Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors[1,2] III. Effect of Ring Opening of Piperazinone Moiety on Inhibition

Hidemitsu Nishida,* Yutaka Miyazaki, Takafumi Mukaihira, Hiroyasu Shimada, Kazuhiro Suzuki, Fumihiko Saitoh, Masashi Mizuno, Tomokazu Matsusue, Atsushi Okamoto, Yoshitaka Hosaka, Miwa Matsumoto, Shuhei Ohnishi, and Hidenori Mochizuki

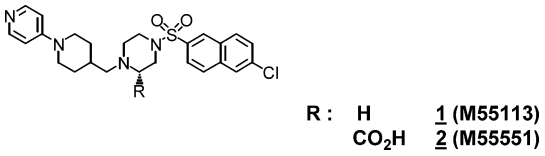
Discovery Research Center, Mochida Pharmaceutical Co., Ltd.; 722 Jimba-aza-uenohara, Gotemba, Shizuoka 412–8524, Japan. Received November 5, 2003; accepted February 2, 2004

Compounds containing an ethylenediamine structure in place of the piperazine ring of M55113 (1) and M55551 (2) were synthesized to investigate the effects of a piperazine moiety and evaluated for activity as factor Xa (FXa) inhibitors. Most such compounds, however, exhibited lower activity (1/10—1/100) than that of M55113 and M55551 as FXa inhibitors.

Key words factor Xa inhibitor; 1-arylsulfonyl-3-piperazinone; M55551; structure–activity relationship

Recently, direct inhibition of factor Xa (FXa), which links the intrinsic and extrinsic mechanisms in the blood coagulation cascade,[3—7] has emerged as an attractive strategy for the discovery of novel antithrombotic agents.[8—11] In previous papers,[1,2] we reported the synthesis and biological activity of new compounds in a series of 1-arylsulfonyl-3-piperazinone derivatives, and through this investigation M55113 (**1**) (IC_{50}: 0.06 μM) and M55551 (**2**) (IC_{50}: 0.006 μM) were confirmed to be somewhat favorable as FXa inhibitors.

In order to investigate the role played a piperazine moiety in these compounds, we focused on comparison of the activity of compounds which have an ethylenediamine structure in place of the piperazine ring of M55113 and M55551. The present paper concerns the synthesis of such compounds together with their inhibition of FXa.



Chemistry

Synthesis of ethylenediamine derivative **9** corresponding to M55113 and M55551 was achieved as shown in Chart 1. Compound **6**, prepared by the reaction of *N-tert*-butoxycarbonyl-1,2-diaminoethane hydrochloride (**4**) with 6-chloro-2-naphthalenesulfonyl chloride (**5**) under basic conditions, was deprotected with trifluoroacetic acid (TFA) to yield compound **7**. The condensation of **7** with 1-(4-pyridinyl)-4-piperidinecarboxaldehyde (**8**) prepared by Swern oxidation[12] of the corresponding methanol yielded the desired ethylenediamine derivative **9** in the presence of reducing agent.[13]

The route of synthesis of compound **13**, which contains an amide group on the ethylenediamine moiety of compound **9**, is shown in Chart 2. Compound **11**, prepared by the reaction

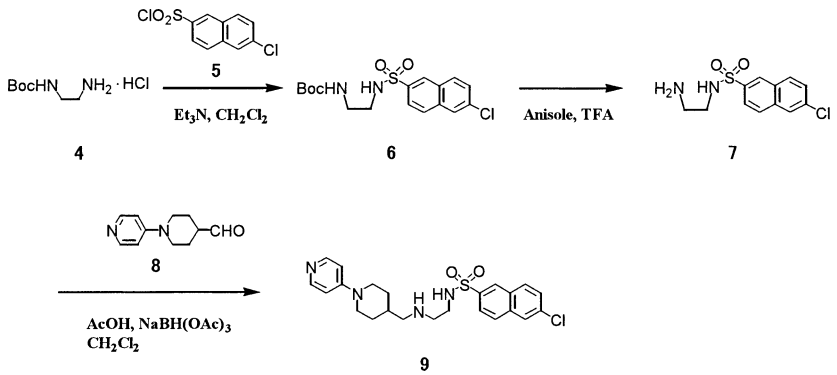


Chart 1. Synthesis of Ethylenediamine Derivative **9**

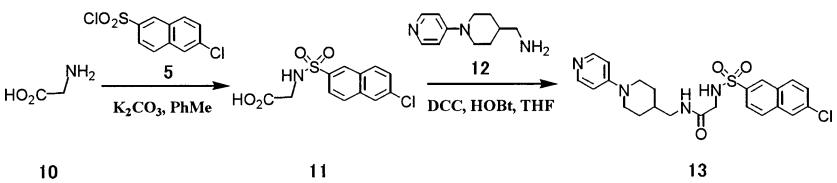


Chart 2. Synthesis of Glycine Derivative **13**

* To whom correspondence should be addressed. e-mail: hnishida@mochida.co.jp

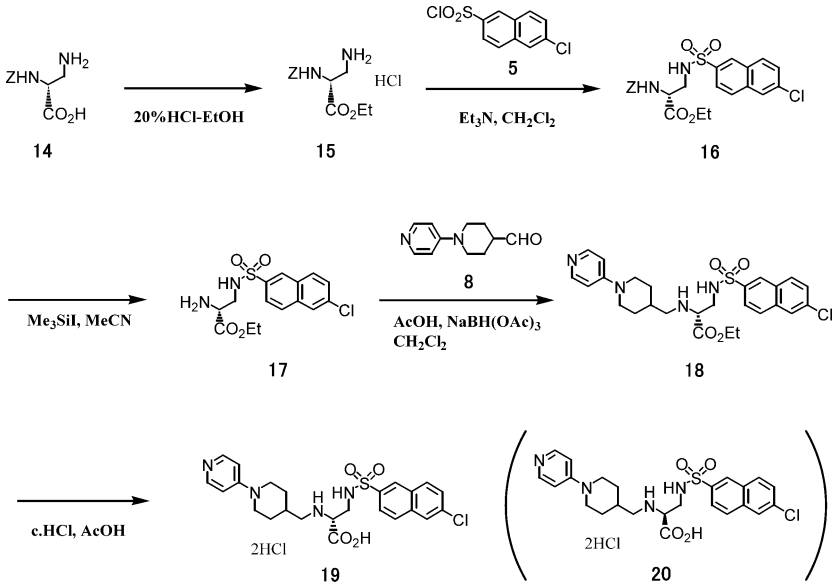


Chart 3. Synthesis of 3-Aminoalanine Derivative **19** and **20**

of glycine (**10**) with sulfonyl chloride **5** under basic conditions, was treated with 1-(4-pyridinyl)-4-aminomethylpiperidine (**12**), which was obtained by Mitsunobu reaction of the corresponding methanol, in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole hydrate (HOBt) to yield the amide **13**.

Synthesis of (*R*)-3-aminoalanine derivative **19** was accomplished according to the route shown in Chart 3. Sulfonylation of ethyl ester **15** derived from (*R*)-3-amino-2-(benzyloxycarbonylamino)propionic acid (**14**) with sulfonyl chloride **5** in CH_2Cl_2 in the presence of Et_3N resulted in smooth formation of the sulfonamide **16**. Deprotection of **16** with trimethylsilyl iodide (TMSI) in MeCN followed by reductive condensation with **8** afforded compound **18**. Hydrolysis of **18** in hydrochloric acid and acetic acid yielded the desired 3-aminoalanine derivative **19**. Starting from (*S*)-3-amino-2-(benzyloxycarbonylamino)propionic acid, the method used to synthesize compound **19** was repeated to obtain compound **20**. Throughout the synthesis described above, no racemization was observed.

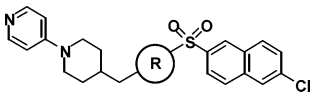
Results and Discussion

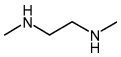
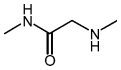
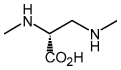
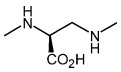
The FXa inhibitory activities of these compounds were measured by a method similar to that described in the preceding paper,[1,2] and are listed in the Table 1 as IC_{50} values. The following conclusions are derived from these data, though they are still provisional.

First, compared with the activity of compound **1** (M55113), those of compounds **9** and **13** are quite low. Similarly, the activity of compound **19** was shown to be 1/100 that of compound **2** (M55551). A similar difference in activity was observed between **3** and **20**. These data suggest that rigidity of the central part of the molecules tested in this series may be an important factor for significantly FXa inhibitory activity.

Second, when a carbonyl group or a carboxyl group was introduced into the ethylenediamine skeleton (**13**, **19**), activity clearly increased with activities of **13** and **19** four and five times that of **9**, respectively. These findings suggest that carbonyl and carboxyl groups favor interaction with FXa protein.

Table 1. FXa Inhibitory Activity of Compounds **1**, **2**, **3**, **9**, **13**, **19** and **20**



Compound	R	IC_{50} (μM)
1 (M55113)		0.060
2 (M55551)		0.006
3		0.079
9		3.27
13		0.80
19		0.60
20		1.76

Finally, regarding the stereochemistry of carboxylic substitution, it is clear that (*R*)-isomers have higher activity than (*S*)-isomers in both the piperazine **2** and ethylenediamine **19** skeleton.

These findings may be useful in guiding molecular design in this field.

Experimental

Melting points (mp) were determined by using METTLER FP82 hotstage melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with JEOL JNM-EX270 FT-NMR or JEOL JNM-

LA300 in $CDCl_3$, dimethyl sulfoxide-d_6 (DMSO-d_6) or CD_3OD using tetramethylsilane as the internal reference. High-resolution mass spectra (HR-MS) were obtained using JEOL JMS-GCMATE. Infrared absorption spectra (IR) were run using HORIBA FT-720 FT-IR. High performance liquid chromatographies (HPLC) were conducted by using Shimadzu LC-10A. Optical rotations were measured with JASCO DIP-1000 digital polarimeter.

Measurement of Factor Xa 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 enzyme and substrate were used: human factor Xa (Enzyme Research Laboratories, Inc., 0.019 U/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}.

***N*-(2-*tert*-Butoxycarbonylaminoethyl)-6-chloro-2-naphthalenesulfonamide (6)** To a solution of *N*-(*tert*-butoxycarbonyl)ethylenediamine hydrochloride (**4**) (310 mg, 1.92 mmol) in dry CH_2Cl_2 (15 ml), 6-chloro-2-naphthalenesulfonyl chloride (**5**) (500 mg, 1.92 mmol) and Et_3N (0.27 ml, 2.30 mmol) were added and the mixture was stirred overnight at room temperature. Water (30 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 and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was crystallized from hexane and Et_2O to yield compound **6** (738 mg, quant.) as colorless powder, mp 121—122 °C.

HR-MS *m/z*: Calcd for $C_{17}H_{21}{}^{35}ClN_2O_4S$: 384.0910, Found: 384.0913. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.42—7.54 (6H, m, naphthyl), 5.50—5.35 (1H, br, NH), 4.90—4.75 (1H, br, NH), 3.29—3.19 (2H, m, BocNHC$\underline{H}_2$), 3.15—3.06 (2H, m, C$\underline{H}_2$NHSO$_2$), 1.41 (9H, s, ^{t}BuOCO(Boc)). IR (film) cm^{-1}: 3383, 3267, 1682, 1508, 1319, 1132.

***N*-(2-Aminoethyl)-6-chloro-2-naphthalenesulfonamide (7)** Anisole (0.49 ml) and TFA (3.8 ml) were added to compound **6** (0.75 g, 1.95 mmol) at cooling with ice bath and the mixture was stirred for 2 h at room temperature. Et_2O (5 ml) was added to the reaction mixture. After vigorous stirring and followed standing, the supernatant was removed by decantation and another 5 ml portion of Et_2O was added. This procedure was repeated three times. The residue was crystallized from CH_2Cl_2 to give compound **7** (0.21 g, 38%) as colorless powder, mp 147—148 °C.

HR-MS *m/z*: Calcd for $C_{12}H_{13}{}^{35}ClN_2O_2S$: 284.0386, Found: 284.0395. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.45—7.54 (6H, m, naphthyl), 3.07—2.95 (2H, m, C$\underline{H}_2$NHSO$_2$), 3.15—3.06 (2H, m, NH$_2$C$\underline{H}_2$). IR (film) cm^{-1}: 3257, 1473, 1317, 1149, 1080, 474.

6-Chloro-*N*-[2-[[1-(4-pyridinyl)-4-piperidinyl]methyl]aminoethyl]-2-naphthalenesulfonamide (9) A solution of 1-(4-pyridinyl)-4-piperidinecarbaldehyde (**8**) (150 mg, 0.79 mmol) and compound **7** (200 mg, 0.70 mmol) in dry CH_2Cl_2 (3 ml) containing AcOH (0.07 ml) was stirred at room temperature for 30 min under Ar. To the solution, NaBH(OAc)$_3$ (298 mg, 1.4 mmol) was added and the mixture was stirred overnight at room temperature. Water (5 ml) was added to the reaction mixture, which was adjusted to pH 9 with 1 N NaOH and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents: CH_2Cl_2 : MeOH = 95 : 5—80 : 20) to give compound **9** (148 mg, 46%) as colorless powder, mp 150—153 °C.

HR-MS *m/z*: Calcd for $C_{23}H_{27}{}^{35}ClN_4O_2S$: 458.1543, Found: 458.1535. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.43—6.57 (10H, m, naphthyl and pyridinyl), 3.86—3.74 (2H, m, C^{2,6}-$\underline{H}$ of piperidine), 3.12—3.01 (2H, m, C$\underline{H}_2$NHSO$_2$), 2.83—2.62 (2H, m, NHC$\underline{H}_2$CH$_2$NHSO$_2$), 2.83—2.62 (2H, m, C^{2,6}-$\underline{H}$ of piperidine), 2.34 (2H, d, J=6.8 Hz, piperidine-C$\underline{H}_2$NH), 1.77—1.03 (5H, m, C^{3,4,5}-$\underline{H}$ of piperidine). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 154.64 (C^4 of pyridine), 149.69 (C^{2,6} of pyridine), 137.15—123.47 (10C, naphthyl), 108.21 (C^{3,5} of pyridine), 54.66 (piperidine-C$\underline{H}_2$NH), 48.24 (NHC$\underline{H}_2$CH$_2$NHSO$_2$), 46.35 (C^{2,6} of piperidine), 42.32 (NHCH$_2$C$\underline{H}_2$NHSO$_2$), 36.11 (C^4 of piperidine), 29.36 (C^{3,5} of piperidine). IR (film) cm^{-1}: 1599, 1325, 1157, 1080, 694.

***N*-[(6-Chloro-2-naphthalenyl)sulfonyl]glycine (11)** To a solution of glycine (**10**) (276 mg, 3.68 mmol) and K_2CO_3 (508 mg, 3.68 mmol) in H_2O (8 ml), 6-chloro-2-naphthalenesulfonyl chloride (**5**) (800 mg, 3.06 mmol) and PhMe (1.0 ml) were added and the mixture was refluxed for 90 min. The reaction mixture was adjusted to pH 1 with 3 N HCl and the mixture was extracted with EtOAc. The organic layer was washed with water and brine and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure to yield compound **11** (820 mg, 89%) as colorless powder, mp 174—176 °C.

^{1}H-NMR (270 MHz, DMSO-d_6) δ: 12.71—12.52 (1H, br, CO$_2\underline{H}$), 8.50—7.65 (7H, m, naphthyl and N$\underline{H}$), 3.65 (2H, d, J=5.9 Hz, NHC$\underline{H}_2$CO$_2$H). IR (film) cm^{-1}: 1702, 1324, 1153, 1108, 889, 827.

2-[(6-Chloro-2-naphthalenyl)sulfonyl]amino-*N*-[(1-(4-pyridinyl)-4-piperidylmethyl]acetamide (13) A solution in CH_2Cl_2 (27 ml) of 1-(4-pyridinyl)-4-aminomethylpiperidine (**12**) (350 mg, 1.83 mmol) was added dropwise to a solution in THF (27 ml) of compound **11** (548 mg, 1.83 mmol). To the mixture, DCC (415 mg, 2.01 mmol) and HOBt (308 mg, 2.01 mmol) were added and the mixture was stirred at room temperature for 17 h under Ar. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents: CH_2Cl_2 : MeOH = 85 : 15—80 : 20) to give compound **13** (469 mg, 54%) as colorless powder, mp 215—217 °C.

HR-MS *m/z*: Calcd for $C_{23}H_{25}{}^{35}ClN_4O_3S$: 472.1336. Found: 472.1342. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.50—6.67 (12H, m, naphthyl, pyridinyl and N$\underline{H}$), 3.83—3.71 (2H, m, C^{2,6}-$\underline{H}$ of piperidine), 3.50 (2H, br, COC$\underline{H}_2$NH), 2.28—2.78 (2H, m, piperidine-C$\underline{H}_2$NH), 2.70—2.54 (2H, m, C^{2,6}-$\underline{H}$ of piperidine), 1.56—0.83 (5H, m, C^{3,4,5}-$\underline{H}$ of piperidine). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 167.36 (HN$\underline{C}$O), 154.15 (C^4 of pyridine), 149.70 (C^{2,6} of pyridine), 137.89—123.80 (10C, naphthyl), 108.26 (C^{3,5} of pyridine), 45.35 (C^{2,6} of piperidine), 45.08 (CO$\underline{C}$H$_2$NH), 43.74 (piperidine-$\underline{C}$H$_2$NH), 35.47 (C^4 of piperidine), 28.40 (C^{3,5} of piperidine). IR (KBr) cm^{-1}: 3153, 1664, 1604, 1522, 1327, 1230, 1151.

Ethyl (*R*)-3-Amino-2-(benzyloxycarbonylamino)propionate Hydrochloride (15) To a 20% (w/w) HCl–EtOH solution (1.5 l) under cooling ice bath, (*R*)-3-amino-2-(benzyloxycarbonylamino)propionic acid (**14**) (68.0 g, 0.28 mol) was added and the mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was crystallized with EtOAc and EtOH to yield compound **15** (75.0 g, 87%) as white powder, mp 136—137 °C.

HR-MS *m/z*: Calcd for $C_{13}H_{18}N_2O_4$: 266.1266, Found: 266.1277. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.27 (2H, br s, N$\underline{H}_2$), 7.92 (1H, d, J=8.3 Hz, N$\underline{H}$), 7.45—7.30 (5H, m, phenyl), 5.07 (2H, s, PhC$\underline{H}_2$O), 4.45—4.35 (1H, m, C$\underline{H}$), 4.13 (2H, q, J=7.1 Hz, CO$_2$C$\underline{H}_2$CH$_3$), 3.21 (1H, dd, J=4.6, 13.0 Hz, NH$_2$C$\underline{H}_2$), 3.06 (1H, dd, J=9.5, 13.0 Hz, NH$_2$C$\underline{H}_2$), 1.19 (3H, t, J=7.1 Hz, CO$_2$CH$_2$C$\underline{H}_3$). IR (KBr) cm^{-1}: 1720, 1527, 1461, 1305, 1261, 1224, 1025. $[\alpha]_D^{26}$ = +37.1° (c=1.000, MeOH).

Ethyl (*R*)-2-(Benzyloxycarbonyl)amino-3-[(6-chloro-2-naphthalenylsulfonyl)amino]propionate (16) To a solution of 6-chloro-2-naphthalenesulfonyl chloride (**5**) (52.5 g, 0.20 mol) in dry CH_2Cl_2 (1130 ml), compound **15** (60.9 g, 0.20 mmol) and Et_3N (56.1 ml, 0.4 mol) were added and the mixture was stirred at room temperature for three days under Ar. Water (700 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 and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was crystallized with hexane and Et_2O to yield compound **16** (97.7 g, 97%) as white powder, mp 96—97 °C.

HR-MS *m/z*: Calcd for $C_{23}H_{23}{}^{35}ClN_2O_6S$: 490.0965, Found: 490.0946. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.41—7.26 (11H, m, naphthyl and phenyl), 5.72—5.62 (1H, m, N$\underline{H}$), 5.35—5.24 (1H, m, N$\underline{H}$), 5.12—4.97 (2H, m, PhC$\underline{H}_2$O), 4.42—4.33 (1H, m, C$\underline{H}$CH$_2$), 4.26—4.08 (2H, m, CO$_2$C$\underline{H}_2$CH$_3$), 3.53—3.36 (2H, m, CHC$\underline{H}_2$NHSO$_2$), 1.23 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C$\underline{H}_3$). IR (KBr) cm^{-1}: 3261, 1730, 1713, 1527, 1336, 1157. $[\alpha]_D^{27}$ = +10.7° (c=1.000, MeOH).

Ethyl (*R*)-2-Amino-3-[(6-chloro-2-naphthalenylsulfonyl)amino]propionate (17) To a solution in MeCN (460 ml) of compound **16** (28.2 g, 57.4 mmol), TMSI (20.4 ml, 143.6 mmol) was added under cooling with ice. After stirring the mixture at the same temperature for 20 min, 2 N HCl (220 ml) was added and the reaction mixture was washed with hexane. The mixture was neutralized by sat. aq. $NaHCO_3$ and was extracted with EtOAc. The organic layer was washed with water and brine and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure to give compound **17** (20.0 g, 98%) as brown amorphous.

HR-MS *m/z*: Calcd for $C_{15}H_{17}{}^{35}ClN_2O_4S$: 356.0597, Found: 356.0564. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.44—7.53 (6H, m, naphthyl), 4.20—4.07 (2H, m, CO$_2$C$\underline{H}_2$CH$_3$), 3.61 (1H, dd, J=4.6, 7.2 Hz, C$\underline{H}$CH$_2$), 3.36 (1H, dd, J=4.6, 12.8 Hz, CHC$\underline{H}_2$NHSO$_2$), 3.07 (1H, dd, J=7.2, 12.8 Hz, CHC$\underline{H}_2$NHSO$_2$), 1.23 (3H, t, J=7.2 Hz, CO$_2$CH$_2$C$\underline{H}_3$). IR (KBr) cm^{-1}: 3224, 1734, 1620, 1329, 1155, 1078. $[\alpha]_D^{26}$ = −22.6° (c=1.000, MeOH).

Ethyl (*R*)-3-[(6-Chloro-2-naphthalenyl)sulfonyl]amino-2-[1-(4-pyridinyl)-4-piperidinylmethylamino]propionate (18) A solution of 1-

(4-pyridinyl)-4-piperidinecarbaldehyde (**8**) (2.63 g, 14 mmol) and compound **17** (5.0 g, 14 mmol) in dry CH_2Cl_2 (117 ml) containing AcOH (1.67 ml) were stirred at room temperature for 50 min under Ar. To the reaction mixture, $NaBH(OAc)_3$ (7.42 g, 35 mmol) was added and the mixture was stirred overnight at room temperature. Water (200 ml) was added to the reaction mixture, which was adjusted to pH 7 by sat. aq. $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried over dry Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluents: CH_2Cl_2 : MeOH=95 : 5—80 : 20) to give compound **18** (3.96 g, 53%) as colorless amorphous.

HR-MS *m/z*: Calcd for $C_{26}H_{31}{}^{35}ClN_4O_4S$: 530.1754. Found: 530.1762. ^{1}H-NMR ($CDCl_3$) δ: 8.43—6.61 (10H, m, naphthyl and pyridinyl), 5.40—5.25 (1H, m, NH), 4.20—4.03 (2H, m, $CO_2CH_2CH_3$), 3.90—3.79 (2H, m, $C^{2,6}$-H of piperidine), 3.32 (1H, dd, *J*=4.6, 11.9 Hz, $CHCH_2NHSO_2$), 3.25 (1H, dd, *J*=4.6, 7.1 Hz, $CHCH_2NHSO_2$), 2.99 (1H, dd, *J*=7.1, 11.9 Hz, $CHCH_2NHSO_2$), 2.85—2.72 (2H, m, $C^{2,6}$-H of piperidine), 2.47 (1H, dd, *J*=6.6, 11.3 Hz, piperidine-CH_2NH), 2.20 (1H, dd, *J*=6.6, 11.3 Hz, piperidine-CH_2NH), 1.82—1.08 (5H, m, $C^{3,4,5}$-H of piperidine), 1.22 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 172.43 ($CO_2CH_2CH_3$), 154.66 (C^4 of pyridine), 150.06 ($C^{2,6}$ of pyridine), 137.20—123.51 (10C, naphthyl), 108.32 ($C^{3,5}$ of pyridine), 61.50 ($CO_2CH_2CH_3$), 60.49 ($CHCH_2NHSO_2$), 53.54 (piperidine-CH_2NH), 46.17 (C^2 or C^6 of piperidine), 46.13 (C^2 or C^6 of piperidine), 44.43 ($CHCH_2NHSO_2$), 36.45 (C^4 of piperidine), 29.45 (C^3 or C^5 of piperidine), 29.34 (C^3 or C^5 of piperidine), 14.16 ($CO_2CH_2CH_3$). IR (KBr) cm^{-1}: 2929, 1732, 1599, 1329, 1157, 1078. $[\alpha]_D^{27}$=+15.3° (*c*=1.000, MeOH).

(*R*)-3-[(6-Chloro-2-naphthalenyl)sulfonyl]amino-2-[1-(4-pyridinyl)-4-piperidinylmethylamino]propionic Acid Dihydrochloride (19) To a solution in AcOH (5.0 ml) of compound **18** (500 mg, 0.94 mmol), c. HCl (5.0 ml) was added and the mixture was heated under reflux for 3.5 h. The reaction mixture was concentrated under reduced pressure to give compound **1**9 (540 mg, quant.) as brown amorphous.

The optical purity of this compound was measured by HPLC [CHIRALPAK™ AD-H (Daicel Chemical Industries, Ltd.); hexane : EtOH : TFA : Et_2NH=70 : 30 : 0.1 : 0.1], and it was found to be 94.1% ee.

^{1}H-NMR (300 MHz, CD_3OD) δ: 8.53—7.16 (10H, m, naphthyl and pyridinyl), 4.40—4.28 (2H, m, $C^{2,6}$-H of piperidine), 4.21—4.14 (1H, m, $CHCH_2NHSO_2$), 3.65—3.01 (6H, dd, $CHCH_2NHSO_2$, $C^{2,6}$-H of piperidine and piperidine-CH_2NH), 2.41—1.34 (5H, m, $C^{3,4,5}$-H of piperidine). ^{13}C-NMR (75 MHz, CD_3OD) δ: 168.71 (CO_2H), 158.20 (C^4 of pyridine), 140.59 ($C^{2,6}$ of pyridine), 138.05—124.60 (10C, naphthyl), 108.73 ($C^{3,5}$ of pyridine), 61.16 ($CHCH_2NHSO_2$), 52.20 (piperidine-CH_2NH), 47.22 ($C^{2,6}$ of piperidine), 42.05 ($CHCH_2NHSO_2$), 34.27 (C^4 of piperidine), 30.20 ($C^{3,5}$ of piperidine). IR (KBr) cm^{-1}: 3435, 3068, 2925, 1741, 1645, 1547, 1331, 1157. $[\alpha]_D^{28}$=+21.2° (*c*=1.000, MeOH).

(*S*)-3-[(6-Chloro-2-naphthalenyl)sulfonyl]amino-2-[1-(4-pyridinyl)-4-piperidinylmethylamino]propionic Acid Dihydrochloride (20) Using (*S*)-3-Amino-2-(benzyloxycarbonylamino)propionic acid, the method of synthesis in above was repeated to yield the title compound as colorless amorphous.

The optical purity of this compound was measured by HPLC [CHIRALPAK™ AD-H (Daicel Chemical Industries, Ltd.); hexane : EtOH : TFA : diethylamine=70 : 30 : 0.1 : 0.1], and it was found to be 98.3% e.e. $[\alpha]_D^{27}$=−21.9° (*c*=1.000, MeOH).

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References and Notes

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