Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitor

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Intravascular clot formation is an important factor in a number of cardiovascular diseases. Therefore, the prevention of blood coagulation has become a major target for new therapeutic agents. One attractive approach is the inhibition of factor Xa (FXa), which is a key enzyme in coagulation cascade responsible for the generation of thrombin by limited proteolysis of its zymogen, prothrombin. We have investigated 1-arylsulfonyl-3-piperazinone derivatives, containing a 4-(piperidino)pyridine group in place of guanidino and/or amidino groups, and discovered compound M55113 (30a: 4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone), as a potent inhibitor of FXa (IC_{50}=0.06 μM) with high selectivity for FXa over trypsin and thrombin.

Key words factor Xa inhibitor; 4-(piperidino)pyridine; structure–activity relationship; M55113

Regarding the prevention of blood coagulation, most research in the past decade has been focused on thrombin inhibition.[1,2] More recently, inhibition of factor Xa (FXa), which is directly responsible for prothrombin activation, has emerged as an attractive target.

FXa, which converts prothrombin to thrombin, holds a central position in the coagulation cascade.[3] One molecule of FXa generates over 100 molecules of thrombin. Therefore, inhibition of FXa may be more effective than inhibition of thrombin for the prevention of blood coagulation.[4,5] In addition, a recent study by Harker *et al.*[6] in a balloon model of thrombosis showed that FXa inhibitors might have less bleeding risk than thrombin inhibitors.[7]

Most of the nonpeptide FXa inhibitors reported in the literature are dibasic compounds. Nagahara *et al.*[8,9] have reported synthesis and evaluation of a series of bis(amidino)-derivatives, and through investigation compound DX-9065a (**1**)[10—14] was found to be a selective FXa inhibitor. Further, a compound YM-60828 (**2**)[15—20] which is closely related to **1** in terms of structure was found to have a more potent inhibitory effect on FXa.

A characteristic common to compounds **1** and **2** is having two amidino groups in their molecules, and is considered the presence of more than one such strongly basic group is seen as an unfavorable element for adequate oral absorption and the good pharmacokinetics necessary for oral antithrombotic agents.

Based on these considerations, a compound (**3**) recently reported by ZENECA Co.[21] is of great interest in the following points:

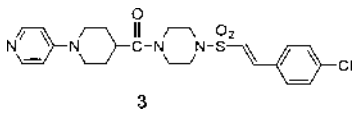
i) The pK_a value of 4-(piperidino)pyridine is about 12 and is nearly equal to that of amidinonaphthalene.

ii) The basicity of two nitrogen atoms in the piperazine ring is reduced by the adjacent acyl and sulfonyl groups.

iii) Due to a resonance structure of 4-dialkylaminopyridines, a 4-(piperidino)pyridine moiety in compound **3** is thought to have a plane structure as well as the naphthalene moiety in compounds **1** and **2**.

To analyze the role of the carbonyl group in compound **3**, the following compounds were synthesized and the inhibitory activity of FXa *in vitro* was evaluated in our laboratory.

In compound **4** the carbonyl group is removed and in compounds **5** and **6** the carbonyl group is replaced by a methylene group. In the present paper we wish to report the process of the above investigation.



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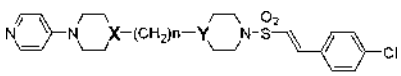
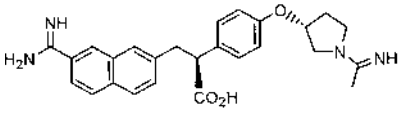
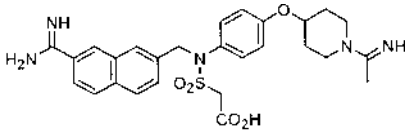


4 n=0, X=N, Y=CH
5 n=1, X=N, Y=CH
6 n=1, X=CH, Y=N



DX-9065a **1**



YM-60828 **2**

Fig. 1

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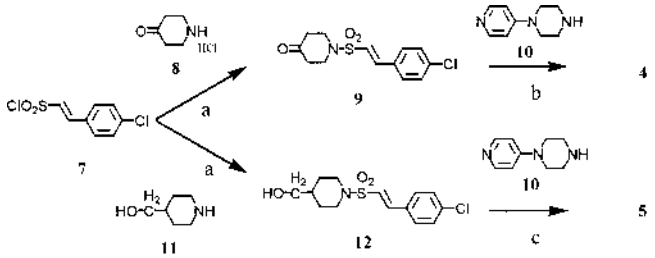
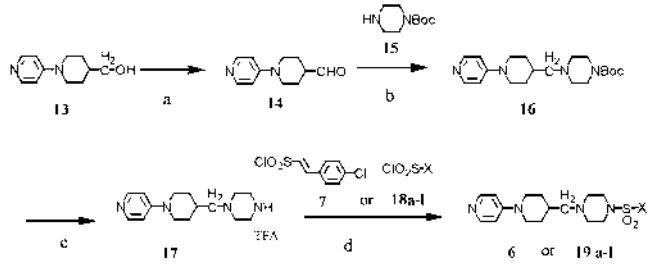


Reagents: a. Et_3N, CH_2Cl_2 ; b. AcOH, $NaBH(OAc)_3$, CH_2Cl_2;
c. i) $(COCl)_2$, DMSO, Et_3N ; ii) AcOH, $NaBH(OAc)_3$, CH_2Cl_2

Chart 1. Synthesis of Compounds **4** and **5**



Reagents: a. $(COCl)_2$, DMSO, Et_3N ; b. AcOH, $NaBH(OAc)_3$, CH_2Cl_2;
c. TFA, anisole, Et_2O ; d. Et_3N, CH_2Cl_2

Chart 2. Synthesis of Compound **6** and General Synthesis of Sulfonamide Derivatives **19a**—**l**

Chemistry

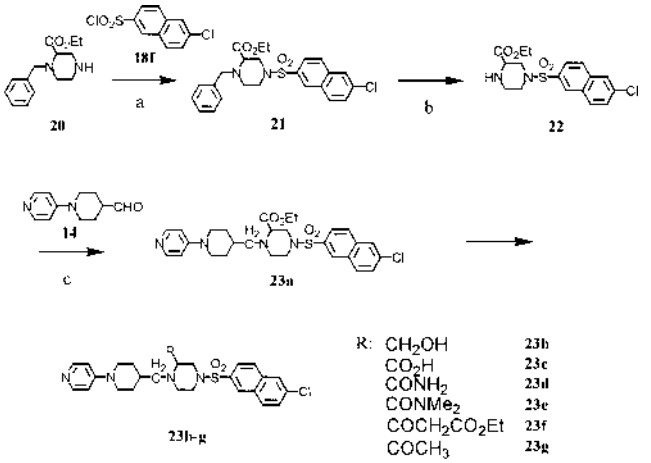
Synthesis of compounds **4** and **5** was achieved as shown in Chart 1. Compound **9**, prepared by the reaction of 4-piperidinone monohydrate hydrochloride (**8**) with (1*E*)-2-(4-chlorophenyl) ethenesulfonyl chloride (**7**) under basic conditions, was treated with 1-(4-pyridinyl)piperazine (**10**) in methylene chloride (CH_2Cl_2) in the presence of sodium triacetoxy borohydride ($NaBH(OAc)_3$) to give desired compound **4**.[22]

A similar reaction was adapted to the synthesis of compound **5**. Namely, 4-piperidinemethanol (**11**) was converted to compound (**12**) by treatment with compound **7** and Swern oxidation[23] of compound **12** afforded the corresponding aldehyde which condensed with compound **10** to give the desired compound **5** in satisfactory yield.

Synthesis of compound **6** and related sulfonamide derivatives (**19a**—**l**) was shown in Chart 2.

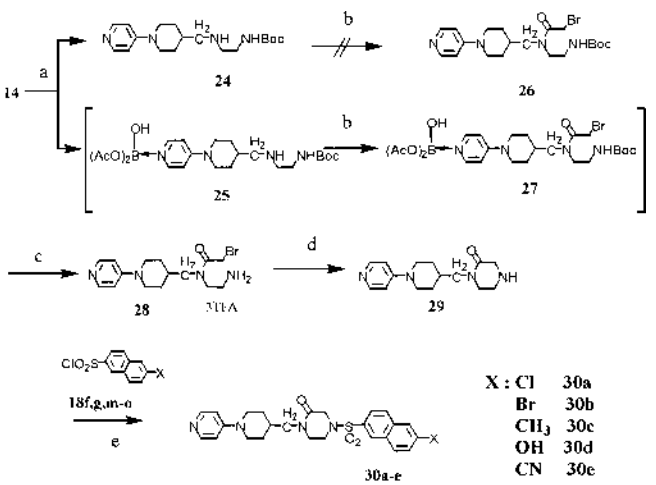
Swern oxidation of 1-(4-pyridinyl)-4-piperidinemethanol (**13**) which was obtained by the reaction of compound **11** with 4-chloropyridine gave the key intermediate carbaldehyde (**14**). Since the aldehyde tended to form a hydrate, the crude **14** was treated with 1-piperazinecarboxylic acid 1,1-dimethylethyl ester (**15**) under reductive conditions to give compound **16**. Deprotection of compound **16** in diethyl ether in the presence of trifluoroacetic acid (TFA) and anisole yielded compound **17**, and the final compounds **6** and **19a**—**l** were obtained smoothly by the condensation with **7** or the aromatic sulfonyl chlorides **18a**—**l** in a similar manner to that described in the synthesis of compounds **9** and **12**.

Synthesis of piperazine derivatives containing a carbon functional group at the 2-position of the piperazine ring was accomplished according to the route shown in Chart 3.



Reagents: a. Et_3N, CH_2Cl_2 ; b. $ClCO_2CHClCH_3$, $C_2H_4Cl_2$;
c. AcOH, $NaBH(OAc)_3$, CH_2Cl_2

Chart 3. Synthetic Route of 2-Substituted Piperazine Derivatives **23a**—**g**



Reagents: a. *N*-Boc-1,2-ethylenediamine, AcOH, $NaBH(OAc)_3$, ;
b. $BrCH_2COCl$, Et_3N, CH_2Cl_2, ; c. TFA, anisole, Et_2O ;
d. Et_3N, DMF ; e. Et_3N, CH_2Cl_2

Chart 4. Synthetic Route of 2-Piperazinone Derivatives 3a—e

Compound **21** was easily prepared by sulfonylation of 1-(phenylmethyl)-2-piperazinecarboxylic acid ethyl ester (**20**) with 6-chloro-2-naphthalenesulfonyl chloride (**18f**) under traditional conditions. Debenzylation of compound **21** with 1-chloroethyl chloroformate afforded compound **22**, and one of the desired compounds (**23a**) was obtained by subsequent reductive amination of compound **22** with the aldehyde **14**. Then, as shown in Chart 3, the conversion of compound **23a** to various derivatives (**23b**—**g**) was carried out. For example, compound **23f** was obtained by coupling reaction of compound **23c** with potassium ethyl malonate in the presence of carbonyl diimidazole at room temperature and the resulting mixture was heated to finish decarboxylation. Hydrolysis of compound **23f** in diluted hydrochloric acid gave the corresponding acetyl compound (**23g**).

Finally, synthesis of the corresponding 2-piperazinone derivatives (**30a**—**e**) was carried out as shown in Chart 4.

When the aldehyde **14** was treated with *N*-(*tert*-butoxycarbonyl)-1,2-diaminoethane in the presence of $NaBH(OAc)_3$ in acetic acid (AcOH), a normal reductive amination product (**24**) was formed together with a considerable amount of a boron complex (**25**) in a ratio of about 1 : 2. The acylation of **24** with bromoacetyl chloride under basic conditions failed to give the desired bromoacetamido derivative (**26**). In contrast, the reaction of the boron complex (**25**) under similar conditions afforded the bromoacetamido derivative (**27**) in good yield, although the reason for these phenomena is not well understood. Deprotection of compound **27** with TFA and anisole was accompanied with removal of the boron moiety to give compound **28**, which smoothly cyclized into the desired 2-piperazinone (**29**) under basic conditions. Compounds **30a**—**e** were obtained by sulfonation of compound **29** with several substituted naphthalenesulfonyl chlorides in yields ranging from 13 to 31%.

Results and Discussion

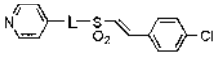
In comparison with compound **3**, the FXa inhibitory activity of compound **4** is remarkably low, while the activity of compounds **5** and **6** is slightly less than that of compound **3** (Table 1). This fact seems to suggest that the whole molecular length is an important factor for the appearance of inhibitory activity of FXa and that the interaction of FXa with the carbonyl group in compound **3** is not strong. Further, compound **6** is 2 fold more active than compound **5**, which means piperidine moiety is rather more favorable than piperazine moiety by the side of pyridine.

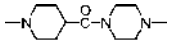
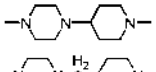
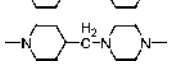
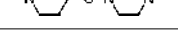
On the basis of this hypothesis, we decided to select compound **6** as the lead substance to search for a more powerful FXa inhibitor by optimization of the compound.

Next, the appropriateness of arylsulfonyl group on compound **6** was investigated, because the bulkiness and co-planarity of this group in the molecule is believed to be another important factor of the interaction between tested compounds and FXa. Among the compounds (**19a**—**e**) tested, naphthalene-2-sulfonic acid (**19b**) and benzo[*b*]thiophene-2-sulfonic acid (**19d**) derivatives were the most powerful inhibitors of FXa, although all the compounds showed impaired activity compared to compound **6**. In addition, compound **19e**, the aza-analogue of compound **19d**, ran counter to our expectation, probably due to the basicity of the nitrogen atom in a thiazole ring.

Then, according to the data shown in Table 2, the substituent effect of naphthyl and benzothienyl groups to the activity was tested. The activity of compounds **19f**—**l** together with that of compound **6** is summarized in Table 3.

Table 1. FXa Inhibitory Activity of Compounds **3**—**6**



Compound	L	IC_{50} (μM)
3		0.21
4		>10
5		1.74
6		0.83

Finally, the structure–activity relationships (SARs) studies focused on the substitution to the 2-position of the piperazine ring in compound **19f** were carried out as follows. Based on the results listed in Tables 1—3, for further development it may be desirable to restrict the mobility of the lone pair on the N1 in the piperazine ring by the electron withdrawing effect of an appropriate neighboring group.

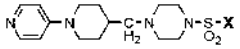
Thus, the compounds containing an electron withdrawing substituent at the 2-position of the piperazine moiety (**23a**—**g**) were evaluated for their FXa inhibitory activity. As listed in Table 4, except for the ethoxycarbonyl group (**23a**), substituents at the 2-position have almost no effect on improvement of the activity. However, it should be emphasized that the introduction of a carbonyl group instead of substituents was found to be the most effective (**30a**), and compound **30a** is about 13 times more effective than compound **6**. This finding suggests that extinguishing the basicity of N1 is a very important factor for exhibition of FXa inhibitor.

In connection with this finding, replacement of the chloro substituent on the naphthalene ring of compound **30a** to other substituents was investigated to prevent overlooking better compounds, but as shown in Table 5 no compound better than compound **30a** could be found.

Conclusion

As described in this paper, through the modification of piperazine derivatives, we accomplished a very active com-

Table 2. FXa Inhibitory Activity of Compounds **19a**—**e**



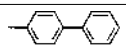
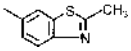
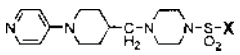
Compound	X	IC_{50} (μM)
19a		>10
19b		8.29
19c		>10
19d		3.95
19e		>10

Table 3. FXa Inhibitory Activity of Compounds **19f**—**l**



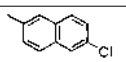
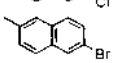
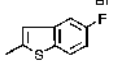
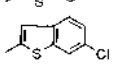
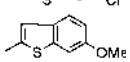
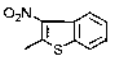
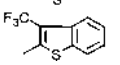
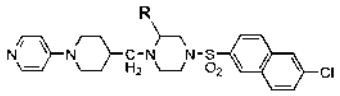
Compound	X	IC_{50} (μM)
19f		0.83
19g		0.30
19h		0.72
19i		0.41
19j		1.75
19k		>10
19l		>10

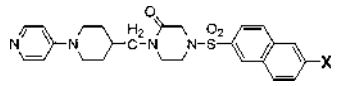
Table 4. FXa Inhibitory Activity and Anticoagulant Activity of Compounds **19f**, **23a**—**g**, and **30a**



Compound	R	IC_{50} (μM)	CT2 (μM)
19f	–H	0.83	20.7
23a	$-CO_2Et$	0.13	2.98
23b	$-CH_2OH$	0.23	3.29
23c	$-CO_2H$	0.70	46.0
23d	$-CONH_2$	0.47	17.1
23e	$-CONMe_2$	0.54	12.3
23f	$-COCH_2CO_2Et$	0.52	14.0
23g	$-COCH_3$	0.42	8.15
30a	=O	0.06	1.04

The concentration required to double the clotting time (CT2) was calculated from each individual dose–response curve ($n=1$).

Table 5. FXa Inhibitory Activity and Anticoagulant Activity of Compounds **30a**—**e**



Compound	X	IC_{50} (μM)	CT2 (μM)
30a	Cl	0.06	1.04
30b	Br	0.10	1.79
30c	CH_3	0.90	8.57
30d	OH	9.08	69.6
30e	CN	12.8	93.6

The concentration required to double the clotting time (CT2) was calculated from each individual dose–response curve ($n=1$).

Table 6. Selectivity of M55113 for FXa over Thrombin and Trypsin

Enzyme	IC_{50} (μM)	Selectivity (enzyme/FXa)
FXa	0.06	
Thrombin	>100	>3000
Trypsin	>100	>3000

pound (**30a**-M55113) as FXa inhibitor using *in vitro* assay.

It should further be mentioned that M55113 showed clear selectivity for FXa over related serine proteases: in particular, the compound is 3000 fold more selective for FXa than for thrombin, as shown in Table 6.

Crystallization of a complex of M55113 with FXa has already been achieved in our laboratory, so the results of crystal elucidation by X-ray analysis will be published in the near future.

Experimental

Nuclear magnetic resonance (NMR) spectra were taken with JEOL JNM-EX270 FT-NMR (JEOL, Ltd.) or JEOL JNM-LA300 (JEOL, Ltd.) in $CDCl_3$ or dimethyl sulfoxide-d_6 (DMSO-d_6) using tetramethylsilane as the internal reference. Data measured by JEOL JNM-LA300 are marked with an asterisk. The following abbreviations were used: s=singlet, d=doublet, dd=double doublet, dt=double triplet, t=triplet, q=quartet, m=multiplet and br=broad. High-resolution mass spectra (HR-MS) were taken with JEOL JMS-GCMATE (JEOL, Ltd.).

Measurement of Factor Xa, Thrombin and Trypsin Inhibition The enzyme solution was mixed with a test compound dissolved at various concentrations in dimethyl sulfoxide (DMSO). Synthetic substrate was added and incubated in a 20 mM Tris–HCl buffer (pH 7.5) containing 0.13 M NaCl at 37 °C. The absorbance at 405 nm was measured continuously. The following enzymes and substrates were used: human factor Xa (Enzyme Research Laboratories, Inc., 0.019 U/ml) and S-2222 (Chromogenix AB, 0.4 mM); human thrombin (Sigma Co., 0.09 U/ml) and S-2238 (Chromogenix AB, 0.2 mM); human trypsin (Athens Research and Technology, Inc., 15 ng/ml) and S-2222 (Chromogenix AB, 0.4 mM). To calculate the inhibitory activity of the test compound, the initial reaction velocity was compared with the value for a control containing no test compound. The inhibitory activity of a test compound was expressed as IC_{50}.

Measurement of Anticoagulant Activity Activated partial thromboplastin time (APTT) was measured with an automatic coagulometer (KC40, Amelung Co.). Briefly, 1.5 μl of test compound diluted with DMSO at various concentrations, 50 μl of normal human plasma and 50 μl of APTT reagent (Dade Behring Inc.) were mixed and incubated for 2 min at 37 °C. Then, 50 μl of 25 mM $CaCl_2$ solution was added to the mixture to measure clotting time. The concentration required to double the clotting time (CT2) was calculated from each individual dose–response curve ($n=1$).

1-[[(1*E*)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-4-piperidinone (9) Triethylamine (Et_3N, 0.7 ml, 5 mmol) and compound **7** (1.1 g, 4.6 mmol) prepared by a documented method[21] were added to a solution of compound **8** (0.5 g, 3.7 mmol) in dry CH_2Cl_2 (60 ml) and the mixture was stirred overnight under Ar at room temperature. Water (30 ml) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry sodium sulfate (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; CH_2Cl_2) to give compound **9** (500 mg, 36%). ^{1}H-NMR (*DMSO-d_6) δ: 7.83—7.77 (2H, m), 7.55—7.38 (4H, m), 3.49 (4H, t, $J=6$ Hz), 2.47 (4H, t, $J=6$ Hz).

1-[[(1*E*)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-4-[4-(4-pyridinyl)-1-piperazinyl]piperidine (4) AcOH (0.18 ml) was added to a solution of compound **9** (490 mg, 1.6 mmol) and compound **10** (254 mg, 1.55 mmol) prepared by a documented method[24] in dry CH_2Cl_2 (12 ml). The mixture was stirred for 30 min under Ar at room temperature. To the stirred mixture, $NaBH(OAc)_3$ (660 mg, 3.1 mmol) was added and the mixture was stirred overnight at room temperature. Water (10 ml) was added to the reaction mixture. The mixture was rendered alkaline with 1 N sodium hydroxide solution and was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : methanol (MeOH)=95 : 5—90 : 10) to give compound **4** (290 mg, 42%). HR-MS *m/z*: Calcd for $C_{22}H_{27}ClN_4O_2S$: 446.1543. Found: 446.1555. ^{1}H-NMR (*DMSO-d_6) δ: 8.20—8.10 (2H, m), 7.81 (2H, d, $J=9$ Hz), 7.52 (2H, d, $J=9$ Hz), 7.46—7.30 (2H, m), 6.90—6.75 (2H, m), 3.65—3.55 (2H, m), 3.43—3.18 (4H, m), 2.75—2.62 (2H, m), 2.61—2.44 (4H, m), 2.44—2.31 (1H, m), 1.90—1.80 (2H, m), 1.58—1.40 (2H, m).

1-[[(1*E*)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-4-piperidinemethanol (12) Et_3N (0.88 ml, 6.3 mmol) and compound **7** (1.03 g, 4.3 mmol) were added to a solution of compound **11** (0.5 g, 4.3 mmol) prepared by a documented method[25] in dry CH_2Cl_2 (10 ml) and the mixture was stirred for 4 h under Ar at room temperature. Water (10 ml) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=99 : 1—97 : 3) to give compound **12** (180 mg, 13%). ^{1}H-NMR (*DMSO-d_6) δ: 7.80 (2H, d, $J=9$ Hz), 7.52 (2H, d, $J=9$ Hz), 7.38 (1H, d, $J=16$ Hz), 7.33 (1H, d, $J=16$ Hz), 4.54 (1H, t, $J=5$ Hz), 3.63—3.50 (2H, m), 3.28—3.21 (2H, m), 2.70—2.56 (2H, m), 1.80—1.35 (3H, m), 1.23—1.07 (2H, m).

1-[[(1*E*)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-4-[[4-(4-pyridinyl)-1-piperazinyl]methyl]piperidine (5) A solution of oxalyl chloride (0.05 ml, 0.62 mmol) in dry CH_2Cl_2 (1.33 ml) was cooled to −78 °C under Ar. To the cooled solution, a solution of dry DMSO (0.09 ml, 1.28 mmol) in dry CH_2Cl_2 (1.33 ml) was added dropwise over 20 min. Then, a solution of compound **12** (150 mg, 0.47 mmol) in dry CH_2Cl_2 (1.33 ml) was added dropwise over 20 min. The reaction mixture was stirred for 1 h at between −65 °C and −60 °C. Then the mixture was cooled to −78 °C and Et_3N (0.25 ml, 1.8 mmol) was added. The reaction mixture was allowed to stand at room temperature. Water (2 ml) was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was suspended in dry CH_2Cl_2 (2.0 ml) and compound **10** (42 mg, 0.25 mmol) and AcOH (0.02 ml) were added in that order. The mixture was

stirred at room temperature for 30 min under Ar, $NaBH(OAc)_3$ (0.10 g, 0.47 mmol) was added and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, which was adjusted to pH 9 with 1 N sodium hydroxide solution and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=95 : 5) to give compound **5** (60 mg, 52%). HR-MS *m/z*: Calcd for $C_{23}H_{29}ClN_4O_2S$: 460.1699. Found: 460.1701. ^{1}H-NMR (*DMSO-d_6) δ: 8.17—8.11 (2H, m), 7.81 (2H, d, J=9 Hz), 7.52 (2H, d, J=9 Hz), 7.44—7.29 (2H, m), 6.83—6.77 (2H, m), 3.63—3.52 (2H, m), 3.31—3.20 (4H, m), 2.72—2.58 (2H, m), 2.47—2.37 (4H, m), 2.17 (2H, d, J=7 Hz), 1.86—1.75 (2H, m), 1.70—1.55 (1H, m), 1.25—1.05 (2H, m).

1-(4-Pyridinyl)-4-piperidinecarboxaldehyde (14) A solution of oxalyl chloride (1.77 ml, 20 mmol) in dry CH_2Cl_2 (85 ml) was cooled to −78 °C under Ar. To the cooled solution, a solution of dry DMSO (3.25 ml, 46 mmol) in dry CH_2Cl_2 (85 ml) was added dropwise over 20 min. Then, a solution of compound **13** (3.0 g, 15 mmol) prepared by a documented method[26] in dry CH_2Cl_2 (48 ml) and dry DMSO (48 ml) were added dropwise over 20 min. The reaction mixture was stirred at between −65 °C and −60 °C for 1 h, then cooled to −78 °C and Et_3N (8.31 ml, 60 mmol) was added. The reaction mixture was allowed to stand at room temperature, water (200 ml) was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting aldehyde **14** was rather unstable and should be used in the next reaction without purification. MS *m/z*: 190 (M^+). ^{1}H-NMR (*$CDCl_3$) δ: 9.56 (1H, s), 8.16—7.99 (2H, m), 6.82—6.69 (2H, m), 3.83—3.71 (2H, m), 3.02—2.90 (2H, m), 2.61—2.45 (1H, m), 1.90—1.78 (2H, m), 1.52—1.36 (2H, m).

4-[[1-(4-Pyridinyl)-4-piperidinyl]methyl]-1-piperazinecarboxylic Acid 1,1-Dimethylethyl Ester (16) A solution of compound **14** and compound **15** (3.19 g, 17 mmol) in dry CH_2Cl_2 (65 ml) containing AcOH (1.55 ml) was stirred at room temperature for 30 min under Ar, $NaBH(OAc)_3$ (6.61 g, 31 mmol) was added and the mixture was stirred overnight at room temperature. Water (30 ml) was added to the reaction mixture, which was adjusted to pH 9 and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=99 : 1) to give compound **16** (0.59 g, 10%). HR-MS *m/z*: Calcd for $C_{20}H_{32}N_4O_2$: 360.2525. Found: 360.2545. ^{1}H-NMR (*$CDCl_3$) δ: 8.26—8.20 (2H, m), 6.68—6.62 (2H, m), 3.92—3.82 (2H, m), 3.46—3.37 (4H, m), 2.90—2.77 (2H, m), 2.40—2.31 (4H, m), 2.20 (2H, d, J=7 Hz), 1.90—1.68 (3H, m), 1.46 (9H, s), 1.30—1.18 (2H, m).

1-[[1-(4-Pyridinyl)-4-piperidinyl]methyl]piperazine Mono(trifluoroacetate) (17) Anisole (2.23 ml) and TFA (17.2 ml) were added to the compound **16** (3.21 g, 8.9 mmol) at cooling with ice bath and the mixture was stirred overnight at room temperature under Ar. Diethyl ether (200 ml) was added to the reaction mixture and vigorous stirring followed. After standing, the supernatant was removed by decantation and another 200 ml portion of diethyl ether was added; this procedure was repeated three times. Diethyl ether (200 ml) was added to the residue and the mixture was divided into fine particles, which were filtered to give compound **17** (3.24 g, 97%). ^{1}H-NMR (*DMSO-d_6) δ: 8.30—8.18 (2H, m), 7.25—7.17 (2H, m), 4.29—4.18 (2H, m), 4.00—3.35 (4H, m), 3.35—3.09 (6H, m), 2.50—2.40 (2H, m), 2.12—1.98 (1H, m), 1.93—1.82 (2H, m), 1.23—1.06 (2H, m).

1-[[(1*E*)-2-(4-Chlorophenyl)ethenyl]sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (6) Et_3N (0.09 ml, 0.65 mmol) and compound **7** (15.6 mg, 0.06 mmol) were added to a suspension in CH_2Cl_2 (1.0 ml) of compound **17** (47 mg, 0.12 mmol). The mixture was stirred overnight at room temperature under Ar. Water (2 ml) was added to the reaction mixture, the mixture was rendered alkaline with 1 N sodium hydroxide solution and was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=95 : 5—90 : 10) to give compound **6** (13 mg, 47%). HR-MS *m/z*: Calcd for $C_{23}H_{29}ClN_4O_2S$: 460.1699. Found: 460.1709. ^{1}H-NMR (*$CDCl_3$) δ: 8.26—8.17 (2H, m), 7.47—7.37 (5H, m), 6.73—6.62 (3H, m), 3.93—3.80 (2H, m), 3.30—3.16 (4H, m), 2.89—2.75 (2H, m), 2.60—2.47 (4H, m), 2.24 (2H, d, J=7 Hz), 1.89—1.65 (3H, m), 1.30—1.13 (2H, m).

1-([1,1′-Biphenyl]-4-ylsulfonyl)-4-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazine (19a) Using 4-biphenylsulfonyl chloride **18a** (20 mg, 0.08 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19a** (15 mg, 41%). HR-MS *m/z*: Calcd for $C_{27}H_{32}N_4O_2S$: 476.2246. Found: 476.2241. ^{1}H-NMR (*$CDCl_3$) δ: 8.25—8.18 (2H, m), 7.83 (2H, d, J=9 Hz), 7.74 (2H, d, J=9 Hz), 7.66—7.58 (2H, m), 7.56—7.40 (3H, m), 6.65—6.57 (2H, m), 3.88—3.76 (2H, m), 3.16—3.02 (4H, m), 2.86—2.71 (2H, m), 2.60—2.47 (4H, m), 2.21 (2H, d, J=7 Hz), 1.85—1.59 (3H, m), 1.30—1.08 (2H, m).

1-(2-Naphthalenylsulfonyl)-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-piperazine (19b) Using 2-naphthalenesulfonyl chloride **18b** (20 mg, 0.08 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19b** (24 mg, 61%). HR-MS *m/z*: Calcd for $C_{25}H_{30}N_4O_2S$: 450.2089. Found: 450.2099. ^{1}H-NMR (*$CDCl_3$) δ: 8.36—8.32 (1H, m), 8.20—8.11 (2H, m), 8.04—7.92 (3H, m), 7.76 (1H, dd, J=2,9 Hz), 7.72—7.60 (2H, m), 6.69—6.62 (2H, m), 3.93—3.82 (2H, m), 3.16—3.04 (4H, m), 2.98—2.78 (2H, m), 2.55—2.44 (4H, m), 2.19 (2H, d, J=7 Hz), 1.86—1.63 (3H, m), 1.29—1.04 (2H, m).

1-(2-Benzofuranylsulfonyl)-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-piperazine (19c) Using 2-benzofuransulfonyl chloride **18c** (20 mg, 0.09 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19c** (25 mg, 62%). HR-MS *m/z*: Calcd for $C_{23}H_{28}N_4O_3S$: 440.1882. Found: 440.1886. ^{1}H-NMR (*$CDCl_3$) δ: 8.25—8.14 (2H, m), 7.75—7.66 (1H, m), 7.61—7.33 (4H, m), 6.77—6.66 (2H, m), 4.00—3.88 (2H, m), 3.38—3.23 (4H, m), 3.05—2.90 (2H, m), 2.59—2.42 (4H, m), 2.22 (2H, d, J=7 Hz), 1.93—1.71 (3H, m), 1.31—1.10 (2H, m).

1-(Benzo[*b*]thien-2-ylsulfonyl)-4-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazine (19d) Using 2-benzo[*b*]thiophenesulfonyl chloride **18d** (10 mg, 0.04 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19d** (24 mg, 12%). HR-MS *m/z*: Calcd for $C_{23}H_{28}N_4O_2S_2$: 456.1653. Found: 456.1637. ^{1}H-NMR (*$CDCl_3$) δ: 8.22—8.16 (2H, m), 7.95—7.86 (2H, m), 7.80 (1H, s), 7.56—7.46 (2H, m), 6.75—6.68 (2H, m), 4.00—3.92 (2H, m), 3.25—3.13 (4H, m), 3.06—2.95 (2H, m), 2.60—2.50 (4H, m), 2.23 (2H, d, J=7 Hz), 1.93—1.72 (3H, m), 1.28—1.10 (2H, m).

1-(2-Methylbenzothiazol-6-ylsulfonyl)-4-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazine (19e) Using 2-methyl-6-benzothiazolesulfonyl chloride **18e** (10 mg, 0.04 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19e** (8 mg, 42%). HR-MS *m/z*: Calcd for $C_{23}H_{29}N_5O_2S_2$: 471.1762. Found: 471.1743. ^{1}H-NMR (*$CDCl_3$) δ: 8.31—8.13 (3H, m), 8.07 (1H, d, J=9 Hz), 7.82 (1H, dd, J=2,9 Hz), 6.66—6.53 (2H, m), 3.88—3.71 (2H, m), 3.14—2.96 (4H, m), 2.92 (3H, s), 2.85—2.68 (2H, m), 2.61—2.39 (4H, m), 2.19 (2H, d, J=7 Hz), 1.90—1.55 (3H, m), 1.31—1.03 (2H, m).

1-[(6-Chloro-2-naphthalenyl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazine (19f) Using 6-chloro-2-naphthalenesulfonyl chloride **18f** (30 mg, 0.12 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19f** (7 mg, 13%). HR-MS *m/z*: Calcd for $C_{25}H_{29}ClN_4O_2S$: 484.1699. Found: 484.1706. ^{1}H-NMR (*$CDCl_3$) δ: 8.32—8.29 (1H, m), 8.22—8.16 (2H, m), 8.01—7.86 (3H, m), 7.77 (1H, dd, J=2,9 Hz), 7.58 (1H, dd, J=2,9 Hz), 6.73—6.65 (2H, m), 3.97—3.84 (2H, m), 3.16—2.88 (6H, m), 2.56—2.43 (4H, m), 2.19 (2H, d, J=7 Hz), 1.90—1.67 (3H, m), 1.25—1.06 (2H, m).

1-[(6-Bromo-2-naphthalenyl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazine (19g) Using 6-bromo-2-naphthalenesulfonyl chloride **18g** (20 mg, 0.07 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19g** (13 mg, 38%). HR-MS *m/z*: Calcd for $C_{25}H_{29}BrN_4O_2S$: 528.1194. Found: 528.1177. ^{1}H-NMR (*$CDCl_3$) δ: 8.32—8.28 (1H, m), 8.23—8.18 (2H, m), 8.11 (1H, d, J=2 Hz), 7.90 (1H, d, J=9 Hz), 7.85 (1H, d, J=9 Hz), 7.78 (1H, dd, J=2,9 Hz), 7.71 (1H, dd, J=2,9 Hz), 6.62—6.57 (2H, m), 3.88—3.74 (2H, m), 3.18—2.99 (4H, m), 2.88—2.70 (2H, m), 2.59—2.42 (4H, m), 2.18 (2H, d, J=7 Hz), 1.81—1.57 (3H, m), 1.35—1.04 (2H, m).

1-[(5-Fluorobenzo[*b*]thien-2-yl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (19h) Using 5-fluoro-2-benzo[*b*]thiophensulfonyl chloride **18h** (10 mg, 0.04 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19h** (15 mg, 82%). HR-MS *m/z*: Calcd for $C_{23}H_{27}FN_4O_2S_2$: 474.1559. Found: 474.1553. ^{1}H-NMR (*DMSO-d_6) δ: 8.21 (1H, dd, J=5,8 Hz), 8.14—8.08 (2H, m), 8.04 (1H, s), 7.94—7.87 (1H, m), 7.51 (1H, dt, J=3,9 Hz), 6.91—6.83 (2H, m), 4.03—3.87 (2H, m), 3.14—2.97 (4H, m), 2.95—2.78 (2H, m), 2.57—2.49 (4H, m), 2.15 (2H, d, J=7 Hz), 1.85—1.62 (3H, m), 1.12—0.93 (2H, m).

1-[(6-Chlorobenzo[*b*]thien-2-yl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (19i) Using 6-chloro-2-benzo[*b*]thiophensulfonyl chloride **18i** (10 mg, 0.04 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19i** (2 mg, 8%). HR-MS *m/z*: Calcd for $C_{23}H_{27}ClN_4O_2S_2$: 490.1264. Found: 490.1272. ^{1}H-NMR

(*$CDCl_3$) δ: 8.25—8.17 (2H, m), 7.90—7.80 (2H, m), 7.76 (1H, s), 7.48—7.42 (1H, m), 6.67—6.59 (2H, m), 3.90—3.78 (2H, m), 3.23—3.11 (4H, m), 2.85—2.74 (2H, m), 2.60—2.48 (4H, m), 2.21 (2H, d, J=7 Hz), 1.85—1.53 (3H, m), 1.30—1.09 (2H, m).

1-[(6-Methoxybenzo[*b*]thien-2-yl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (19j) Using 6-methoxy-2-benzo[*b*]thiophenesulfonyl chloride **18j** (10 mg, 0.04 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19j** (2 mg, 11%). HR-MS *m/z*: Calcd for $C_{24}H_{30}N_4O_3S_2$: 486.1759. Found: 486.1734. ^{1}H-NMR (*$CDCl_3$) δ: 8.24—8.18 (2H, m), 7.77 (1H, d, J=9 Hz), 7.71 (1H, s), 7.29 (1H, d, J=2 Hz), 7.09 (1H, dd, J=2,9 Hz), 6.65—6.59 (2H, m), 3.91 (3H, s), 3.89—3.78 (2H, m), 3.24—3.06 (4H, m), 2.85—2.72 (2H, m), 2.58—2.44 (4H, m), 2.21 (2H, d, J=7 Hz), 1.85—1.56 (3H, m), 1.35—1.08 (2H, m).

1-[(3-Nitrobenzo[*b*]thien-2-yl)sulfonyl]-4-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (19k) Using 3-nitro-2-benzo[*b*]thiophenesulfonyl chloride **18k** (20 mg, 0.07 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19k** (16mg, 44%). ^{1}H-NMR (*$CDCl_3$) δ: 8.48—8.40 (1H, m), 8.38—8.17 (2H, m), 7.60—7.22 (3H, m), 6.74—6.64 (2H, m), 4.00—3.85 (2H, m), 3.60—3.44 (4H, m), 2.98—2.82 (2H, m), 2.75—2.61 (4H, m), 2.31 (2H, d, J=7 Hz), 1.97—1.50 (3H, m), 1.40—1.16 (2H, m).

1-[[1-(4-Pyridinyl)-4-piperidinyl]methyl]-4-[[3-(trifluoromethyl)-benzo[*b*]thien-2-yl]sulfonyl]piperazine (19l) Using 3-(trifluoromethyl)-2-benzo[*b*]thiophenesulfonyl chloride **18l** (10 mg, 0.03 mmol), synthesis was performed by the synthetic method of compound **6** to give compound **19l** (4 mg, 23%). HR-MS *m/z*: Calcd for $C_{24}H_{27}F_3N_4O_2S_2$: 524.1527. Found: 524.1524. ^{1}H-NMR (*$CDCl_3$) δ: 8.25—8.17 (2H, m), 8.14—8.07 (1H, m), 7.93—7.86 (1H, m), 7.62—7.53 (2H, m), 6.71—6.63 (2H, m), 3.95—3.84 (2H, m), 3.47—3.35 (4H, m), 2.94—2.80 (2H, m), 2.60—2.49 (4H, m), 2.24 (2H, d, J=7 Hz), 1.91—1.67 (3H, m), 1.35—1.12 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-(phenylmethyl)-2-piperazinecarboxylic Acid Ethyl Ester (21) Et_3N (6.2 ml, 45 mmol) was added to a solution in CH_2Cl_2 (70 ml) of compound **20** (3.7 g, 15 mmol) prepared by a documented method.[27] To this was added a solution of compound **18f** (4.3 g, 16 mmol) in CH_2Cl_2 (40 ml) under cooling with ice. After stirring the reaction mixture overnight at room temperature, water (50 ml) was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; hexane : ethyl acetate (AcOEt)=90 : 10—80 : 20) to give compound **21** (6.4g, 85%). ^{1}H-NMR (*$CDCl_3$) δ: 8.29 (1H, s), 7.94—7.87 (3H, m), 7.78—7.73 (1H, m), 7.61—7.55 (1H, m), 7.33—7.18 (5H, m), 4.27—4.11 (2H, m), 3.88 (1H, d, J=13 Hz), 3.61 (1H, d, J=13 Hz), 3.57—3.47 (1H, m), 3.42—3.36 (1H, m), 3.26—3.08 (3H, m), 2.98—2.88 (1H, m), 2.52—2.43 (1H, m), 1.30 (3H, t, J=7 Hz).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-2-piperazinecarboxylic Acid Ethyl Ester (22) To a solution in dichloroethane (70 ml) of compound **21** (6.4 g, 14 mmol), 1-chloroethyl chloroformate (3.7 ml, 34 mmol) was added and the mixture was heated under reflux for 24 h and concentrated under reduced pressure. MeOH (60 ml) was added to the residue and the reaction mixture was heated under reflux for 2 h. This mixture was concentrated under reduced pressure and the residue was neutralized with 1 N sodium hydroxide solution and extracted with AcOEt. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; hexane : AcOEt=67 : 33 and AcOEt : Et3N=99.9 : 0.1) to give compound **22** (4.1 g, 79%). ^{1}H-NMR ($CDCl_3$) δ: 8.32 (1H, s), 7.96—7.88 (3H, m), 7.80—7.75 (1H, m), 7.58 (1H, dd, J=2,9 Hz), 4.25—4.15 (2H, m), 3.79—3.72 (1H, m), 3.58 (1H, dd, J=3,9 Hz), 3.47—3.39 (1H, m), 3.16—3.06 (1H, m), 2.96—2.63 (3H, m), 1.32—1.25 (3H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]-2-piperazinecarboxylic Acid Ethyl Ester (23a) A crude product **14** obtained by Swern oxidation using compound **13** (2.0 g, 10 mmol) was suspended in dry CH_2Cl_2 (20 ml). To the suspension, a solution in dry CH_2Cl_2 (30 ml) of compound **22** (2.0 g, 5.2 mmol) and AcOH (1.0 ml) were added in that order. After stirring the reaction mixture at room temperature for 30 min under Ar, $NaBH(OAc)_3$ (2.2 g, 10 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into water (50 ml), adjusted to pH 9 and was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=98 : 2—90 : 10) to yield compound **23a** (2.6 g, 45%). HR-MS *m/z*: Calcd for $C_{28}H_{33}ClN_4O_4S$: 556.1911. Found: 556.1867. ^{1}H-NMR ($CDCl_3$) *δ: 8.31 (1H, s), 8.26—8.15 (2H, m), 7.98—7.88 (3H, m), 7.80—7.74 (1H, m), 7.63—7.56 (1H, m), 6.63—6.56 (2H, m), 4.25—4.10 (2H, m), 3.85—3.76 (2H, m), 3.63—3.52 (1H, m), 3.37—3.18 (3H, m), 3.07—2.99 (1H, m), 2.94—2.84 (1H, m), 2.82—2.70 (2H, m), 2.62—2.46 (2H, m), 2.37—2.27 (1H, m), 1.80—1.54 (3H, m), 1.34—1.23 (3H, m), 1.20—1.03 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]-2-piperazinemethanol (23b) A solution in CH_2Cl_2 (3 ml) of compound **23a** (9 mg, 0.016 mmol) was cooled to −78 °C. To the cooled solution, 24 ml of diisobutyl aluminum hydride (as 1.5 M toluene solution) was added dropwise. The reaction mixture was stirred to room temperature, saturated ammonium chloride was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=95 : 5) to give compound **23b** (3 mg, 30%). ^{1}H-NMR ($CDCl_3$) *δ: 8.31 (1H, s), 8.20—8.16 (2H, m), 7.97—7.88 (3H, m), 7.80—7.74 (1H, m), 7.62—7.55 (1H, m), 6.68—6.62 (2H, m), 3.95—3.79 (3H, m), 3.66—3.55 (1H, m), 3.36—3.30 (2H, m), 3.06—2.78 (5H, m), 2.65—2.40 (3H, m), 2.25—2.14 (1H, m), 1.89—1.70 (3H, m), 1.30—1.10 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-2-piperazinecarboxylic acid (23c) To a solution in MeOH (4 ml) of compound **23a** (240 mg, 0.43 mmol), 2 N of sodium hydroxide solution (0.86 ml) was added and the mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in water (20 ml) and the mixture rendered acidic with AcOH. The supernatant was removed by decantation and the residue was dissolved in MeOH, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was crystallized with diethyl ether to yield compound **23c** (219 mg, 96%). HR-MS *m/z*: Calcd for $C_{26}H_{29}ClN_4O_4S$: 528.1598. Found: 528.1543. ^{1}H-NMR (DMSO-d_6) *δ: 8.51 (1H, s), 8.34—8.02 (5H, m), 7.87—7.68 (2H, m), 6.82—6.68 (2H, m), 3.95—3.74 (2H, m), 3.57—2.20 (11H, m), 1.78—1.52 (3H, m), 1.07—0.82 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-2-piperazinecarboxamide (23d) To a solution in dry dimethylformamide (0.5 ml) of compound **23c** (50 mg, 0.09 mmol), 4-dimethylaminopyridine (in a catalytic amount) and carbonyl diimidazole (17 mg, 0.1 mmol) were added in that order and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 27% aqueous ammonia (1 ml) and stirred at room temperature for 2 h. The reaction mixture was extracted with AcOEt and the organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was crystallized with diethyl ether to give compound **23d** (21 mg, 42%). HR-MS *m/z*: Calcd for $C_{26}H_{30}ClN_5O_3S$: 527.1758. Found: 527.1730. ^{1}H-NMR ($CDCl_3$) *δ: 8.32 (1H, s), 8.28—8.17 (2H, m), 8.00—7.89 (3H, m), 7.85—7.75 (1H, m), 7.67—7.57 (1H, m), 6.65—6.56 (2H, m), 6.33—6.25 (1H, m), 5.39—5.32 (1H, m), 3.91—3.75 (2H, m), 3.75—3.65 (1H, m), 3.65—3.52 (1H, m), 3.14—2.99 (2H, m), 2.87—2.62 (4H, m), 2.46—2.31 (2H, m), 2.29—2.16 (1H, m), 1.91—1.53 (3H, m), 1.32—1.04 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-*N*,*N*-dimethyl-1-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-2-piperazinecarboxamide (23e) To a solution in dry dimethylformamide (0.5 ml) of compound **23c** (50 mg, 0.09 mmol), 4-dimethylaminopyridine (in a catalytic amount) and carbonyl diimidazole (17 mg, 0.1 mmol) were added in that order and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 50% dimethylamine solution (1 ml) and stirred at room temperature for 2 h. The reaction mixture was extracted with AcOEt and the organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was crystallized with diethyl ether to give compound **23e** (21 mg, 40%). HR-MS *m/z*: Calcd for $C_{28}H_{34}ClN_5O_3S$: 555.2070. Found: 555.2068. ^{1}H-NMR ($CDCl_3$) *δ: 8.29 (1H, s), 8.31—8.03 (2H, m), 8.03—7.82 (3H, m), 7.82—7.69 (1H, m), 7.57 (1H, dd, J=2,9 Hz), 6.74—6.50 (2H, m), 3.95—3.75 (2H, m), 3.65 (2H, d, J=11 Hz), 3.60—3.43 (1H, m), 3.28—2.40 (6H, m), 3.15 (3H, s), 2.94 (3H, s), 2.26 (1H, dd, J=9,12 Hz), 2.12—1.97 (1H, m), 1.87 (1H, d, J=13 Hz), 1.80—1.55 (2H, m), 1.35—1.02 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-β-oxo-1-[[1-(4-pyridinyl)-4-piperidinyl]methyl]-2-piperazinepropanoic Acid Ethyl Ester (23f) To a solution in dry dimethylformamide (0.5 ml) of compound **23c** (50 mg, 9.4 mmol), 4-dimethylaminopyridine (in a catalytic amount) and carbonyl diimidazole (17 mg, 0.1 mmol) were added in that order and the mixture was stirred at room temperature for 2 h. To the stirred mixture, a solution prepared by stirring potassium ethyl malonate (40 mg, 0.23 mmol), magnesium chloride (27 mg, 0.29 mmol) and Et_3N (33 μl, 0.23 mmol) in dry acetonitrile

(0.5 ml) for 2 h was added and the resulting mixture was stirred at room temperature for 2 h, then at 40—60 °C for 3 h. To the reaction mixture, 1 N HCl was added until a pH of 2 was reached. After stirring for 10 min, the mixture was neutralized with saturated sodium hydrogen carbonate and was extracted with AcOEt. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure to give compound **23f** (40 mg, 76%). ^{1}H-NMR ($CDCl_3$) *δ: 8.37—8.27 (1H, m), 8.26—8.15 (2H, m), 8.00—7.92 (3H, m), 7.81—7.71 (1H, m), 7.64—7.53 (1H, m), 6.66—6.53 (2H, m), 4.26—4.10 (2H, m), 3.90—3.34 (5H, m), 3.33—1.94 (10H, m), 1.90—1.57 (3H, m), 1.35—0.94 (5H, m).

2-Acetyl-4-[(6-chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]methyl]piperazine (23g) A solution in 1 N HCl (1 ml) of compound **23f** (35 mg, 0.06 mmol) was stirred at 60—70 °C for 2 h. The reaction mixture was rendered alkaline and was extracted with AcOEt. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure to yield compound **23g** (31 mg, 99%). HR-MS *m*/*z*: Calcd for $C_{27}H_{31}ClN_4O_3S$: 526.1805. Found: 526.1843. ^{1}H-NMR ($CDCl_3$) *δ: 8.38—8.14 (3H, m), 8.00—7.84 (3H, m), 7.81—7.69 (1H, m), 7.64—7.54 (1H, m), 6.66—6.51 (2H, m), 3.89—3.24 (2H, m), 3.38—2.92 (6H, m), 2.84—2.67 (2H, m), 2.50—2.11 (3H, m), 2.18 (3H, s), 1.89—1.56 (3H, m), 1.36—1.00 (2H, m).

4-[*N*-[2-(*tert*-Butoxycarbonylamino)ethyl]aminomethyl]-1-(4-pyridyl)-piperidine (24) and 4-[*N*-[2-(*tert*-Butoxycarbonylamino)ethyl]aminomethyl]-1-(4-pyridyl)piperidine Boron Complex (25) [Unpurified][28] A crude product obtained from compound **14** (3.0 g, 15.7 mmol) by Swern oxidation was suspended in dry CH_2Cl_2 (13 ml). To the suspension, *N*-(*tert*-butoxycarbonyl)-1,2-diaminoethane (0.54 g, 3.2 mmol) and AcOH (0.31 ml) were added in that order. After stirring the resulting mixture at room temperature for 30 min under Ar, $NaBH(OAc)_3$ (1.33 g, 6.3 mmol) was added and the mixture was stirred overnight at room temperature. Water (10 ml) was added to the reaction mixture, the mixture was adjusted to pH 9 with 1 N sodium hydroxide solution, and was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated at reduced pressure. Compound **24** (0.25 g, 23%) was obtained by silica gel column chromatography of the residue (eluents; CH_2Cl_2 : MeOH=99 : 1) together with unpurified **25** (0.62 g, 40%).

Compound **24**: ^{1}H-NMR ($CDCl_3$) δ: 8.24—8.18 (2H, m), 6.68—6.62 (2H, m), 5.03—4.98 (1H, br), 3.95—3.83 (2H, m), 3.29—3.12 (2H, m), 2.90—2.78 (2H, m), 2.73 (2H, t, *J*=6 Hz), 2.53 (2H, d, *J*=7 Hz), 1.97—1.65 (3H, m), 1.45 (9H, s), 1.33—1.16 (2H, m).

Compound **25**: ^{1}H-NMR ($CDCl_3$) δ: 8.22—8.14 (2H, m), 6.73—6.64 (2H, m), 4.93—4.78 (1H, br), 4.20—3.92 (2H, m), 3.29—3.12 (2H, m), 3.12—2.98 (2H, m), 2.73 (2H, t, *J*=6 Hz), 2.54 (2H, d, *J*=7 Hz), 2.03 (6H, s), 1.99—1.72 (3H, m), 1.45 (9H, s), 1.33—1.15 (2H, m).

Compound **25**: ^{11}B-NMR ($CDCl_3$) δ: −18.9 (br).

2-Bromo-*N*-[2-(*tert*-butoxycarbonylamino)ethyl]-*N*-[[1-(4-pyridinyl)-4-piperidinyl]methyl] Acetamide Boron Complex (27) [Unpurified][28] Et_3N (0.28 ml, 2.0 mmol) was added to a solution in dry CH_2Cl_2 (5 ml) of a portion of compound **25** (0.6 g, 1.25 mmol). To the mixture, a solution of bromoacetyl chloride (0.31 g, 2.0 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise under cooling with ice water and the mixture was stirred at room temperature for 2 h under Ar. Ice water (10 ml) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was isolated by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=99 : 1) to give compound **27** (0.61 g, 81%). ^{1}H-NMR (*$CDCl_3$) δ: 8.26—8.15 (2H, m), 6.75—6.65 (2H, m), 4.95—4.73 (1H, m), 4.18—3.84 (4H, m), 3.56—3.45 (2H, m), 3.37—3.21 (4H, m), 3.13—2.99 (2H, m), 2.25—2.10 (1H, m), 2.04 (6H, s), 1.92—1.77 (2H, m), 1.44 (9H, s), 1.39—1.19 (2H, m). ^{11}B-NMR ($CDCl_3$) δ: −18.8 (br).

***N*-(2-Aminoethyl)-2-bromo-*N*-[[1-(4-pyridinyl)-4-piperidinyl]methyl] Acetamide Tri(trifluoroacetate) (28)** To a portion of compound **27** (0.54 g, 0.89 mmol), anisole (0.29 g) and TFA (2.3 ml) were added under cooling with ice water and the mixture was stirred at room temperature for 1.5 h under Ar. Diethyl ether (50 ml) was added and the reaction mixture was stirred vigorously. After standing, the supernatant was removed by decantation and another 50 ml of diethyl ether was added; this procedure was repeated three times. Diethyl ether (50 ml) was added to the residue and the mixture was divided into fine particles, which were filtered to give compound **28** (0.58 g, 93%). ^{1}H-NMR (*DMSO-d_6) δ: 8.26—8.16 (2H, m), 7.23—7.13 (2H, m), 4.55—4.35 (2H, m), 4.34—4.18 (2H, m), 3.60—3.45 (2H, m), 3.29—2.87 (6H, m), 2.15—1.96 (1H, m), 1.78—1.63 (2H, m), 1.32—1.04 (2H, m).

1-[[1-(4-Pyridinyl)-4-piperidinyl]methyl]piperazinone (29) To a solution in dry dimethylformamide (20 ml) of a portion of compound **28** (0.46 g, 0.65 mmol), Et_3N (1.43 ml, 10 mmol) was added under cooling with ice water; the mixture was stirred at the same temperature for 1 h, then at room temperature for another 1 h. The solvent was evaporated under reduced pressure and the residue was used in the next reaction without purification. HR-MS *m*/*z*: Calcd for $C_{15}H_{22}N_4O$: 274.1793. Found: 274.1767. ^{1}H-NMR (*$CDCl_3$) δ: 8.24—8.20 (2H, m), 6.67—6.63 (2H, m), 3.96—3.86 (2H, m), 3.55 (2H, s), 3.40—3.26 (4H, m), 3.14—3.06 (2H, m), 2.92—2.81 (2H, m), 2.10—1.94 (1H, m), 1.90—1.72 (2H, m), 1.42—1.24 (2H, m).

4-[(6-Chloro-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone (30a) The crude product of compound **29** was suspended in dry CH_2Cl_2 (34 ml), to the suspension, Et_3N (0.72 ml, 5.2 mmol) and a solution of 6-chloro-2-naphthalensulfonyl chloride (245 mg, 0.94 mmol) in dry CH_2Cl_2 (5 ml) were added in that order, and the mixture was stirred overnight at room temperature under Ar. Water (30 ml) was added to the reaction mixture, which was adjusted to pH 9 with 1 N sodium hydroxide solution and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over dry Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents; CH_2Cl_2 : MeOH=99 : 1—95 : 5) to give compound **30a** (130 mg, 28%). HR-MS *m*/*z*: Calcd for $C_{25}H_{27}ClN_4O_3S$: 498.1492. Found: 498.1494. ^{1}H-NMR (*$CDCl_3$) δ: 8.29 (1H, s), 8.20—8.11 (2H, m), 7.91—7.83 (3H, m), 7.73 (1H, dd, *J*=2,9 Hz), 7.55 (1H, dd, *J*=2,9 Hz), 6.57—6.50 (2H, m), 3.78—3.68 (4H, m), 3.40—3.30 (4H, m), 3.17 (2H, d, *J*=8 Hz), 2.74—2.60 (2H, m), 1.90—1.70 (1H, m), 1.60—1.48 (2H, m), 1.28—1.07 (2H, m).

4-[(6-Bromo-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone (30b) Using 6-bromo-2-naphthalenesulfonyl chloride (22.3 mg, 0.07 mmol), synthesis was performed by the synthetic method of compound **30a** to give compound **30b** (12 mg, 32%). HR-MS *m*/*z*: Calcd for $C_{25}H_{27}BrN_4O_3S$: 542.0987. Found: 542.1022. ^{1}H-NMR (*$CDCl_3$) δ: 8.37—8.34 (1H, m), 8.26—8.19 (2H, m), 8.16—8.11 (1H, m), 7.93 (1H, d, *J*=9 Hz), 7.88 (1H, d, *J*=9 Hz), 7.80 (1H, dd, *J*=2,9 Hz), 7.75 (1H, dd, *J*=2,9 Hz), 6.66—6.59 (2H, m), 3.89—3.77 (2H, m), 3.80 (2H, s), 3.49—3.38 (4H, m), 3.25 (2H, d, *J*=7 Hz), 2.84—2.72 (2H, m), 1.99—1.83 (1H, m), 1.68—1.57 (2H, m), 1.35—1.17 (2H, m).

4-[(6-Methyl-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone (30c) Using 6-methyl-2-naphthalenesulfonyl chloride (41 mg, 0.17 mmol), synthesis was performed by the synthetic method of compound **30a** to yield compound **30c** (14 mg, 17%). HR-MS *m*/*z*: Calcd for $C_{26}H_{30}N_4O_3S$: 478.2038. Found: 478.2031. ^{1}H-NMR (*$CDCl_3$) δ: 8.35—8.32 (1H, m), 8.26—8.19 (2H, m), 7.94—7.88 (2H, m), 7.77—7.70 (2H, m), 7.54—7.48 (1H, m), 6.65—6.58 (2H, m), 3.86—3.76 (4H, m), 3.48—3.37 (4H, m), 3.27—3.21 (2H, m), 2.83—2.70 (2H, m), 2.59 (3H, s), 1.97—1.81 (1H, m), 1.66—1.56 (2H, m), 1.29—1.16 (2H, m).

4-[(6-Hydroxy-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone (30d) Using 6-hydroxy-2-naphthalenesulfonyl chloride (20 mg, 0.08 mmol), synthesis was performed by the synthetic method of compound **30a** to yield compound **30d** (7.4 mg, 19%). HR-MS *m*/*z*: Calcd for $C_{25}H_{28}N_4O_4S$: 480.1831. Found: 480.1834. ^{1}H-NMR (*$CDCl_3$) δ: 8.30—8.24 (1H, m), 8.13—8.05 (2H, m), 7.92—7.86 (1H, m), 7.84—7.78 (1H, m), 7.72—7.65 (1H, m), 7.32—7.20 (2H, m), 6.70—6.61 (2H, m), 3.93—3.74 (4H, m), 3.49—3.36 (4H, m), 3.28—3.19 (2H, m), 2.85—2.61 (2H, m), 1.96—1.82 (1H, m), 1.60—1.50 (2H, m), 1.35—1.10 (2H, m).

4-[(6-Cyano-2-naphthalenyl)sulfonyl]-1-[[1-(4-pyridinyl)-4-piperidinyl]-methyl]piperazinone (30e) Using 6-cyano-2-naphthalenesulfonyl chloride (43 mg, 0.15 mmol), synthesis was performed by the synthetic method of compound **30a** to yield compound **30e** (11 mg, 15%). HR-MS *m*/*z*: Calcd for $C_{26}H_{27}N_5O_3S$: 489.1834. Found: 489.1868. ^{1}H-NMR (*$CDCl_3$) δ: 8.45—8.43 (1H, m), 8.37—8.34 (1H, m), 8.26—8.21 (2H, m), 8.14—8.09 (2H, m), 7.94—7.88 (1H, m), 7.84—7.79 (1H, m), 6.65—6.60 (2H, m), 3.92—3.79 (4H, m), 3.54—3.40 (4H, m), 3.30—3.24 (2H, m), 2.88—2.75 (2H, m), 2.00—1.50 (3H, m), 1.37—1.16 (2H, m).

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