidine), 3.55 (1H, dd, CONHCH₂), 3.69 (1H, dd, CONHCH₂), 3.75 (1H, dd, CONHCH₂CH), 3.80 (2H, br d, piperidine), 7.11 (1H, ddd, C₆H₄), 7.22 (1H, ddd, C₆H₄), 7.29 (1H, dd, C₆H₄), 7.43 (1H, dd, C₆H₄), 7.46–7.52 (2H, m, C₆H₅), 7.52–7.58 (1H, m, C₆H₅), 7.84–7.89 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₆H₃₄N₆O₅S: 543.2390. Found: 543.2380; [α]_D²⁵ +66 (c 0.32, MeOH).

6.7.2. Preparation of compound 32 (method D, Scheme 4)

6.7.2.1. Compound 48. MeOH (50 ml) was added to 2-deoxy-D-ribose (1.3 g, 10 mmol) to prepare a solution. Separately, CH₂Cl₂ (50 ml) was added to ethyl 3-aminobenzoate (1.6 g, 9.7 mmol) to prepare a solution which was then added to the above methanol solution. A reaction was allowed to proceed at room temperature for 16 h. Acetic acid (1.0 ml) and 500 mg of sodium cyanoborohydride (500 mg) were then added thereto, and a reaction was allowed to proceed at room temperature for 4 h. The reaction solution was concentrated under reduced pressure, and the residue was extracted with CHCl₃ (300 ml). The organic layer was washed with an aqueous NaHCO₃ solution (200 ml) containing a minor amount of sodium chloride. The aqueous layer was subjected to back extraction with CHCl₃ (100 ml). The chloroform layers were combined and were then dried over anhydrous Na₂SO₄, followed by concentration under reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH/concd NH₄OH, 10:1.3:0.1) to prepare compound **48** (2.2 g, 78%); ¹H NMR (400 MHz, CDCl₃) δ: 1.36 (3H, t, Et), 1.80 (2H, m, NHCH₂CH₂), 3.32 (2H, m, NHCH₂), 3.62 (1H, br s, CHOH), 3.77 (2H, br s, CH₂OH), 3.89 (1H, br s, CHOH), 4.33 (2H, q, Et),

6.78 (1H, br dd, C₆H₄), 7.20 (1H, t, C₆H₄), 7.29 (1H, br s, C₆H₄), 7.37 (1H, br d, C₆H₄); TSPMS *m/z* 284 (M+H)⁺; [α]_D²⁵ -17 (c 1.0, CHCl₃).

6.7.2.2. Compound 50. THF (15 ml) was added to compound **48** (370 mg, 1.3 mmol) to prepare a solution. Carbon tetrabromide (653 mg, 2.0 mmol) was added to the solution. The mixture was cooled to 0 °C, and triphenylphosphine (690 mg, 2.6 mmol) was then added thereto. The temperature of the mixture was gradually raised to room temperature over a period of 1 h. Moreover, this solution was kept at room temperature for two more hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (40 g, CHCl₃/MeOH/concd NH₄OH, 20:1:0.05) to prepare the title compound as a crude compound. The crude compound was purified by preparative thin-layer chromatography (CHCl₃/MeOH/benzene/ethyl acetate, 9:1:6:4) to prepare compound **50** (160 mg, 46%); ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.94 (2H, m, NCH₂CH₂), 2.99 (1H, m, NCH₂CH₂), 3.16 (1H, dd, NCH₂CHOH), 3.42 (1H, m, NCH₂CH₂), 3.51 (1H, ddd, NCH₂CHOH), 3.84 (1H, br s, CHOH), 3.95 (1H, br s, CHOH), 4.37 (2H, q, Et), 7.14 (1H, br ddd, C₆H₄), 7.32 (1H, t, C₆H₄), 7.56 (1H, br ddd, C₆H₄), 7.63 (1H, br dd, C₆H₄); FABMS *m/z* 266 (M+H)⁺; [α]_D²⁵ +3.0 (c 1.0, CHCl₃).

6.7.2.3. Compounds 51 and 52. Trimethyl orthoacetate (0.50 ml) was added to compound **50** (134 mg, 0.51 mmol) to prepare a suspension. *p*-Toluenesulfonic acid monohydrate (15.4 mg, 0.082 mmol) was added to the suspension at room temperature, and a reaction was allowed to proceed for 3 h. The reaction solution was concentrated under reduced pressure. Acetic acid (1.0 ml) was then added to the residue at room temperature, and a reaction was allowed to proceed for 45 min. Water (100 ml) was then added thereto. The mixture was extracted twice with ethyl acetate (100 ml). The organic layers were combined, and the combined organic layers were washed with saturated brine (100 ml), were dried over anhydrous MgSO₄, and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/benzene/ethyl acetate, 9:1:6:4) to prepare compound **51** (47 mg, 30%) and compound **52** (86 mg, 55%);

6.7.2.4. Compound 51. ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.90–2.04 (2H, m, piperidine), 2.10 (3H, s, acetyl), 3.20–3.28 (1H, m, piperidine), 3.88 (1H, dd, piperidine), 3.44 (1H, ddd, piperidine), 3.52 (1H, dd, piperidine), 4.07 (1H, dddd, piperidine), 4.37 (2H, q, Et), 5.04 (1H, ddd, CH(OAc)), 7.12 (1H, ddd, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.51 (1H, ddd, C₆H₄), 7.60 (1H, dd, C₆H₄); EIMS *m/z* 307 (M)⁺; [α]_D²⁵ -25 (c 1.1, CH₂Cl₂).

6.7.2.5. Compound 52. ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.94–1.99 (1H, m, piperidine), 2.07–2.16 (1H, m, piperidine), 2.15 (3H, s, acetyl), 3.07 (1H, ddd, piperidine), 3.23 (1H, dd, piperidine), 3.43 (1H, m, piperidine), 3.50 (1H, ddd, piperidine), 4.08 (1H, br

s, piperidine), 4.38 (2H, q, Et), 5.00 (1H, ddd, CH(OAc)), 7.16 (1H, dd, C₆H₄), 7.33 (1H, dd, C₆H₄), 7.58 (1H, m, C₆H₄), 7.64 (1H, m, C₆H₄); EIMS *m/z* 307 (M)⁺; [α]_D²⁵ +4.9 (c 1.1, CH₂Cl₂).

The chemical structure of compound **52** was determined by ¹H NMR analysis and COSY spectrum.

6.7.2.6. Compound 53. CH₂Cl₂ (3.0 ml) was added to compound **51** (47 mg, 0.15 mmol) to prepare a solution. TEA (45 μl, 0.32 mmol) and methanesulfonyl chloride (15 μl, 0.20 mmol) were added to the solution at room temperature, and a reaction was allowed to proceed for 5 min. Water (100 ml) was added thereto, and the mixture was extracted twice with CH₂Cl₂ (50 ml). The combined organic layers were dried over anhydrous MgSO₄ and were concentrated under reduced pressure to prepare ethyl 3-{(3*R*)-acetoxy-(4*S*)-methanesulfonyloxypiperidin-1-yl}benzoate (40 mg, 67%).

DMF (2.0 ml) was added to ethyl 3-{(3*R*)-acetoxy-(4*S*)-methanesulfonyloxypiperidin-1-yl}benzoate (39 mg, 0.10 mmol) to prepare a solution. Sodium azide (15 mg, 0.23 mmol) was added to the solution, and a reaction was allowed to proceed at 90 °C for 10 h. The reaction mixture was returned to room temperature, water (100 ml) was then added thereto, and the mixture was extracted twice with ethyl acetate (70 ml). The combined organic layers were washed twice with water (100 ml) and once with saturated brine (100 ml), were then dried over anhydrous MgSO₄, and were concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:1) to give ethyl 3-{(3*R*)-acetoxy-(4*R*)-azidopiperidin-1-yl}benzoate (34 mg, 100%).

THF (11 ml) was added to ethyl 3-{(3*R*)-acetoxy-(4*R*)-azidopiperidin-1-yl}benzoate (390 mg, 1.2 mmol) to prepare a solution. Sodium ethoxide (99 mg, 1.4 mmol) was added to the solution, and a reaction was allowed to proceed at 30 °C for 3.5 h. The reaction solution was adjusted to pH 4 by the addition of 1 N hydrochloric acid, and water (100 ml) was added thereto. The mixture was extracted twice with ethyl acetate (150 ml). The combined organic layers were then washed with saturated brine (150 ml), were dried over anhydrous MgSO₄, and were concentrated under reduced pressure to prepare compound **53** (350 mg, 100%); ¹H NMR (400 MHz, CDCl₃) δ: 1.39 (3H, t, Et), 1.79 (1H, dddd, piperidine), 2.15 (1H, dddd, piperidine), 2.84 (1H, ddd, piperidine), 2.94 (1H, ddd, piperidine), 3.45 (1H, ddd, piperidine), 3.60 (1H, dddd, piperidine), 3.72 (1H, dd, piperidine), 3.76 (1H, ddd, piperidine), 4.37 (2H, q, Et), 7.11 (1H, dd, C₆H₄), 7.32 (1H, dd, C₆H₄), 7.56 (1H, ddd, C₆H₄), 7.60 (1H, dd, C₆H₄); EIMS *m/z* 290 (M)⁺.

6.7.2.7. Compound 57. 1,4-Dioxane (1.0 ml) and water (0.50 ml) were successively added to compound **53** (11 mg, 0.039 mmol) to prepare a solution. 10% Pd/C (3.0 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature for 3 h. The insolubles were filtered and were

washed with solvent (20 ml) having the same composition as the mixed solvent used in the reaction. The filtrate and the washings were combined, followed by concentration under reduced pressure to give ethyl 3-{(4*R*)-amino-(3*R*)-hydroxypiperidin-1-yl}benzoate (11 mg, 100%).

DMSO (3.0 ml) was added to ethyl 3-{(4*R*)-amino-(3*R*)-hydroxypiperidin-1-yl}benzoate (87 mg, 0.33 mmol) to prepare a solution. 2-Bromopyrimidine (55 mg, 0.33 mmol) and *N,N*-diisopropylethylamine (320 μ l, 1.9 mmol) were successively added to the solution, and a reaction was allowed to proceed at 120 °C for 14 h. The reaction mixture was returned to room temperature, and water (500 ml) was added thereto, followed by extraction three times with ethyl acetate (250 ml). The combined organic layers were washed twice with water (200 ml) and twice with saturated brine (200 ml), were then dried over anhydrous $MgSO_4$, and were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (benzene/ethyl acetate, 1:4) to prepare compound **57** (51 mg, 45%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.39 (3H, t, Et), 1.80 (1H, dddd, piperidine), 2.14 (1H, dddd, piperidine), 2.74 (1H, dd, piperidine), 2.89 (1H, ddd, piperidine), 3.72–3.86 (3H, m, piperidine), 3.97 (1H, ddd, piperidine), 4.37 (2H, q, Et), 6.64 (1H, t, pyrimidine), 7.14 (1H, dd, C_6H_4), 7.32 (1H, dd, C_6H_4), 7.53 (1H, ddd, C_6H_4), 7.63 (1H, dd, C_6H_4), 8.29 (2H, d, pyrimidine); TSPMS m/z 343 ($M+H$)⁺.

6.7.2.8. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-{(3*R*)-hydroxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. 3-{(3*R*)-Hydroxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid was prepared from compound **57** by the same procedure as employed for compound **26** from compound **29**.

The title compound was prepared from 3-{(3*R*)-hydroxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid by the same procedure as employed for compound **30**. Yield: (18 mg, 21%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.29 (9H, s, *t*-Bu), 1.72–1.83 (1H, m, piperidine), 2.09–2.15 (1H, m, piperidine), 2.75 (1H, dd, piperidine), 2.90 (1H, ddd, piperidine), 3.54–3.63 (1H, m, piperidine), 3.70–3.83 (3H, m, piperidine and $CONHCH_2CH$), 3.86–3.95 (2H, m, piperidine and $CONHCH_2$), 3.98 (1H, ddd, piperidine), 6.62 (1H, t, pyrimidine), 7.10 (1H, dd, C_6H_4), 7.18 (1H, br d, C_6H_4), 7.31 (1H, dd, C_6H_4), 7.43 (1H, dd, C_6H_4), 7.47–7.60 (3H, m, C_6H_5), 7.84–7.88 (2H, m, C_6H_5), 8.29 (2H, d, pyrimidine); TSPMS m/z 597 ($M+H$)⁺; $[\alpha]_D^{25}$ +75 (*c* 0.48, CH_2Cl_2).

6.7.2.9. Compound 32. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-{(3*R*)-hydroxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (3.1 mg, 21%); 1H NMR (400 MHz, CD_3OD) δ : 1.68 (1H, dddd, piperidine), 1.95 (2H, dddd, tetrahydropyrimidine), 1.92–2.02 (1H, m, piperidine), 2.67 (1H, dd, piperidine), 2.83 (1H, ddd, piperidine), 3.26–3.32 (1H, m, piperidine), 3.36

(4H, br t, tetrahydropyrimidine), 3.50–3.57 (1H, m, piperidine), 3.56 (1H, dd, $CONHCH_2$), 3.67 (1H, dd, $CONHCH_2$), 3.74 (1H, dd, $CONHCH_2CH$), 3.77–3.85 (1H, m, piperidine), 3.91 (1H, m, piperidine), 7.11 (1H, ddd, C_6H_4), 7.24 (1H, ddd, C_6H_4), 7.31 (1H, dd, C_6H_4), 7.42 (1H, dd, C_6H_4), 7.46–7.52 (2H, m, C_6H_5), 7.52–7.58 (1H, m, C_6H_5), 7.85–7.89 (2H, m, C_6H_5); FAB-HRMS ($M+H$)⁺ calcd for $C_{25}H_{32}N_6O_6S$: 545.2182. Found: 545.2189; $[\alpha]_D^{25}$ +70 (*c* 0.14, MeOH).

6.7.3. Preparation of compound 33

6.7.3.1. Compound 55. THF (5.0 ml) was added to sodium hydride (60%, 35 mg, 0.87 mmol) in an argon atmosphere to prepare a suspension. Separately, compound **53** (208 mg, 0.72 mmol) was dissolved in THF (2.0 ml). This solution was added dropwise to the above suspension at room temperature, and the mixture was stirred for 30 min. A solution (1.0 ml) of methyl iodide (67 μ l, 1.1 mmol) in THF was added dropwise thereto. The mixture was stirred for 4 h, an aqueous ammonium chloride solution was then added to stop the reaction, and water (100 ml) was added thereto. The mixture was extracted twice with ethyl acetate (100 ml). The combined organic layers were then dried over anhydrous $MgSO_4$ and were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CH_2Cl_2/MeOH$, 10:1) to prepare the title compound (77 mg, 35%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.39 (3H, t, Et), 1.70 (1H, m, piperidine), 2.06 (1H, m, piperidine), 2.68 (1H, dd, piperidine), 2.84 (1H, ddd, piperidine), 3.34 (1H, ddd, piperidine), 3.44 (1H, ddd, piperidine), 3.55 (3H, s, OMe), 3.63 (1H, br d, piperidine), 3.88 (1H, ddd, piperidine), 4.37 (2H, q, Et), 7.12 (1H, d, C_6H_4), 7.32 (1H, dd, C_6H_4), 7.55 (1H, d, C_6H_4), 7.60 (1H, br s, C_6H_4); TSPMS m/z 305 ($M+H$)⁺.

6.7.3.2. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-{(3*R*)-methoxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. 1,4-Dioxane (4.0 ml) and water (2.0 ml) were successively added to compound **55** (69 mg, 0.23 mmol) to prepare a solution. 10% Pd/C (18 mg) was added to the solution, and the mixture was stirred in a hydrogen atmosphere at room temperature for 4 h. The insolubles were filtered and were washed with a solvent (90 ml) having the same composition as the mixed solvent used in the reaction. The filtrate and the washings were combined followed by concentration under reduced pressure to give ethyl 3-{(4*R*)-amino-(3*R*)-methoxypiperidin-1-yl}benzoate (66 mg, 100%).

DMSO (2.5 ml) was added to the ethyl 3-{(4*R*)-amino-(3*R*)-methoxypiperidin-1-yl}benzoate (66 mg, 0.23 mmol) thus obtained to prepare a solution. *N,N*-Diisopropylethylamine (230 μ l, 1.3 mmol) and 2-bromopyrimidine (42 mg, 0.27 mmol) were added in that order to the solution. A reaction was allowed to proceed at 120 °C for 24 h, and the temperature of the reaction mixture was then returned to room temperature. Water (500 ml) was added thereto, and the mixture was extracted twice with ethyl acetate (500 ml). The combined organic layers were washed twice with water (500 ml) and once with saturated brine (500 ml), were

dried over anhydrous MgSO_4 , and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate) to give ethyl 3-[(3*R*)-methoxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoate (**58**) (34 mg, 40%).

THF (1.5 ml) and MeOH (0.50 ml) were added to compound **58** (34 mg, 0.096 mmol) thus obtained to prepare a solution, and a 1 N NaOH (0.50 ml) was added to the solution. A reaction was allowed to proceed at 50 °C for 3 h. The temperature of the reaction mixture was then returned to room temperature, the reaction mixture was adjusted to pH 3 by the addition of 1 N hydrochloric acid, and water (50 ml) was added thereto. The mixture was extracted twice with ethyl acetate (50 ml), and the extract was then dried over anhydrous MgSO_4 and was concentrated under reduced pressure to give 3-[(3*R*)-methoxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid (29 mg, 95%).

DMF (1.5 ml) was added to 3-[(3*R*)-methoxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid (28 mg, 0.086 mmol) to prepare a solution, and *tert*-butyl (2*S*)-*N*-benzenesulfonyl-2,3-diaminopropionate (32 mg, 0.10 mmol) was added to the solution. Further, 1-hydroxybenzotriazole (19 mg, 0.14 mmol), *N*-methylmorpholine (47 μl , 0.43 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (34 mg, 0.18 mmol) were added thereto, and a reaction was allowed to proceed at room temperature for 2.5 h. An aqueous NaHCO_3 solution (10 ml) was added to stop the reaction, and water (100 ml) was added thereto. The mixture was extracted twice with ethyl acetate (100 ml), and the combined organic layers were washed with saturated brine (100 ml) and were dried over anhydrous MgSO_4 , followed by concentration under reduced pressure. The residue was purified by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1) to prepare the title compound (36 mg, 26% (four steps)); ^1H NMR (400 MHz, CDCl_3) δ : 1.29 (9H, s, *t*-Bu), 1.65–1.70 (1H, m, piperidine), 2.41 (1H, m, piperidine), 2.85 (1H, dd, piperidine), 3.01 (1H, ddd, piperidine), 3.37 (1H, ddd, piperidine), 3.49 (3H, s, OMe), 3.49–3.58 (1H, m, CONHCH_2), 3.60–3.68 (1H, m, piperidine), 3.87–4.03 (4H, m, piperidine and CONHCH_2CH), 6.65 (1H, t, pyrimidine), 7.09 (1H, d, C_6H_4), 7.21 (1H, d, C_6H_4), 7.32 (1H, dd, C_6H_4), 7.46 (1H, br s, C_6H_4), 7.48–7.61 (3H, m, C_6H_5), 7.84–7.88 (2H, m, C_6H_5), 8.29 (2H, d, pyrimidine); TSPMS m/z 611 (M+H) $^+$; $[\alpha]_D^{25}$ +17 (c 0.54, CH_2Cl_2).

6.7.3.3. Compound 33. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-[(3*R*)-methoxy-(4*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (15 mg, 32% (two steps)); ^1H NMR (400 MHz, CD_3OD) δ : 1.71 (1H, dddd, piperidine), 1.95 (2H, dddd, tetrahydropyrimidine), 1.95–2.03 (1H, m, piperidine), 2.59 (1H, dd, piperidine), 2.82 (1H, ddd, piperidine), 3.22 (1H, ddd, piperidine), 3.27–3.38 (1H, m, CONHCH_2), 3.36 (4H, br t, tetrahydropyrimidine), 3.50 (3H, s, OMe), 3.45–3.60 (1H, m, piperidine), 3.67–3.82 (3H, m, piperidine)

and CONHCH_2CH), 4.17 (1H, ddd, piperidine), 7.15 (1H, ddd, C_6H_4), 7.27 (1H, d, C_6H_4), 7.32 (1H, dd, C_6H_4), 7.46–7.52 (3H, m, C_6H_4 and C_6H_5), 7.53–7.59 (1H, m, C_6H_5), 7.84–7.89 (2H, m, C_6H_5); FAB-HRMS (M+H) $^+$ calcd for $\text{C}_{26}\text{H}_{34}\text{N}_6\text{O}_6\text{S}$: 559.2339. Found: 559.2350; $[\alpha]_D^{25}$ +93 (c 0.44, MeOH).

6.7.4. Preparation of compound 34 (method A)

6.7.4.1. (3*S*)-Aminopiperidin-2-one. MeOH (770 ml) was added to L-ornithine hydrochloride (131 g, 0.78 mol) in an argon atmosphere to prepare a suspension, to which thionyl chloride (170 ml, 2.0 mol) was added dropwise at an internal temperature of –45 °C over a period of 30 min or longer, followed by stirring for 30 min. The temperature of the reaction mixture was then returned to room temperature, and the reaction mixture was vigorously stirred for 19 h and was concentrated under reduced pressure. Water (500 ml) was then added to the residue to prepare a solution. The solution was subjected to column chromatography using a column packed with an Amberlite IRA-400 (OH^-) anion exchange resin (1.1 kg), eluting with water to prepare the title compound as a crude product. MeOH (500 ml) was added to the crude product to prepare a solution, and the solution was slowly poured into CHCl_3 (5.0 l). The suspension thus obtained was then filtered, and the filtrate was concentrated under reduced pressure to prepare the title compound (81 g, 69%); ^1H NMR (400 MHz, CD_3OD) δ : 1.48 (1H, m, piperidine), 1.72 (2H, m, piperidine), 1.99 (1H, dddd, piperidine), 3.16 (2H, dd, piperidine), 3.24 (1H, dd, piperidine); EIMS m/z 114 (M) $^+$.

6.7.4.2. (3*S*)-Aminopiperidine. THF (100 ml) was added to aluminum lithium hydride (3.3 g, 87 mmol) to prepare a suspension, to which (3*S*)-aminopiperidin-2-one (4.1 g, 27 mmol) was added under ice cooling. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was then stirred for 5.5 h, and, while vigorously stirring, water (3.3 ml), 5 N NaOH (3.3 ml), and water (10 ml) were added in that order to stop the reaction, followed by filtration. The filtrate was then dried over anhydrous MgSO_4 . A 4 N hydrogen chloride ethyl acetate solution (14 ml) was added thereto, and the mixture was concentrated under reduced pressure. The residue was subjected to azeotropic distillation with MeOH to prepare dihydrochloride of the title compound (5.1 g, 100%); ^1H NMR (400 MHz, CD_3OD) δ : 1.75 (1H, dddd, piperidine), 1.90 (1H, m, piperidine), 2.09 (1H, dddd, piperidine), 2.23 (1H, br d, piperidine), 3.02 (1H, ddd, piperidine), 3.09 (1H, dd, piperidine), 3.41 (1H, br d, piperidine), 3.62 (2H, m, piperidine); EIMS m/z 100 (M) $^+$.

6.7.4.3. 3-[(3*S*)-Aminopiperidin-1-yl]benzotrile. The title compound was prepared from (3*S*)-aminopiperidine by the same procedure as employed for compound **23**. Yield: (137 mg, 30%); ^1H NMR (400 MHz, CD_3OD) δ : 1.32 (1H, ddd, piperidine), 1.50–1.67 (1H, m, piperidine), 1.79–1.87 (1H, m, piperidine), 1.96 (1H, dddd, piperidine), 2.62 (1H, dd, piperidine), 2.82 (1H, ddd, piperidine), 2.88 (1H, dddd, piperidine), 3.53 (1H, ddd, piperidine), 3.65 (1H, dddd, piperidine), 7.05 (1H, ddd,

C₆H₄), 7.20–7.25 (2H, m, C₆H₄), 7.33 (1H, ddd, C₆H₄); EIMS *m/z* 201 (M)⁺.

6.7.4.4. 3-[(3*S*)-(Pyrimidin-2-ylamino)piperidin-1-yl]benzotrile. The title compound was prepared from 3-[(3*S*)-aminopiperidin-1-yl]benzotrile by the same procedure as employed for compound **25**. Yield: (144 mg, 75%); ¹H NMR (400 MHz, CD₃OD) δ: 1.60–1.81 (2H, m, piperidine), 1.83–1.93 (1H, m, piperidine), 1.96–2.04 (1H, m, piperidine), 2.95 (1H, dd, piperidine), 3.11 (1H, dd, piperidine), 3.41 (1H, ddd, piperidine), 3.75 (1H, dd, piperidine), 4.15 (1H, dddd, piperidine), 6.58 (1H, t, pyrimidine), 7.06 (1H, d, C₆H₄), 7.15 (1H, dd, C₆H₄), 7.24 (1H, br s, C₆H₄), 7.29 (1H, dd, C₆H₄), 8.32 (2H, d, pyrimidine); EIMS *m/z* 279 (M)⁺; [α]_D²⁵ +8.6 (c 0.67, CH₂Cl₂).

6.7.4.5. 3-[(3*S*)-(Pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid. The title compound was prepared from 3-[(3*S*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzotrile by the same procedure as employed for compound **26** from compound **25**. Yield: (79 mg, 60%); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.46–1.67 (2H, m, piperidine), 1.74–1.84 (1H, m, piperidine), 1.91–1.99 (1H, m, piperidine), 2.64 (1H, dd, piperidine), 2.77 (1H, br dd, piperidine), 3.67 (1H, br d, piperidine), 3.83 (1H, br d, piperidine), 3.86–3.97 (1H, m, piperidine), 6.58 (1H, t, pyrimidine), 7.13 (1H, d, C₆H₄), 7.19 (1H, ddd, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.53 (1H, br s, C₆H₄), 8.29 (2H, d, pyrimidine); EIMS *m/z* 298 (M)⁺.

6.7.4.6. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-[(3*S*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoylamino]propionate. The title compound was prepared from 3-[(3*S*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid by the same procedure as employed for compound **30**. Yield: (130 mg, 85%); ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (9H, s, *t*-Bu), 1.62–1.71 (1H, m, piperidine), 1.71–1.81 (1H, m, piperidine), 1.85–2.00 (2H, m, piperidine), 3.02 (1H, dd, piperidine), 3.10–3.20 (1H, m, piperidine), 3.32–3.39 (1H, m, piperidine), 3.60 (1H, ddd, CONHCH₂), 3.67 (1H, dd, piperidine), 3.85–3.96 (2H, m, CONHCH₂CH), 4.16–4.25 (1H, m, piperidine), 6.53 (1H, t, pyrimidine), 7.10 (1H, dd, C₆H₄), 7.16 (1H, d, C₆H₄), 7.29 (1H, dd, C₆H₄), 7.44 (1H, dd, C₆H₄), 7.46–7.52 (2H, m, C₆H₅), 7.54–7.59 (1H, m, C₆H₅), 7.83–7.87 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); TSPMS *m/z* 581 (M+H)⁺; [α]_D²⁵ +40 (c 0.54, CH₂Cl₂).

6.7.4.7. Compound 34. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-[(3*S*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (59 mg, 59%); ¹H NMR (400 MHz, CD₃OD) δ: 1.60 (1H, ddd, piperidine), 1.70–1.81 (1H, m, piperidine), 1.85–1.93 (4H, m, piperidine and tetrahydropyrimidine), 3.06 (1H, dd, piperidine), 3.10–3.15 (1H, m, piperidine), 3.28 (1H, m, piperidine), 3.33 (4H, br t, tetrahydropyrimidine), 3.48 (1H, dd, piperidine), 3.52 (1H, dd, CONHCH₂), 3.65–3.72 (1H, m, piperidine), 3.71 (1H, dd, CONHCH₂), 3.77 (1H, dd, CONHCH₂CH), 7.13 (1H, ddd, C₆H₄), 7.26 (1H, ddd, C₆H₄), 7.31 (1H, dd, C₆H₄), 7.46 (1H, dd, C₆H₄), 7.47–7.53 (2H, m,

C₆H₅), 7.53–7.59 (1H, m, C₆H₅), 7.85–7.90 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₂N₆O₅S: 529.2233. Found: 529.2239; [α]_D²⁵ +66 (c 0.57, MeOH).

6.7.5. Preparation of compound **35** (method A)

6.7.5.1. (3*R*)-Aminopiperidin-2-one. The title compound was prepared from *D*-ornithine hydrochloride by the same procedure as employed for (3*S*)-aminopiperidin-2-one. Yield: (1.7 g, 63%); ¹H NMR (400 MHz, CD₃OD) δ: 1.48 (1H, m, piperidine), 1.72 (2H, m, piperidine), 1.99 (1H, dddd, piperidine), 3.16 (2H, dd, piperidine), 3.24 (1H, dd, piperidine); EIMS *m/z* 114 (M)⁺.

6.7.5.2. (3*R*)-Aminopiperidine. The title compound was prepared from (3*R*)-aminopiperidin-2-one by the same procedure as employed for (3*S*)-aminopiperidine. Yield: (1.0 g, 60%); ¹H NMR (400 MHz, CD₃OD) δ: 1.75 (1H, dddd, piperidine), 1.90 (1H, m, piperidine), 2.09 (1H, dddd, piperidine), 2.23 (1H, br d, piperidine), 3.02 (1H, ddd, piperidine), 3.09 (1H, dd, piperidine), 3.41 (1H, br d, piperidine), 3.62 (2H, m, piperidine); EIMS *m/z* 100 (M)⁺.

6.7.5.3. 3-[(3*R*)-(Pyrimidin-2-ylamino)piperidin-1-yl]benzotrile. The title compound was prepared from (3*R*)-aminopiperidine by the same procedure as employed for compound **25**. Yield: (59 mg, 10% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.60–1.95 (3H, m, piperidine), 1.96–2.05 (1H, m, piperidine), 2.97 (1H, dd, piperidine), 3.11 (1H, ddd, piperidine), 3.37–3.45 (1H, m, piperidine), 3.74 (1H, dd, piperidine), 4.12–4.21 (1H, m, piperidine), 6.60 (1H, t, pyrimidine), 7.06 (1H, ddd, C₆H₄), 7.15 (1H, ddd, C₆H₄), 7.24 (1H, dd, C₆H₄), 7.29 (1H, dd, C₆H₄), 8.33 (2H, d, pyrimidine); TSPMS *m/z* 280 (M+H)⁺; [α]_D²⁵ –7.0 (c 0.65, CH₂Cl₂).

6.7.5.4. 3-[(3*R*)-(Pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid. The title compound was prepared from 3-[(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzotrile by the same procedure as employed for compound **26** from compound **25**. Yield: (44 mg, 71%); ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.45–1.66 (2H, m, piperidine), 1.74–1.82 (1H, m, piperidine), 1.95 (1H, br d, piperidine), 2.63 (1H, dd, piperidine), 2.76 (1H, ddd, piperidine), 3.65 (1H, br d, piperidine), 3.81 (1H, br d, piperidine), 3.86–3.96 (1H, m, piperidine), 6.57 (1H, t, pyrimidine), 7.11 (1H, d, C₆H₄), 7.18 (1H, ddd, C₆H₄), 7.28 (1H, dd, C₆H₄), 7.52 (1H, br s, C₆H₄), 8.29 (2H, d, pyrimidine); TSPMS *m/z* 299 (M+H)⁺.

6.7.5.5. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-[(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoylamino]propionate. The title compound was prepared from 3-[(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl]benzoic acid by the same procedure as employed for compound **30**. Yield: (80 mg, 100%); ¹H NMR (400 MHz, CDCl₃) δ: 1.29 (9H, s, *t*-Bu), 1.63–1.72 (1H, m, piperidine), 1.73–1.82 (1H, m, piperidine), 1.86–2.00 (2H, m, piperidine), 3.03 (1H, dd, piperidine), 3.16 (1H, ddd, piperidine), 3.30–3.39 (1H, m, piperidine), 3.61 (1H, ddd, CONHCH₂), 3.67 (1H, dd, piperidine), 3.88 (1H, m,

CONHCH₂), 3.90–3.96 (1H, m, CONHCH₂CH), 4.10–4.25 (1H, m, piperidine), 6.53 (1H, t, pyrimidine), 7.10 (1H, dd, C₆H₄), 7.17 (1H, d, C₆H₄), 7.29 (1H, dd, C₆H₄), 7.44 (1H, dd, C₆H₄), 7.46–7.52 (2H, m, C₆H₅), 7.53–7.59 (1H, m, C₆H₅), 7.83–7.87 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); TSPMS *m/z* 581 (M+H)⁺; [α]_D²⁵ +34 (c 0.64, CH₂Cl₂).

6.7.5.6. Compound 35. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-{(3*R*)-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (29 mg, 37% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.55–1.65 (1H, m, piperidine), 1.71–1.81 (1H, m, piperidine), 1.84–1.95 (4H, m, piperidine and tetrahydropyrimidine), 3.05 (1H, dd, piperidine), 3.08–3.18 (1H, m, piperidine), 3.25–3.38 (5H, m, piperidine and tetrahydropyrimidine), 3.42–3.54 (1H, m, piperidine), 3.54 (1H, dd, CONHCH₂), 3.65–3.77 (3H, m, piperidine and CONHCH₂CH), 7.13 (1H, ddd, C₆H₄), 7.27 (1H, ddd, C₆H₄), 7.32 (1H, dd, C₆H₄), 7.47 (1H, dd, C₆H₄), 7.48–7.53 (2H, m, C₆H₅), 7.54–7.60 (1H, m, C₆H₅), 7.85–7.90 (2H, m, C₆H₅); TSPMS *m/z* 529 (M+H)⁺; [α]_D²⁵ +72 (c 0.55, MeOH).

6.7.6. Preparation of compound 36

6.7.6.1. Compound 36. The title compound was prepared from compound 52 via compounds 54 and 59 by the same procedure as employed for compounds 32 from compound 51 via compounds 53 and 57. Yield: (66 mg, 20% (eight steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.64 (2H, ddd, tetrahydropyrimidine), 2.00–2.12 (1H, m, pyrrolidine), 2.21–2.31 (1H, m, pyrrolidine), 3.10–3.26 (6H, m, tetrahydropyrimidine and NHCH₂), 3.51 (1H, dd, CONHCH₂), 3.51–3.62 (2H, m, pyrrolidine), 3.76 (1H, dd, CONHCH₂), 3.86 (1H, dd, CONHCH₂CH), 4.01 (1H, ddd, pyrrolidine), 4.48 (1H, ddd, pyrrolidine), 6.74–6.78 (1H, m, C₆H₄), 7.04–7.10 (2H, m, C₆H₄), 7.27 (1H, dd, C₆H₄), 7.50–7.56 (2H, m, C₆H₅), 7.56–7.62 (1H, m, C₆H₅), 7.86–7.91 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₂N₆O₆S: 545.2182. Found: 545.2189; [α]_D²⁵ +89 (c 0.058, MeOH).

6.7.7. Preparation of compound 37

6.7.7.1. Compound 37. The title compound was prepared from compound 54 via compounds 56 and 60 by the same procedure as employed for compound 33 from compound 53 via compounds 55 and 58. Yield: (3.1 mg, 5.3% (nine steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.56 (2H, ddd, tetrahydropyrimidine), 2.06 (1H, dddd, pyrrolidine), 2.37 (1H, dddd, pyrrolidine), 3.00–3.10 (4H, m, tetrahydropyrimidine), 3.20 (1H, ddd, pyrrolidine), 3.26 (1H, dd, NHCH₂), 3.45–3.58 (3H, m, pyrrolidine and CONHCH₂ and NHCH₂), 3.47 (3H, s, OMe), 3.78 (1H, dd, CONHCH₂CH), 3.84 (1H, dd, CONHCH₂), 4.08 (1H, ddd, pyrrolidine), 4.22 (1H, ddd, pyrrolidine), 6.74 (1H, dd, C₆H₄), 7.06 (1H, d, C₆H₄), 7.12 (1H, dd, C₆H₄), 7.27 (1H, dd, C₆H₄), 7.50–7.57 (2H, m, C₆H₅), 7.57–7.63 (1H, m, C₆H₅), 7.86–7.93 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₆H₃₄N₆O₆S: 559.2339. Found: 559.2343.

6.8. Preparation of the compounds displayed in Table 5

6.8.1. Preparation of *tert*-butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate, which is the common intermediate for replacement of the C-terminus

6.8.1.1. *tert*-Butyl (2*S*)-(benzyloxycarbonyl)amino-3-[3-{4-(pyrimidin-2-ylamino)-piperidin-1-yl}benzoylamino]propionate. DMF (10 ml) was added to compound 26 (201 mg, 0.67 mmol) to prepare a solution, and *tert*-butyl (2*S*)-*N*-benzyloxycarbonyl-2,3-diaminopropionate (WO9938849) (212 mg, 0.74 mmol) was added to the solution. Further, 1-hydroxybenzotriazole (142 mg, 1.0 mmol), *N*-methylmorpholine (370 μl, 3.4 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (270 mg, 1.4 mmol) were added thereto, and a reaction was allowed to proceed at room temperature for 13 h. An aqueous NaHCO₃ solution (20 ml) was added to stop the reaction, and water (400 ml) was added thereto. The mixture was extracted twice with ethyl acetate (250 ml). The organic layers were combined, and the combined organic layers were washed with saturated brine (400 ml), were dried over anhydrous MgSO₄, and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 20:1) to prepare the title compound (370 mg, 95%); ¹H NMR (400 MHz, CDCl₃) δ: 1.47 (9H, s, *t*-Bu), 1.64 (2H, m, piperidine), 2.18 (2H, m, piperidine), 2.99 (2H, dd, piperidine), 3.72 (2H, br d, piperidine), 3.82 (2H, m, CONHCH₂), 4.01 (1H, m, piperidine), 4.46 (1H, m, CONHCH₂CH), 5.11 (2H, s, CO₂CH₂Ph), 6.54 (1H, t, pyrimidine), 7.07 (1H, dd, C₆H₄), 7.12 (1H, br d, C₆H₄), 7.28–7.35 (6H, m, C₆H₅ and C₆H₄), 7.42 (1H, br s, C₆H₄), 8.28 (2H, d, pyrimidine); EIMS *m/z* 574 (M)⁺; [α]_D²⁵ –2.4 (c 1.1, CH₂Cl₂).

6.8.1.2. *tert*-Butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. THF (60 ml) was added to *tert*-butyl (2*S*)-(benzyloxycarbonyl)amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate (230 mg, 0.40 mmol) to prepare a solution. To the solution was added 10% Pd/C (230 mg). The mixture was stirred in a hydrogen atmosphere at room temperature for 4 h. The insolubles were filtered and were washed with THF (200 ml). The filtrate and the washings were combined followed by concentration under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 10:1) to prepare the title compound (110 mg, 63%); ¹H NMR (400 MHz, CDCl₃) δ: 1.48 (9H, s, *t*-Bu), 1.62–1.74 (2H, m, piperidine), 2.18 (2H, br d, piperidine), 2.99 (2H, br dd, piperidine), 3.48 (1H, ddd, CONHCH₂), 3.61 (1H, dd, CONHCH₂CH), 3.68–3.76 (2H, m, piperidine), 3.83 (1H, ddd, CONHCH₂), 3.96–4.06 (1H, m, piperidine), 6.54 (1H, t, pyrimidine), 7.07 (1H, dd, C₆H₄), 7.14 (1H, br d, C₆H₄), 7.29 (1H, dd, C₆H₄), 7.43 (1H, br s, C₆H₄), 8.28 (2H, d, pyrimidine); EIMS *m/z* 440 (M)⁺; [α]_D²⁵ +6.5 (c 1.0, CH₂Cl₂).

6.8.2. Preparation of compound 38. 6.8.2.1. *tert*-Butyl (2*S*)-acetamido-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. CH₂Cl₂ (10 ml) was added

to *tert*-butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate (101 mg, 0.25 mmol) to prepare a solution. TEA (70 μ l, 0.50 mmol) and acetic anhydride (24 μ l, 0.30 mmol) were added in that order to the solution at room temperature, and a reaction was allowed to proceed for 1 h. Water (50 ml) was added thereto, and the mixture was extracted twice with CH₂Cl₂ (100 ml). The extract was dried over anhydrous MgSO₄ and was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 10:1) to prepare the title compound (94 mg, 77%); ¹H NMR (400 MHz, CDCl₃) δ : 1.49 (9H, s, *t*-Bu), 1.60–1.72 (2H, m, piperidine), 2.05 (3H, s, Ac), 2.19 (2H, m, piperidine), 3.00 (2H, m, piperidine), 3.68–3.75 (3H, ddd, piperidine and CONHCH₂), 3.86 (1H, ddd, CONHCH₂), 4.01 (1H, m, piperidine), 4.67 (1H, ddd, CONHCH₂CH), 6.54 (1H, t, pyrimidine), 7.07 (1H, dd, C₆H₄), 7.08 (1H, m, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.42 (1H, dd, C₆H₄), 8.27 (2H, d, pyrimidine); EIMS *m/z* 482 (M)⁺; [α]_D²⁵ –6.8 (*c* 1.0, CH₂Cl₂).

6.8.2.2. Compound 38. The title compound was prepared from *tert*-butyl (2*S*)-acetamido-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (29 mg, 47% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ : 1.64 (2H, dddd, piperidine), 1.97 (3H, s, Ac), 1.92–2.05 (4H, m, piperidine and tetrahydropyrimidine), 2.90 (2H, br dd, piperidine), 3.37 (4H, br t, tetrahydropyrimidine), 3.48 (1H, m, piperidine), 3.67 (1H, dd, CONHCH₂), 3.70–3.78 (2H, m, piperidine), 3.74 (1H, dd, CONHCH₂), 4.48 (1H, dd, CONHCH₂CH), 7.12 (1H, m, C₆H₄), 7.23 (1H, br d, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.38 (1H, br s, C₆H₄); FAB-HRMS (M+H)⁺ calcd for C₂₁H₃₀N₆O₄: 431.2407. Found: 431.2403; [α]_D²⁵ +11 (*c* 0.32, MeOH).

6.8.3. Preparation of compound 39

6.8.3.1. *tert*-Butyl (2*S*)-{2-(morpholin-4-yl-acetyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate. DMF (10 ml) was added to morpholin-4-ylacetic acid (36 mg, 0.25 mmol) and *tert*-butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate (110 mg, 0.25 mmol) to prepare a solution. 1-Hydroxybenzotriazole (53 mg, 0.37 mmol), *N*-methylmorpholine (140 μ l, 1.3 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (97 mg, 0.50 mmol) were further added to the solution, and a reaction was allowed to proceed at room temperature for 19 h. An aqueous NaHCO₃ solution (5.0 ml) was added to stop the reaction, and water (100 ml) was added thereto. The mixture was extracted twice with ethyl acetate (100 ml). The combined organic layers were washed with saturated brine (100 ml), were dried over anhydrous MgSO₄, and were then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 10:1) to prepare the title compound (94 mg, 66%); ¹H NMR (400 MHz, CDCl₃) δ : 1.50 (9H, s, *t*-Bu), 1.65 (2H, m, piperidine), 2.18 (2H, m, piperidine), 2.55 (4H, m, piperidine and morpholine), 3.00 (2H, m, piperidine), 3.04 (2H, br d, COCH₂N),

3.74 (7H, m, morpholine and CONHCH₂), 3.91 (1H, ddd, CONHCH₂), 4.02 (1H, m, piperidine), 4.68 (1H, ddd, CONHCH₂CH), 6.55 (1H, t, pyrimidine), 7.07 (1H, m, C₆H₄), 7.15 (1H, br d, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.44 (1H, br s, C₆H₄), 8.28 (2H, d, pyrimidine); EIMS *m/z* 567 (M)⁺; [α]_D²⁵ –19 (*c* 1.1, CH₂Cl₂).

6.8.3.2. Compound 39. The title compound was prepared from *tert*-butyl (2*S*)-{2-(morpholin-4-yl-acetyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (42 mg, 68% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ : 1.48 (2H, dddd, piperidine), 1.77–1.92 (4H, m, piperidine and tetrahydropyrimidine), 2.39 (4H, m, morpholine), 2.79 (2H, br dd, piperidine), 2.88 (2H, d, COCH₂N), 3.24 (4H, br dd, tetrahydropyrimidine), 3.40–3.51 (3H, m, piperidine and CONHCH₂), 3.55 (4H, br s, morpholine), 3.68 (2H, br dd, piperidine), 4.03 (1H, dd, CONHCH₂CH), 7.01 (1H, dd, C₆H₄), 7.13 (1H, d, C₆H₄), 7.25 (1H, dd, C₆H₄), 7.32 (1H, br s, C₆H₄); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₇N₇O₅: 516.2934. Found: 516.2929; [α]_D²⁵ +2.2 (*c* 0.75, MeOH).

6.8.4. Preparation of compound 40

6.8.4.1. *tert*-Butyl (2*S*)-{4-(4-methoxybenzenesulfonyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate. DMF (3.0 ml) was added to *tert*-butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate (61 mg, 0.14 mmol) to prepare a solution. *N,N*-Diisopropylethylamine (48 μ l, 0.28 mmol) and 4-methoxybenzenesulfonyl chloride (29 mg, 0.14 mmol) were added in that order to the solution at room temperature, and a reaction was allowed to proceed for 1 h. Piperazine was added to stop the reaction, and an aqueous NaHCO₃ solution (20 ml) and water (30 ml) were added thereto. The mixture was extracted twice with ethyl acetate (50 ml). The combined organic layers were washed twice with water (50 ml) and once with saturated brine (50 ml), were dried over anhydrous MgSO₄, and were concentrated under reduced pressure to prepare the title compound (79 mg, 94%); ¹H NMR (400 MHz, CDCl₃) δ : 1.32 (9H, s, *t*-Bu), 1.60–1.72 (2H, m, piperidine), 2.19 (2H, br d, piperidine), 3.00 (2H, br dd, piperidine), 3.51–3.61 (1H, m, CONHCH₂), 3.69–3.79 (2H, m, piperidine), 3.85 (3H, s, OMe), 3.86–3.96 (2H, m, CONHCH₂CH), 3.97–4.08 (1H, m, piperidine), 6.53 (1H, t, pyrimidine), 6.95 (2H, d, C₆H₄OMe), 7.07 (1H, dd, C₆H₄), 7.17 (1H, d, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.43 (1H, dd, C₆H₄), 7.78 (2H, d, C₆H₄OMe), 8.28 (2H, d, pyrimidine); TSPMS *m/z* 611 (M+H)⁺; [α]_D²⁵ +40 (*c* 1.6, CH₂Cl₂).

6.8.4.2. Compound 40. The title compound was prepared from *tert*-butyl (2*S*)-{4-(4-methoxybenzenesulfonyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl} benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (8.7 mg, 17% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ : 1.58–1.70 (2H, m, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 2.01 (2H, br d, piperidine), 2.92 (2H, ddd, piperidine), 3.36 (4H, br t, tetrahydropyrimidine), 3.44–3.52 (1H, m, piperidine), 3.54 (1H, dd, CONHCH₂), 3.65–3.76

(2H, m, CONHCH₂CH), 3.76 (2H, br d, piperidine), 3.82 (3H, s, OMe), 6.95–7.00 (2H, m, C₆H₄OMe), 7.13 (1H, ddd, C₆H₄), 7.24 (1H, ddd, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.43 (1H, dd, C₆H₄), 7.76–7.80 (2H, m, C₆H₄OMe); FAB-HRMS (M+H)⁺ calcd for C₂₆H₃₄N₆O₆S: 559.2339. Found: 559.2343; [α]_D²⁵ +71 (c 0.30, MeOH).

6.8.5. Preparation of compound 41

6.8.5.1. Compound 41. 1,2-Dichloroethane (7.0 ml) was added to *tert*-butyl (2*S*)-{(4-methoxybenzenesulfonyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate (44 mg, 0.072 mmol) to prepare a solution, and a 1.0 M boron tribromide methylene chloride solution (0.40 ml) was added to the solution. A reaction was allowed to proceed at 40 °C for 3.5 h, and 1,4-dioxane (3.0 ml), water (1.0 ml), and TEA (1.0 ml) were then added thereto. The mixture was concentrated under reduced pressure. 1,4-Dioxane (20 ml) was added to the residue, followed by filtration. The filtrate was then concentrated under reduced pressure to give (2*S*)-{(4-hydroxybenzenesulfonyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid.

1,4-Dioxane (20 ml) and water (10 ml) were added to (2*S*)-{(4-hydroxybenzenesulfonyl)amino}-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionic acid to prepare a solution, 10% Pd/C (24 mg) was added to the solution, and a reaction was allowed to proceed in a hydrogen atmosphere at room temperature for 6 h. The insolubles were filtered and were washed with a solvent (60 ml) having the same composition as the mixed solvent used in the reaction. The filtrate and the washings were combined followed by concentration under reduced pressure. The residue was purified by column chromatography on silica gel (CH₂Cl₂/EtOH/H₂O/concd NH₄OH, 8:8:1:1) and was then purified by Sephadex LH-20 (MeOH) to prepare compound 41 (11 mg, 26% (two steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.58–1.70 (2H, m, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 2.01 (2H, br d, piperidine), 2.87–2.98 (2H, m, piperidine), 3.36 (4H, br t, tetrahydropyrimidine), 3.43–3.53 (1H, m, piperidine), 3.53 (1H, dd, CONHCH₂), 3.66–3.74 (2H, m, CONHCH₂CH), 3.76 (2H, br d, piperidine), 6.81–6.85 (2H, m, C₆H₄OH), 7.13 (1H, ddd, C₆H₄), 7.25 (1H, ddd, C₆H₄), 7.31 (1H, dd, C₆H₄), 7.44 (1H, dd, C₆H₄), 7.66–7.71 (2H, m, C₆H₄OH); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₂N₆O₆S: 545.2182. Found: 545.2187; [α]_D²⁵ +76 (c 0.28, MeOH).

6.8.6. Preparation of compound 42

6.8.6.1. Compound 42. The title compound was prepared from *tert*-butyl (2*S*)-amino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 40. Yield: (31 mg, 42% (three steps)); ¹H NMR (400 MHz, CD₃OD) δ: 1.64 (2H, ddd, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 2.01 (2H, br d, piperidine), 2.23 (3H, s, Me), 2.64 (6H, s, Me), 2.91 (2H, br dd, piperidine), 3.36 (4H, br t, tetrahydropyrimidine), 3.44–3.52 (1H, m, piperidine), 3.54 (1H, dd, CONHCH₂), 3.63 (1H, dd, CONHCH₂), 3.69 (1H, dd, CONHCH₂CH),

3.76 (2H, br d, piperidine), 6.94 (2H, s, C₆H₂), 7.12 (1H, ddd, C₆H₄), 7.23 (1H, ddd, C₆H₄), 7.30 (1H, dd, C₆H₄), 7.43 (1H, dd, C₆H₄); FAB-HRMS (M+H)⁺ calcd for C₂₈H₃₈N₆O₅S: 571.2703. Found: 571.2702; [α]_D²⁵ +75 (c 0.32, MeOH).

6.9. Preparation of the compounds displayed in Table 6

6.9.1. Preparation of compound 43 (method B)

6.9.1.1. 3-Bromo-2-fluorobenzoic acid (Tetrahedron Lett. 1995, 36, 881). THF (60 ml) was added to diisopropylamine (9.6 ml, 68 mmol) in an argon atmosphere. *n*-Butyllithium (hexane solution, 1.5 M, 38 ml, 57 mmol) was added dropwise thereto at –10 °C, and the mixture was stirred for 1 h. Separately, THF (55 ml) was added to 1-bromo-2-fluorobenzene (10 g, 57 mmol) to prepare a solution, which was then added dropwise to the lithium reagent solution at –78 °C. The mixture was stirred for 2 h and was then stirred for additional 30 min while blowing carbon dioxide thereto. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was concentrated under reduced pressure. Water (200 ml) was added to the residue to prepare a solution, and the solution was washed twice with diethyl ether (100 ml). The aqueous layer was adjusted to pH 1 by the addition of 1 N hydrochloric acid, was extracted twice with CH₂Cl₂ (300 ml), was dried over anhydrous MgSO₄, and was concentrated under reduced pressure to prepare the title compound (7.1 g, 57%); ¹H NMR (400 MHz, CDCl₃) δ: 7.14 (1H, ddd, C₆H₃), 7.81 (1H, ddd, C₆H₃), 7.98 (1H, ddd, C₆H₃); EIMS *m/z* 218, 220 (M)⁺.

6.9.1.2. Ethyl 3-bromo-2-fluorobenzoate. EtOH (30 ml) was added to 3-bromo-2-fluorobenzoic acid (3.0 g, 14 mmol) to prepare a solution. Concentrated sulfuric acid (0.30 ml) was added to the solution, and the mixture was heated under reflux for 8 h. The temperature of the reaction mixture was returned to room temperature, the reaction mixture was then slowly poured into an aqueous NaHCO₃ solution (500 ml), and the mixture was extracted twice with ethyl acetate (500 ml). The combined organic layers were dried over anhydrous MgSO₄ and were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1) to prepare the title compound (2.7 g, 79%); ¹H NMR (400 MHz, CDCl₃) δ: 1.40 (3H, t, Et), 4.41 (2H, q, Et), 7.10 (1H, ddd, C₆H₃), 7.73 (1H, ddd, C₆H₃), 7.87 (1H, ddd, C₆H₃); EIMS *m/z* 246, 248 (M)⁺.

6.9.1.3. Ethyl 2-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate. Toluene (30 ml) was added to 4-(*tert*-butyldimethylsilyloxy)piperidine (4.2 g, 20 mmol) and ethyl 3-bromo-2-fluorobenzoate (3.6 g, 15 mmol) in an argon atmosphere to prepare a solution. Tri(*tert*-butyl)phosphine (350 mg, 1.7 mmol), sodium *tert*-butoxide (2.1 g, 22 mmol), and palladium acetate (340 mg, 1.5 mmol) were added in that order to the solution, and the mixture was stirred at 80 °C for 19 h. The temperature of the reaction mixture was returned to room temperature, the insolubles were then filtered, and water (400 ml) was added thereto. The mixture was extracted twice with

ethyl acetate (200 ml), and the extract was then dried over anhydrous $MgSO_4$ and was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CH_2Cl_2/MeOH$, 10:1) and was then purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 1:2) to prepare the title compound (82 mg, 2.1%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.39 (3H, t, Et), 1.76 (2H, dddd, piperidine), 2.00–2.09 (2H, m, piperidine), 2.87 (2H, ddd, piperidine), 3.35 (2H, m, piperidine), 3.87 (1H, dtt, piperidine), 4.38 (2H, q, Et), 7.08 (1H, dd, C_6H_3), 7.13 (1H, ddd, C_6H_3), 7.47 (1H, ddd, C_6H_3); EIMS m/z 267 (M)⁺.

6.9.1.4. Ethyl 3-(4-aminopiperidin-1-yl)-2-fluorobenzoate. The title compound was prepared from ethyl 2-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate by the same procedure as employed for compound 28. Yield: (85 mg, 85% (three steps)); 1H NMR (400 MHz, $CDCl_3$) δ : 1.39 (3H, t, Et), 1.50–1.63 (2H, m, piperidine), 1.90–1.98 (2H, m, piperidine), 2.75 (2H, ddd, piperidine), 2.81 (1H, tt, piperidine), 3.41 (2H, br d, piperidine), 4.38 (2H, q, Et), 7.07 (1H, dd, C_6H_3), 7.10 (1H, ddd, C_6H_3), 7.46 (1H, ddd, C_6H_3); EIMS m/z 266 (M)⁺.

6.9.1.5. Ethyl 2-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate. The title compound was prepared from ethyl 3-(4-aminopiperidin-1-yl)-2-fluorobenzoate by the same procedure as employed for compound 29. Yield: (39 mg, 38%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.39 (3H, t, Et), 1.74 (2H, dddd, piperidine), 2.15–2.23 (2H, m, piperidine), 2.91 (2H, ddd, piperidine), 3.49–3.47 (2H, m, piperidine), 3.95–4.06 (1H, m, piperidine), 4.39 (2H, q, Et), 6.54 (1H, t, pyrimidine), 7.09 (1H, dd, C_6H_3), 7.14 (1H, ddd, C_6H_3), 7.48 (1H, ddd, C_6H_3), 8.29 (2H, d, pyrimidine); EIMS m/z 344 (M)⁺.

6.9.1.6. 2-Fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid. The title compound was prepared from ethyl 2-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate by the same procedure as employed for compound 26 (method B). Yield: (18 mg, 53%); 1H NMR (400 MHz, $DMSO-d_6$) δ : 1.67 (2H, m, piperidine), 1.93–2.01 (2H, m, piperidine), 2.74–2.82 (2H, m, piperidine), 3.24–3.41 (2H, m, piperidine), 3.82–3.90 (1H, m, piperidine), 6.55 (1H, t, pyrimidine), 7.16 (1H, dd, C_6H_3), 7.26 (1H, ddd, C_6H_3), 7.37 (1H, ddd, C_6H_3), 8.27 (2H, d, pyrimidine); TSPMS m/z 317 ($M+H$)⁺.

6.9.1.7. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[2-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. The title compound was prepared from 2-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid by the same procedure as employed for compound 30. Yield: (34 mg, 100%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.30 (9H, s, *t*-Bu), 1.76 (2H, dddd, piperidine), 2.22 (2H, br d, piperidine), 2.92 (2H, dddd, piperidine), 3.36–3.44 (2H, m, piperidine), 3.80–3.97 (2H, t, $CONHCH_2$), 3.97–4.07 (2H, m, piperidine and $CONHCH_2CH$), 6.55 (1H, t, pyrimidine), 7.09–7.16 (2H, m, C_6H_3), 7.44–7.50 (2H, m, C_6H_5), 7.51–7.58 (2H, m, C_6H_3 and C_6H_5), 7.83–7.88 (2H, m, C_6H_5), 8.30 (2H, d, pyrimidine); TSPMS m/z 599 ($M+H$)⁺.

6.9.1.8. Compound 43. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[2-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (16 mg, 78%); 1H NMR (400 MHz, CD_3OD) δ : 1.76 (2H, br ddd, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 2.02 (2H, br d, piperidine), 2.83 (2H, br dd, piperidine), 3.33–3.50 (7H, m, piperidine and tetrahydropyrimidine), 3.66 (1H, d, $CONHCH_2$), 3.68 (1H, d, $CONHCH_2$), 3.74 (1H, dd, $CONHCH_2CH$), 7.13–7.20 (2H, m, C_6H_3), 7.34–7.40 (1H, m, C_6H_3), 7.47–7.53 (2H, m, C_6H_5), 7.53–7.59 (1H, m, C_6H_5), 7.85–7.89 (2H, m, C_6H_5); FAB-HRMS ($M+H$)⁺ calcd $C_{25}H_{31}N_6O_5S$: 547.2139. Found: 547.2148; [α]_D²⁵ +54 (*c* 0.27, MeOH).

6.9.2. Preparation of compound 44 (method B)

6.9.2.1. Methyl 4-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate. The title compound was prepared from methyl 3-bromo-4-fluorobenzoate and 4-hydroxypiperidine by the same procedure as employed for compound 27. Yield: (420 mg, 12%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.77 (2H, m, piperidine), 2.05 (2H, m, piperidine), 2.89 (2H, ddd, piperidine), 3.39 (2H, m, piperidine), 3.87 (1H, m, piperidine), 3.90 (3H, s, Me), 7.06 (1H, dd, C_6H_3), 7.65 (1H, ddd, C_6H_3), 7.67 (1H, dd, C_6H_3); FABMS m/z 254 ($M+H$)⁺.

6.9.2.2. Methyl 3-(4-aminopiperidin-1-yl)-4-fluorobenzoate. The title compound was prepared from methyl 4-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate by the same procedure as employed for compound 28. Yield: (288 mg, 60% (three steps)); 1H NMR (400 MHz, $CDCl_3$) δ : 1.57 (2H, m, piperidine), 1.95 (2H, br d, piperidine), 2.78 (2H, br t, piperidine), 2.83 (1H, m, piperidine), 3.45 (2H, br d, piperidine), 3.90 (3H, s, Me), 7.05 (1H, dd, C_6H_3), 7.63 (1H, ddd, C_6H_3), 7.66 (1H, dd, C_6H_3); TSPMS m/z 253 ($M+H$)⁺.

6.9.2.3. Methyl 4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate. The title compound was prepared from methyl 3-(4-aminopiperidin-1-yl)-4-fluorobenzoate by the same procedure as employed for compound 29. Yield: (250 mg, 67%); 1H NMR (400 MHz, $CDCl_3$) δ : 1.74 (2H, m, piperidine), 2.21 (2H, m, piperidine), 2.93 (2H, br t, piperidine), 3.47 (2H, br d, piperidine), 3.90 (3H, s, Me), 4.01 (1H, m, piperidine), 6.54 (1H, t, pyrimidine), 7.06 (1H, dd, C_6H_3), 7.65 (1H, ddd, C_6H_3), 7.68 (1H, dd, C_6H_3), 8.29 (2H, d, pyrimidine); TSPMS m/z 331 ($M+H$)⁺.

6.9.2.4. 4-Fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid. The title compound was prepared from methyl 4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate by the same procedure as employed for compound 26 (method B). Yield: (230 mg, 94%); 1H NMR (400 MHz, $DMSO-d_6$) δ : 1.67 (2H, br dq, piperidine), 1.98 (2H, br d, piperidine), 2.81 (2H, br t, piperidine), 3.39 (2H, br d, piperidine), 3.88 (1H, m, piperidine), 6.56 (1H, t, pyrimidine), 7.24 (1H, dd, C_6H_3), 7.56 (1H, ddd, C_6H_3), 7.59 (1H, dd, C_6H_3), 8.28 (2H, d, pyrimidine); TSPMS m/z 317 ($M+H$)⁺.

6.9.2.5. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. The title compound was prepared from 4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoic acid by the same procedure as employed for compound 30. Yield: (94 mg, 22%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.28 (9H, s, *t*-Bu), 1.71 (2H, m, piperidine), 2.17 (2H, m, piperidine), 2.91 (2H, br t, piperidine), 3.46 (1H, br d, piperidine), 3.59 (1H, ddd, CONHCH_2), 3.89 (1H, ddd, CONHCH_2), 3.97 (2H, m, CONHCH_2CH and piperidine), 6.53 (1H, t, pyrimidine), 7.03 (1H, dd, C_6H_3), 7.32 (1H, ddd, C_6H_3), 7.49 (3H, m, 2H of C_6H_5 and 1H of C_6H_3), 7.57 (1H, m, C_6H_5), 7.85 (2H, m, C_6H_5), 8.29 (2H, d, pyrimidine); FABMS m/z 599 ($\text{M}+\text{H}$) $^+$; $[\alpha]_{\text{D}}^{25} +50$ (*c* 1.0, CHCl_3).

6.9.2.6. Compound 44. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (52 mg, 61%); $^1\text{H NMR}$ (400 MHz, 10% concd $\text{ND}_4\text{OD}/\text{CD}_3\text{OD}$) δ : 1.64 (2H, m, piperidine), 1.89 (2H, quintet, tetrahydropyrimidine), 1.97 (2H, br d, piperidine), 2.81 (2H, br t, piperidine), 3.30 (4H, t, tetrahydropyrimidine), 3.38 (2H, br d, piperidine), 3.46 (1H, dd, CONHCH_2), 3.67 (1H, dd, CONHCH_2), 3.75 (1H, dd, CONHCH_2CH), 7.07 (1H, dd, C_6H_3), 7.38 (1H, ddd, C_6H_3), 7.42 (2H, m, Ph), 7.48 (2H, m, C_6H_5 and C_6H_3), 7.80 (2H, m, C_6H_5); FAB-HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{N}_6\text{O}_5\text{SF}$: 547.2139. Found: 547.2148; $[\alpha]_{\text{D}}^{25} +63$ (*c* 1.0, 10% concd $\text{NH}_4\text{OH}/\text{MeOH}$).

6.9.3. Preparation of compound 45 (method B)

6.9.3.1. Methyl 5-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate. The title compound was prepared from methyl 3-bromo-5-fluorobenzoate by the same procedure as employed for compound 27. Yield: (160 mg, 4.6%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.67 (2H, dddd, piperidine), 2.01 (2H, m, piperidine), 3.02 (2H, ddd, piperidine), 3.61 (2H, ddd, piperidine), 3.90 (1H, m, piperidine), 3.90 (3H, s, CO_2Me), 6.77 (1H, ddd, C_6H_3), 7.13 (1H, ddd, C_6H_3), 7.39 (1H, dd, C_6H_3); EIMS m/z 253 (M) $^+$.

6.9.3.2. Methyl 3-(4-aminopiperidin-1-yl)-5-fluorobenzoate. The title compound was prepared from methyl 5-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate by the same procedure as employed for compound 28. Yield: (54 mg, 35% (three steps)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.46 (2H, m, piperidine), 1.93 (2H, m, piperidine), 2.82–2.94 (3H, m, piperidine), 3.71 (2H, m, piperidine), 3.90 (3H, s, CO_2Me), 6.76 (1H, ddd, C_6H_3), 7.12 (1H, ddd, C_6H_3), 7.52 (1H, dd, C_6H_3); EIMS m/z 252 (M) $^+$.

6.9.3.3. Methyl 5-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate. The title compound was prepared from methyl 3-(4-aminopiperidin-1-yl)-5-fluorobenzoate by the same procedure as employed for compound 29. Yield: (36 mg, 51%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.63 (2H, m, piperidine), 2.18 (2H, m, piperidine), 3.01 (2H, m, piperidine), 3.72 (2H, m, piperidine),

3.91 (3H, s, CO_2Me), 4.03 (1H, m, piperidine), 6.55 (1H, t, pyrimidine), 6.78 (1H, ddd, C_6H_3), 7.14 (1H, ddd, C_6H_3), 7.40 (1H, m, C_6H_3), 8.29 (2H, d, pyrimidine); EIMS m/z 330 (M) $^+$.

6.9.3.4. 5-Fluoro-3-{4-(pyrimidin-2-ylamino)-piperidin-1-yl}benzoic acid. The title compound was prepared from methyl 5-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoate by the same procedure as employed for compound 26 (method B). Yield: (28 mg, 91%); $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ : 1.55 (2H, br ddd, piperidine), 1.93 (2H, br d, piperidine), 2.91 (2H, br dd, piperidine), 3.79 (2H, br d, piperidine), 3.88–4.00 (1H, m, piperidine), 6.55 (1H, t, pyrimidine), 6.96 (1H, br d, C_6H_3), 7.12 (1H, d, C_6H_3), 7.29 (1H, s, C_6H_3), 8.27 (2H, d, pyrimidine); EIMS m/z 316 (M) $^+$.

6.9.3.5. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[5-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. The title compound was prepared from 5-fluoro-3-{4-(pyrimidin-2-ylamino)-piperidin-1-yl}benzoic acid by the same procedure as employed for compound 30. Yield: (52 mg, 100%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.30 (9H, s, *t*-Bu), 1.60–1.64 (2H, m, piperidine), 2.18 (2H, br d, piperidine), 3.03 (2H, br dd, piperidine), 3.54 (1H, ddd, CONHCH_2), 3.75 (2H, br d, piperidine), 3.91 (1H, ddd, CONHCH_2), 3.91 (1H, m, CONHCH_2CH), 3.98–4.08 (1H, m, piperidine), 6.54 (1H, t, pyrimidine), 6.72 (1H, ddd, C_6H_3), 6.85 (1H, br d, C_6H_3), 7.18 (1H, br dd, C_6H_3), 7.48–7.54 (2H, m, C_6H_5), 7.56–7.61 (1H, m, C_6H_5), 7.84–7.87 (2H, m, C_6H_5), 8.28 (2H, d, pyrimidine); EIMS m/z 598 (M) $^+$; $[\alpha]_{\text{D}}^{25} +31$ (*c* 2.2, CH_2Cl_2).

6.9.3.6. Compound 45. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[5-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound 22. Yield: (27 mg, 61%); $^1\text{H NMR}$ (400 MHz, CD_3OD) δ : 1.55–1.67 (2H, m, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 1.96–2.03 (2H, m, piperidine), 2.95 (2H, ddd, piperidine), 3.36 (4H, br t, tetrahydropyrimidine), 3.45–3.51 (1H, m, piperidine), 3.52 (1H, dd, CONHCH_2), 3.69 (1H, dd, CONHCH_2), 3.77 (1H, dd, CONHCH_2CH), 3.81 (2H, br d, piperidine), 6.82 (1H, ddd, C_6H_3), 6.91 (1H, ddd, C_6H_3), 7.24 (1H, dd, C_6H_3), 7.46–7.52 (2H, m, C_6H_5), 7.53–7.58 (1H, m, C_6H_5), 7.84–7.88 (2H, m, C_6H_5); FAB-HRMS ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{N}_6\text{O}_5\text{SF}$: 547.2139, found 547.2148; $[\alpha]_{\text{D}}^{25} +64$ (*c* 0.30, MeOH).

6.9.4. Preparation of compound 46 (method B)

6.9.4.1. Methyl 6-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate. The title compound was prepared from methyl 3-bromo-6-fluorobenzoate by the same procedure as employed for compound 27. Yield: (47 mg, 16%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.66–1.76 (2H, m, piperidine), 1.98–2.08 (2H, m, piperidine), 2.87–2.97 (2H, m, piperidine), 3.45–3.53 (2H, m, piperidine), 3.83–3.91 (1H, m, piperidine), 3.93 (3H, s, CO_2Me), 7.03 (1H, br dd, C_6H_3), 7.08 (1H, br s, C_6H_3), 7.45 (1H, br s, C_6H_3); EIMS m/z 253 (M) $^+$.

6.9.4.2. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate. The title compound was prepared from methyl 6-fluoro-3-(4-hydroxypiperidin-1-yl)benzoate by the same procedure as employed for compound **30** from compound **27** via compounds **28** and **29**. Yield: (53 mg, 10% (six steps)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.29 (9H, s, *t*-Bu), 1.59–1.72 (2H, m, piperidine), 2.12–2.22 (2H, m, piperidine), 2.88–2.97 (2H, m, piperidine), 3.56–3.65 (2H, m, piperidine), 3.70–3.85 (2H, m, CONHCH₂), 3.90–4.00 (1H, m, piperidine), 4.13 (1H, ddd, CONHCH₂CH), 6.54 (1H, t, pyrimidine), 6.98–7.10 (2H, m, C₆H₃), 7.43–7.49 (2H, m, C₆H₅), 7.50–7.55 (1H, m, C₆H₅), 7.57 (1H, dd, C₆H₃), 7.82–7.88 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); EIMS m/z 598 (M)⁺; [α]_D²⁵ +30 (*c* 1.1, CH₂Cl₂).

6.9.4.3. Compound 46. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[4-fluoro-3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (8.3 mg, 14% (two steps)); $^1\text{H NMR}$ (400 MHz, CD₃OD) δ : 1.65 (2H, dddd, piperidine), 1.96 (2H, dddd, tetrahydropyrimidine), 1.96–2.04 (2H, m, piperidine), 2.86 (2H, ddd, piperidine), 3.36 (4H, br t, tetrahydropyrimidine), 3.41 (1H, m, piperidine), 3.60–3.66 (2H, m, piperidine), 3.61 (1H, dd, CONHCH₂), 3.70 (1H, dd, CONHCH₂), 3.75 (1H, dd, CONHCH₂CH), 7.06 (1H, dd, C₆H₃), 7.11 (1H, ddd, C₆H₃), 7.41 (1H, m, C₆H₃), 7.46–7.52 (2H, m, C₆H₅), 7.52–7.58 (1H, m, C₆H₅), 7.84–7.88 (2H, m, C₆H₅); FAB-HRMS (M+H)⁺ calcd for C₂₅H₃₁N₆O₅SF: 547.2139. Found: 547.2148; [α]_D²⁵ +63 (*c* 0.20, MeOH).

6.9.5. Preparation of compound 47 (method C)

6.9.5.1. Methyl 3-nitro-5-(trifluoromethyl)benzoate. MeOH (20 ml) was added to 3-nitro-5-(trifluoromethyl)benzoic acid (5.1 g, 22 mmol) to prepare a solution, and concentrated sulfuric acid (2.0 ml) was added to the solution. The mixture was heated under reflux for 1.5 h. The temperature of the reaction mixture was returned to room temperature, and the reaction mixture was then slowly poured into NaHCO₃. The insolubles were filtered, water (300 ml) was then added thereto, and the mixture was extracted twice with ethyl acetate (200 ml). The combined organic layers were dried over anhydrous MgSO₄ and were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate, 6:1) to prepare the title compound (5.0 g, 91%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 4.04 (3H, s, CO₂Me), 8.63 (1H, br s, C₆H₃), 8.68 (1H, br s, C₆H₃), 9.05 (1H, br s, C₆H₃); TSPMS m/z 249 (M+H)⁺.

6.9.5.2. Methyl 3-amino-5-(trifluoromethyl)benzoate. MeOH (20 ml) was added to methyl 3-nitro-5-(trifluoromethyl)benzoate (5.0 g, 20 mmol) to prepare a solution, and 10% Pd/C (3.0 g) was added to the solution. The mixture was stirred in a hydrogen atmosphere at room temperature for 23.5 h. The insolubles were filtered and were concentrated under reduced pressure to prepare the title compound (4.3 g, 100%); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 3.92 (3H, s, CO₂Me), 7.05 (1H,

br s, C₆H₃), 7.49 (1H, br s, C₆H₃), 7.65 (1H, br s, C₆H₃); EIMS m/z 219 (M)⁺.

6.9.5.3. Methyl 3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzoate. The title compound was prepared from methyl 3-amino-5-(trifluoromethyl)benzoate by the same procedure as employed for compound **27** by method C. Yield: (4.3 g, 71% (two steps)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.70 (2H, dddd, piperidine), 1.99–2.07 (2H, m, piperidine), 3.07 (2H, ddd, piperidine), 3.66 (2H, ddd, piperidine), 3.89–3.96 (1H, m, piperidine), 3.94 (3H, s, CO₂Me), 7.28 (1H, br s, C₆H₃), 7.69 (1H, br s, C₆H₃), 7.74 (1H, br s, C₆H₃); TSPMS m/z 304 (M+H)⁺.

6.9.5.4. *tert*-Butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}-5-(trifluoromethyl)benzoylamino]propionate. The title compound was prepared from methyl 3-(4-hydroxypiperidin-1-yl)-5-(trifluoromethyl)benzoate by the same procedure as employed for compound **30** from compound **27** via compounds **28** and **29**. Yield: (97 mg, 11% (six steps)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 1.30 (9H, s, *t*-Bu), 1.49–1.74 (2H, m, piperidine), 2.20 (2H, br d, piperidine), 3.07 (2H, br t, piperidine), 3.57 (2H, ddd, CONHCH₂), 3.77–3.82 (2H, m, piperidine), 3.88–3.98 (2H, m, CONHCH₂CH), 4.00–4.09 (1H, m, piperidine), 6.55 (1H, t, pyrimidine), 7.22 (1H, br s, C₆H₃), 7.38 (1H, br s, C₆H₃), 7.46–7.52 (2H, m, C₆H₅), 7.54–7.60 (2H, m, C₆H₃ and C₆H₅), 7.83–7.87 (2H, m, C₆H₅), 8.29 (2H, d, pyrimidine); TSPMS m/z 649 (M+H)⁺; [α]_D²⁵ +45 (*c* 0.63, CHCl₃).

6.9.5.5. Compound 47. The title compound was prepared from *tert*-butyl (2*S*)-benzenesulfonylamino-3-[3-{4-(pyrimidin-2-ylamino)piperidin-1-yl}-5-(trifluoromethyl)benzoylamino]propionate by the same procedure as employed for compound **22**. Yield: (67 mg, 73% (two steps)); $^1\text{H NMR}$ (400 MHz, CD₃OD) δ : 1.69 (2H, dq, $J = 3.6, 10.5$, piperidine), 1.96 (2H, quintet, $J = 5.8$, tetrahydropyrimidine), 2.01 (2H, br d, $J = 11.2$, piperidine), 2.98 (2H, br t, $J = 11.2$, piperidine), 3.36 (4H, br t, $J = 5.8$, tetrahydropyrimidine), 3.45–3.54 (1H, m, piperidine), 3.54 (1H, dd, $J = 8.5, 13.2$, CONHCH₂), 3.72 (1H, dd, $J = 4.6, 13.2$, CONHCH₂), 3.80 (1H, dd, $J = 4.6, 8.5$, CONHCH₂CH), 3.85 (2H, br d, $J = 11.2$, piperidine), 7.29 (1H, br s, C₆H₃), 7.44–7.50 (3H, br s, C₆H₅ and C₆H₃), 7.50–7.56 (1H, m, C₆H₅), 7.64 (1H, br s, C₆H₃), 7.83–7.87 (2H, m, C₆H₅); $^{13}\text{C NMR}$ (CD₃OD) δ 21.2, 32.4, 39.8, 44.4, 48.9 (d, $J_{\text{CF}} = 335.2$ Hz), 58.7, 115.1 (q, $J_{\text{CF}} = 46$ Hz), 115.6 (q, $J_{\text{CF}} = 46$ Hz), 119.1, 125.6 (d, $J_{\text{CF}} = 1,080$ Hz), 128.2, 130.1, 132.8 (q, $J_{\text{CF}} = 118.4$ Hz), 133.7, 137.8, 141.7, 152.7, 153.8, 169.3, 175.0; FAB-HRMS (M+H)⁺ calcd for C₂₆H₃₁N₆O₅SF₃: 597.2107. Found: 597.2102; [α]_D²⁵ +54 (*c* 0.50, MeOH).

6.10. Integrin-binding assays

Compounds were evaluated for their inhibitory activities in $\alpha_v\beta_3$ - and $\alpha_{\text{IIb}}\beta_3$ -ELISA (enzyme-linked immunosorbent assay). $\alpha_v\beta_3$ ¹⁷ was purified from human placenta, using RGDSPK-Sepharose CL-4B chromatography,