Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors[1—4] V. A Series of New Derivatives Containing a Spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one Scaffold

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We have already reported unique compounds containing a *N*,*O*-spiro acetal structure as an orally active factor Xa (FXa) inhibitor. This time, we described a *N*,*N*-spiro acetal structure as an analogue of the *N*,*O*-spiro acetal structure for an orally active FXa inhibitor. The synthesis of these analogues could be achieved in a similar fashion to the *N*,*O*-spiro acetal synthesis. Consequently, FXa inhibitory activity was increased and more active compounds could be found (M58163: IC_{50}=0.61 nM, M58169: IC_{50}=0.58 nM). Additionally, the absolute configuration could be determined by X-ray crystallography analysis (M58169: (*R*)-config.).

Key words factor Xa inhibitor; *N*,*N*-spiro acetal; M58163; M58169; structure–activity relationship; intramolecular cyclization

Factor Xa (FXa), a trypsin-like serine protease, occupies the central position that links the intrinsic and extrinsic mechanisms in the blood coagulation cascade. FXa is known to activate prothrombin to thrombin. Thrombin has several procoagulant functions, including the activation of platelets, feedback activation of other coagulation factors, and conversion of fibrinogen to insoluble fibrin clots.[6—10] Comparison of hirudin[11—15] (a thrombin inhibitor) and tick anticoagulant peptide[16—22] (a FXa inhibitor) suggests that inhibition of FXa may result in less risk of bleeding, leading to a more favorable safety/efficacy ratio.[23—26] Direct inhibition of FXa has therefore emerged as an attractive strategy for the discovery of novel antithrombotic agents.[27—33]

In a previous paper,[4] we reported the synthesis and evaluation of compounds in a series of spiro[5*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5-one (*N*,*O*-spiro acetal) derivatives. In this paper, we discuss the synthesis and structure–activity relationship of compounds containing *N*,*N*-spiro acetal, which is a spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one scaffold, as an analogue in the central part of the compound (Fig. 1).

According to calculations for *N*,*N*- and *N*,*O*-spiro acetal (MOPAC PM3 calculation),[34] both C–N bonds (C2–N, N–C8a: 1.50 Å) in cyclic *N*,*N*-spiro acetal are longer than C–O bond (C2–O: 1.44 Å, O–C8a: 1.43 Å) in *N*,*O*-spiro acetal, and the bond angle of C–N–C (110.3°) is smaller than that of C–O–C (111.7°), indicating that *N*,*N*-spiro acetal is slightly more bulky than *N*,*O*-spiro acetal (Table 1).

These differences will affect the overall conformation of the compound, and differences in conformation between *N*,*N*-spiro acetal and *N*,*O*-spiro acetal might affect FXa inhibitory activity. In addition, differences in basicity between *N*,*N*-spiro acetal and *N*,*O*-spiro acetal might work on FXa inhibitory activity.

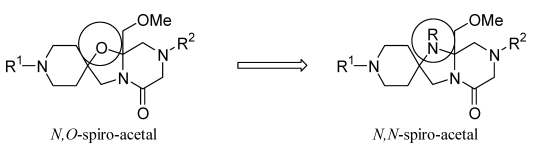

Fig. 1

Chemistry

First, the keto-ester **5**, an acyclic precursor, was prepared as shown in Chart 1.

Ethyl glycinate **1** was converted by ring opening glycidyl methyl ether **2** to the corresponding amino-alcohol. The amino-alcohol was treated with benzyl chloroformate in THF–H_2O in the presence of sodium carbonate with an *N*-protected amino-alcohol **3** obtained in good yield. In the next step, the amino-alcohol **3** was oxidized to the keto-ester **5** by the 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl benzoate **4**–NaClO oxidation method.[35]

Second, the key intermediate **7**, which has the spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one scaffold (*N*,*N*-spiro acetal), was prepared as shown in Chart 2.

When 4-amino-4-aminomethyl-1-benzylpiperidine **6**[36] was allowed to react with keto-ester **5** in toluene, the key intermediate **7** containing a *N*,*N*-spiro acetal structure on the

Table 1. Cyclic *N*,*N*-Spiro Acetal *vs.* Cyclic *N*,*O*-Spiro Acetal

X	N(R)	O
Bond length C2–X (Å)	1.50	1.44
Bond length X–C8a (Å)	1.50	1.43
Bond angle C2–X–C8 (°)	110.3	111.7

Calculated by MOPAC PM3.

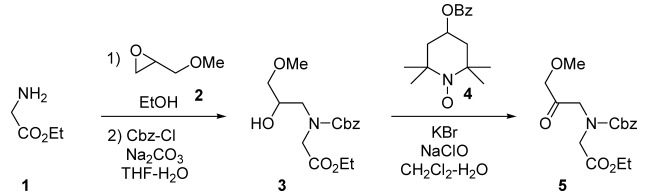

Chart 1. Synthesis of Keto-Ester **5** as an Acyclic Precursor

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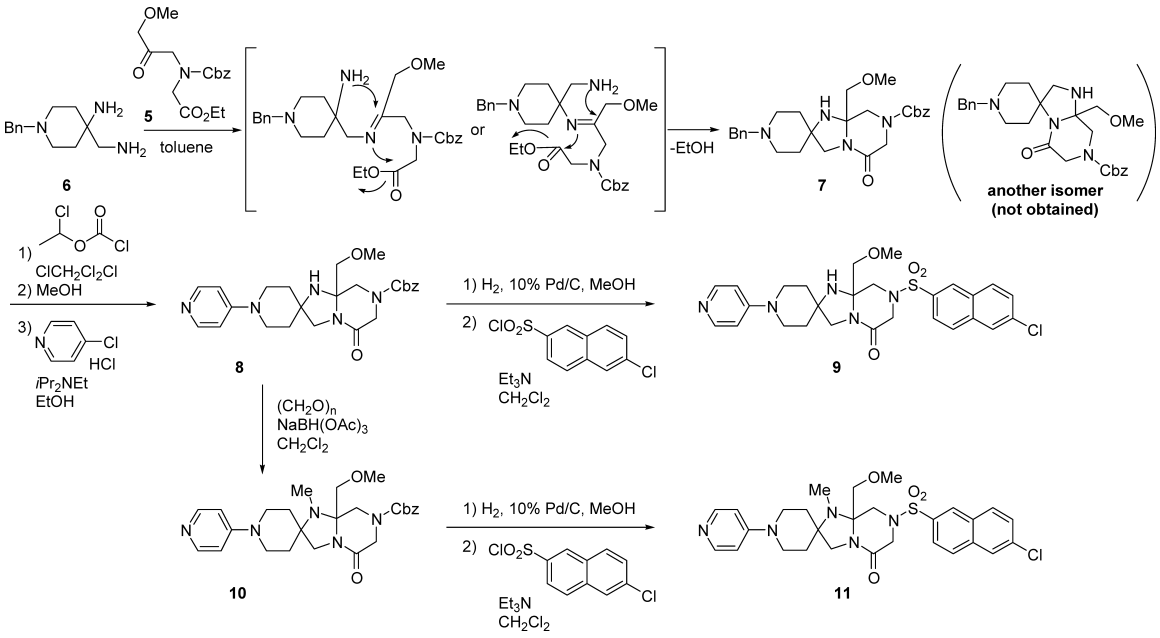


Chart 2. Synthesis of the Key Intermediate **7** and Compounds **9** and **11**

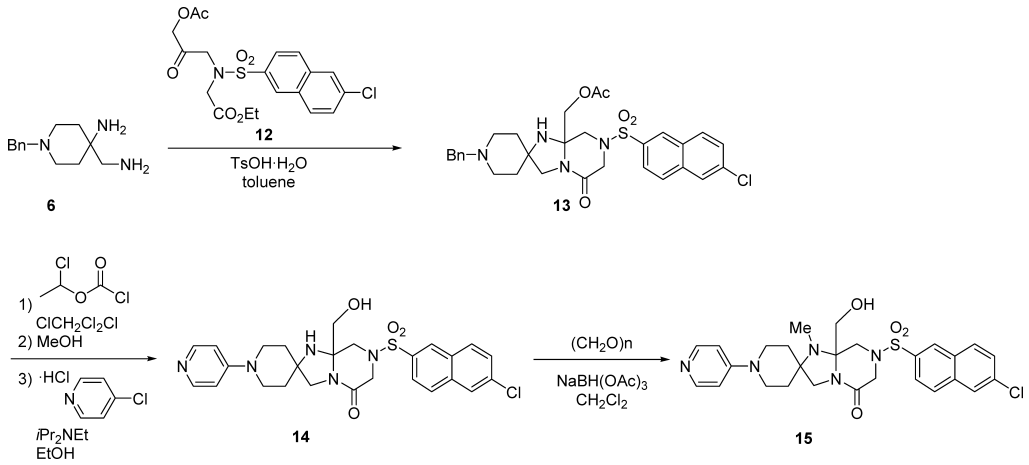


Chart 3. Synthesis of Compounds **14** and **15**

piperazinone ring was obtained as well as *N*,*O*-spiro acetal, which was described in a previous paper.[4] Although two isomers might have been obtained in this reaction, the expected compound was obtained as a single isomer.

The pathway of formation of the *N*,*N*-spiro acetal scaffold from **5** and **6** is illustrated in Chart 2.

In the first step, the imine is formed, and then the cyclic *N*,*N*-spiro acetal can be formed by spontaneous intramolecular nucleophilic attack of the amine toward the imine bond. In the second step, the nitrogen atom attacks the ethyl ester to yield the tricyclic scaffold.

Then benzyl substituent in compound **7** was selectively deprotected with α-chloroethyl chloroformate in the presence of proton sponge® and was coupled with 4-chloropyridine in a sealed tube to afford compound **8**. In the next steps, the carbobenzyloxy group was deprotected by catalytic hydrogenation with Pd/C in 10% HCl–MeOH and was sulfonylated with 6-chloro-2-naphthalenesulfonyl chloride to obtain the expected compound **9**.

Meanwhile, compound **8** was converted to compound **10**, which was methylated on a central nitrogen atom, with parafolmaldehyde and sodium triacetoxyborohydride in CH_2Cl_2. Then deprotection and sulfonylation reactions were carried out to afford compound **11** in a fashion similar to the above reactions.

Additionally, compounds **14** and **15**, which has a hydroxylmethyl moiety as a side-chain, were prepared according to another route of synthesis, as shown in Chart 3.

Another key intermediate **13** was prepared with diamine **6** and the other keto-ester **12**[4] instead of the keto-ester **5** under an acidic condition. Compound **13** was converted by *O*- and *N*-deprotection and pyridine coupling reaction to the expected compound **14** as well as other compounds. *N*-Methylation reaction was then carried out to afford compound **15**.

Meanwhile, non-side-chain compounds were prepared as shown in Charts 4 and 5.

Compound **16**[2] was treated with benzyl chloroformate in CH_2Cl_2 in the presence of Et_3N to obtaine the *N*-protected compound **17**. Then the diethylacetal portion of compound **17** was removed to obtain the desired aldehyde-ester **18**,

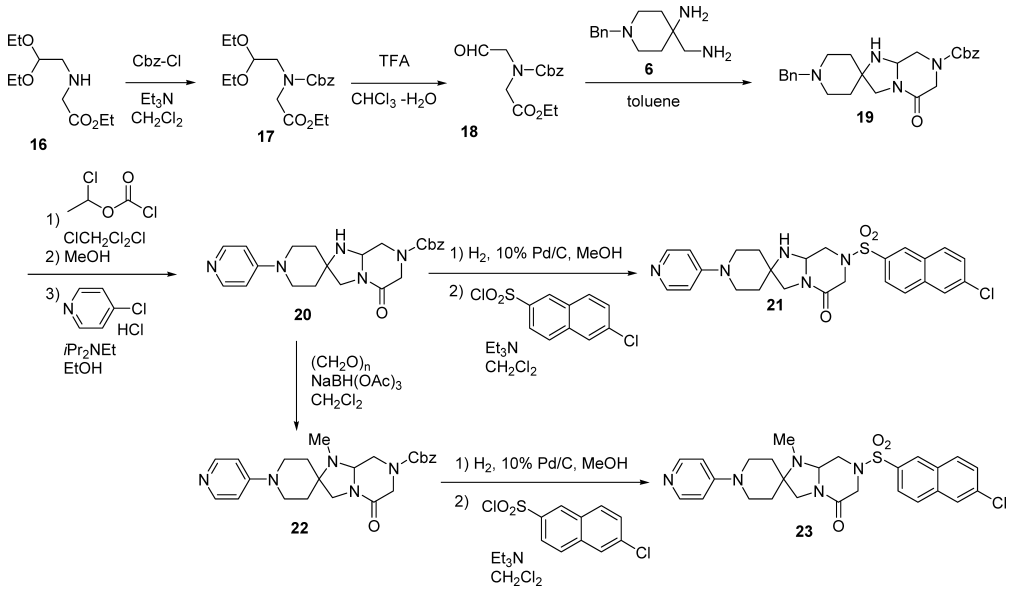


Chart 4. Synthesis of Compounds **21** and **23**

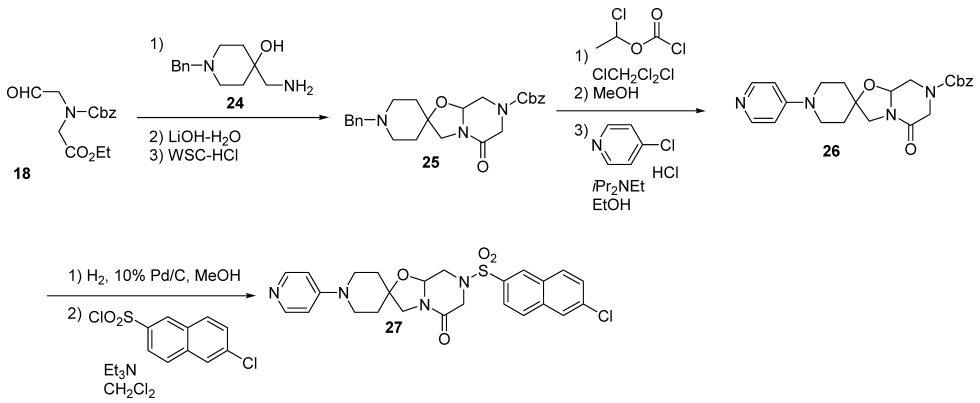


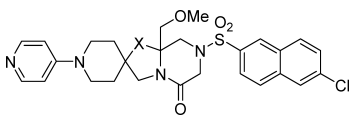
Chart 5. Synthesis of Compound **27**

which was reacted with diamine **6** in toluene to obtain the non-side-chain key intermediate **19**.

Furthermore, deprotection of the *N*-benzyl group, pyridine coupling reaction, central *N*-methylation reaction, deprotection of *N*-Cbz group, and sulfonylation reaction were carried out to obtain compound **21** and **23** in a fashion similar to that shown in Chart 2.

Next, the aldehyde-ester **18** was also reacted with the amino-alcohol **24**[4] to afford the key non-side-chain *N*,*O*-spiro acetal intermediate **25**. Unlike the synthesis of *N*,*N*-spiro acetal compound **19**, the one-pot reaction including the *N*,*O*-spiro acetal formation and intramolecular cyclization reaction didn't proceed. Therefore, ester moiety of *N*,*O*-spiro acetal derived from the amino-alcohol **24** and the aldehyde ester **18** was hydrolyzed with LiOH for conversion to the corresponding carboxy acid. Then the intramolecular cyclization reaction was performed with WSC-HCl to obtain compound **25**. Furthermore, deprotection of the *N*-benzyl group, pyridine coupling reaction, deprotection of *N*-Cbz group, and sulfonylation reaction were carried out to obtain compound **27** in a fashion similar to Charts 2 and 4.

Table 2. Comparison of FXa Inhibitory Activity of Cyclic *N*,*N*- and *N*,*O*-Acetal Compounds



Compound	X	IC_{50} (nM)
9	NH	1.5
11	NMe	1.6
28	O	5.0[4]

Results and Discussion

The FXa inhibitory activities of new compounds with a *N*,*N*-spiro acetal structure synthesized in the present investigation were measured using the same method as described in a previous paper.[4]

The inhibitory activities (IC_{50}) of the new compounds are summarized in Table 2.

Compared with previously tested compound **28** (the *N*,*O*-spiro acetal),[4] compounds **9** and **11** had approximately 3-fold higher activity.

Almost all chemical shifts in ^{1}H-NMR were very similar between imidazo[1,2-*a*]pyrazinone (compounds **9**, **11**) and oxazolo[3,2-*a*]pyrazinone (compound **28**) (Table 3). These findings suggested that the topological surface of *N*,*N*-spiro acetal compounds could also be as suitable as *N*,*O*-spiro acetal compounds for binding with the active site of FXa.

Meanwhile, there were remarkable differences in the ^{13}C-NMR chemical shifts of compounds **9**, **11**, and **28**. More specifically, C2 chemical shifts of compounds **9** and **11** (*N*,*N*-spiro acetal) were 58.34 and 60.63 ppm, respectively, while the C8a chemical shifts of these compounds were 73.36 and 78.71 ppm, respectively. On the one hand, the C2 chemical shifts of compound **28** (*N*,*O*-spiro acetal) was 80.67 ppm and the C8a chemical shift was 92.85 ppm. The *N*,*N*-spiro acetal thus had higher chemical shifts on C2 and C8a than the *N*,*O*-spiro acetal (Table 4).

Since nitrogen is less electronegative than oxygen (Pauling's electronegativity value: N: 3.04 <O: 3.44),[37] this difference might be reflected in the ^{13}C-NMR chemical shifts on C2 and C8a between *N*,*N*-spiro acetal and *N*,*O*-spiro acetal, supporting the calculations described above. This difference could indicate that cyclic *N*,*N*-spiro acetal compounds **9** and **11** had slight differences in overall conformation from *N*,*O*-spiro acetal compound **28**.

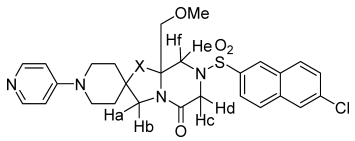
As shown in Fig. 2, it is essential for FXa inhibitory activity that the pyridine ring on the compound is located in the S4 pocket, which consists of Tyr99, Phe174, and Trp215 and that the naphthyl ring enters into the S1 pocket. In addition, the halogen-π interaction between the chlorine atom on the naphthyl ring of the compound and phenyl ring on Tyr228, which exists in the bottom of S1 pocket, is important for this activity.

As mentioned above, the overall conformations of the *N*,*N*-spiro acetal compounds **9** and **11** might differ slightly from that of *N*,*O*-spiro acetal compound **28**. Therefore, in the case of compounds **9** and **11**, the position of the pyridine ring in the S4 pocket and that of the chloronaphthyl ring in the S1 pocket might be more suitable than compound **28**.

This may be the reason why compounds **9** and **11** had approximately 3-fold higher activity than compound **28**. Though the basicity of nitrogen on compounds **9** and **11** might play a role in inhibiting FXa, we think that the contribution ratio concerning the basicity could not be so high. The methylated nitrogen atom in compound **11** ought to be more basic than the non-substituted nitrogen atom in compound **9**. However, there was little difference of the activity in both compounds **9** and **11**. Hence it was thought that the overall conformations could contribute for the activity rather than the basicity of nitrogen atom.

In further investigation, several side-chain effects of *N*,*N*-spiro acetal compounds (**9**, **11**, **14**, **15**, **21**, **23**) were com-

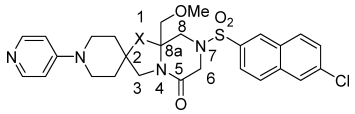
Table 3. ^{1}H-NMR Data of Compounds **9**, **11** and **28** (in $CDCl_3$)



	9 (X=NH) (ppm)	**11** (X=NMe) (ppm)	**28** (X=O) (ppm)
Ha	4.18 (d, 11.7)	4.19 (d, 11.6)	4.23 (d, 11.7)
Hb	2.97 (d, 11.7)	3.22 (d, 11.6)	3.08 (d, 11.7)
Hc	4.35 (d, 16.9)	4.33 (d, 16.7)	4.33 (d, 16.7)
Hd	3.31 (d, 16.9)	3.34 (d, 16.7)	3.33 (d, 16.7)
He	4.18 (d, 11.7)	4.24 (d, 11.4)	4.38 (d, 11.7)
Hf	2.25 (d, 11.7)	2.26 (d, 11.4)	2.32 (d, 11.7)

Coupling constants are given in parentheses in Hz.

Table 4. ^{13}C-NMR Data of *N*,*N*- and *N*,*O*-Spiro Acetal (in $CDCl_3$)



	9 (X=NH) (ppm)	**11** (X=NMe) (ppm)	**28** (X=O) (ppm)
C2	58.34	60.63	80.67
C3	53.13	51.46	52.15
C5	163.28	162.35	162.75
C6	47.65	48.00	47.98
C8	51.46	50.79	49.69
C8a	73.36	78.71	92.85

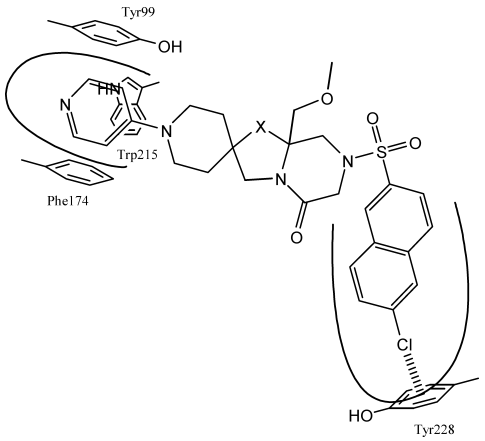
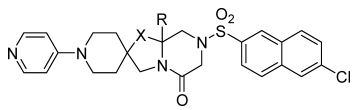


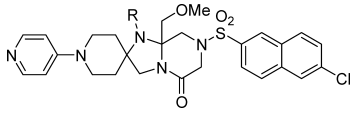
Fig. 2

Table 5. Comparison of Side-Chain Effects



R	Compound (X=NH)	IC_{50} (nM)	Compound (X=NMe)	IC_{50} (nM)	Compound (X=O)	IC_{50} (nM)
CH_2OMe	**9**	1.5	**11**	1.6	**28**	5.0[4]
CH_2OH	**14**	2.4	**15**	1.7	**29**	5.0[4]
H	**21**	5.7	**23**	18.2	**27**	17.2

Table 6. Comparison of Racemate and Both Enantiomers



Compound (R=H)	IC_{50} (nM)	Compound (R=Me)	IC_{50} (nM)
9 (racemate)	1.5	**11** (racemate)	1.6
30 ((+)-form)	43.2	**31** ((+)-form)	10.3
M58163 ((−)-form)	0.61	M58169 ((−)-form)	0.58

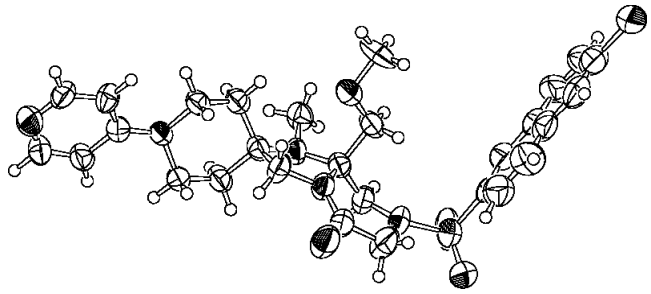


Fig. 3. Ortep Drawing of M58169

pared to the corresponding *N*,*O*-spiro acetal compounds (**28**, **29**, **27**), as shown in Table 5.[4)]

As noted above, because the *N*,*N*-spiro acetal structure was superior to the *N*,*O*-spiro acetal structure for binding with the FXa active site as a general rule, *N*,*N*-spiro acetal compounds had higher activity than *N*,*O*-spiro acetal compounds. However, non-side-chain compounds unfortunately had low activity regardless of *N*,*N*- or *N*,*O*-spiro acetal structure.

Finally, comparison was made of stereoisomers. The activities of stereoisomers obtained by optical resolution with preparative HPLC are summarized in Table 6. The (−)-isomers M58163 and M58169 (IC_{50}: 0.61, 0.58 nM) had higher activity than the (+)-isomers **30** and **31** (IC_{50}: 43.2, 10.3 nM), respectively.

In addition, since a single crystal of M58169 was obtained, determination of the absolute configuration of M58169 was accomplished by X-ray crystallographic structure analysis. The absolute configuration of M58169 could be determined as the (*R*)-isomer (Fig. 3, Table 7).[38—43)]

In conclusion, we have reported novel active FXa inhibitors with an *N*,*N*-spiro acetal structure as an analogue of *N*,*O*-spiro acetal. We found that slight deferences in the *N*,*X*-acetal moiety affected the overall conformation of the compound, and that changes in overall conformation can affect FXa inhibitory activity. Further investigations concerning other scaffolds are going in our laboratory and results will be published in due course.

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) using tetramethylsilane as the internal reference. Mass spectra (MS) were obtained using JEOL JMS-GCMATE or BRUKER Auto FLEX TOF/TOF. Infrared absorption spectra (IR) were run using HORIBA FT-720 FT-IR. High performance liquid chromatographies (HPLC) were conducted by using Shimadzu LC-10A or Waters Deltaprep 4000. Optical rotations were measured with JASCO DIP-1000 digital polarimeter.

Table 7. Crystallographic Data for M58169

	M58169
Chemical formula	$C_{28}H_{32}ClN_5O_4S$
Fw	570.10
Diffractometer	Rigaku AFC7R
Scan type	ω–2θ
Crystal system	Monoclinic
Space group	$P2_1$ (#4)
a (Å)	8.571(1) Å
b (Å)	26.272(2) Å
c (Å)	6.049(1) Å
β (°)	95.97(1)°
V (Å^3)	1354.5(3) (Å^3)
Z	2
ρ_{calc} (g/cm^3)	1.398
μ (cm^{-1})	23.38
T (K)	293(2)
λ (Cu$K\alpha$), (Å)	1.54178
$2\theta_{max}$, deg	120.2
No. obsd rflns (N_o)	4328
No. of params refined (N_v)	353
$R1$[a)] [$I>2\sigma(I)$]	0.059
R_w[b)]	0.166
GOF[c)]	1.17
Flack parameter	0.01(3)

a) $R1=\Sigma(|F_O|-|F_C|)/\Sigma|F_O|$. *b*) $R_w=[\Sigma w(F_O{}^2-F_C{}^2)^2/\Sigma w(F_O{}^2)^2]^{1/2}$. *c*) $GOF=[\Sigma w(|F_O|-|F_C|)^2/(N_o-N_v)]^{1/2}$.

Measurement of Factor Xa Inhibition 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. Enzyme and substrate were used as follows: 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-Hydroxy-3-methoxypropyl)-*N*-[(phenylmethoxy)carbonyl]-glycine Ethyl Ester (3)** Ethyl glycinate (**1**) (19.3 g) was added to glycidyl methyl ether (**2**) (16.5 g) in EtOH (60 ml). After stirring for 6 h at ambient temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in THF (100 ml) and water (100 ml) and sodium carbonate (16 g) was added into the solution. To this solution benzyl chloroformate (21.6 ml) was dropwised at 0 °C, then the reaction mixture was stirred at room temperature over night. Water was added to the reaction mixture and it was extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$ aqueous solution. and brine then was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluant: Hex/AcOEt=1/1) to afford compound **3** (13.5 g, 22% yield) as pale yellow oil. EI-MS *m/z*: 325 (M^+), 280, 252, 251, 218, 207, 190, 107. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.40—7.20 (5H, m), 5.07 (2H, s), 4.48 (1H, d, J=5.1 Hz), 4.09 (2H, q, J=7.2 Hz), 4.07 (2H, s), 3.85—3.75 (1H, m), 3.46 (1H, dd, J=4.6, 14.5 Hz), 3.30—3.22 (2H, m), 3.24 (3H, s), 3.18 (1H, dd, J=7.3, 14.5 Hz), 1.16 (3H, t, J=7.2 Hz).

***N*-(3-Methoxy-2-oxopropyl)-*N*-[(phenylmethoxy)carbonyl]-glycine Ethyl Ester (5)** To a solution of compound **3** (20 g) in CH_2Cl_2 (80 ml) were added aqueous solution of potassium bromide (0.73 g) in H_2O (123 ml) and 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl benzoate free radical (170 mg). Then within 5 °C, alkaline NaClO aqueous solution, which were prepared with 5 wt% NaClO aqueous solution (115 ml), water (115 ml) and sodium hydrogen carbonate (11.5 g), was dropwised into the above mixture. This oxidation reaction ended almost as soon as dropping the NaClO solution. Then the reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with 10% $Na_2S_2O_3$ aqueous solution and brine and was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford compound **5** (19.6 g, 99% yield) as pale yellow oil. EI-MS *m/z*: 323 (M^+), 278, 250, 206, 188, 107. ^{1}H-NMR (300 MHz, DMSO-d_6,

100 °C) δ: 7.40—7.25 (5H, m), 5.07 (2H, s), 4.23 (2H, s), 4.10 (2H, q, J=7.2 Hz), 4.05 (2H, s), 4.03 (2H, s), 3.29 (3H, s), 1.17 (3H, t, J=7.2 Hz).

Tetrahydro-8*a*-(methoxymethyl)-5-oxo-1′-(phenylmethyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (7) Compound **6** (15.4 g) and **5** (19.0 g) were dissolved in toluene (300 ml) and the mixture was refluxed for 2.5 h with Dean–Stark apparatus. After cooling, the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (eluant: Hex/AcOEt=4/1–2/1–1/1) to afford compound **7** (23.9 g, 85% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS m/z (M+H): Calcd for $C_{27}H_{35}N_4O_4S$: 479.2658. Found: 479.2653. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.37—7.17 (10H, m), 5.14 (1H, d, J=12.7 Hz), 5.08 (1H, d, J=12.7 Hz), 4.22 (1H, d, J=13.2 Hz), 4.18 (1H, d, J=17.8 Hz), 3.99 (1H, d, J=11.4 Hz), 3.73 (1H, d, J=17.8 Hz), 3.46 (2H, s), 3.32 (1H, d, J=9.9 Hz), 3.25 (1H, d, J=9.9 Hz), 3.22 (3H, s), 2.94 (1H, s), 2.86 (1H, d, J=11.4 Hz), 2.80 (1H, d, J=13.2 Hz), 2.58—2.45 (2H, m), 2.29—2.17 (2H, m), 1.75—1.59 (2H, m), 1.44—1.38 (2H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.93, 153.52, 138.09, 136.21, 128.13 (2C), 127.78 (2C), 127.47 (2C), 127.26, 126.93 (2C), 126.18, 75.81, 74.60, 66.17, 61.44, 58.36, 57.21, 52.04, 49.90, 49.67, 48.71, 45.86, 37.02, 35.87. IR (film) cm^{-1}: 2914, 2848, 1707, 1662, 1454, 1412, 1232, 1120, 739, 698.

Tetrahydro-8*a*-(methoxymethyl)-5-oxo-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (8) [Step 1]: To a solution of compound **7** (18.9 g) in 1,2-dichloroethane (250 ml) was added 1,8-bis(dimethylamino)naphthalene (10.2 g). Then α-chloroethyl chloroformate (10.7 ml) was dropwised into the above solution at 0 °C. After stirring the reaction mixture at ambient temperature for 1 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in MeOH (250 ml) and the mixture was refluxed for 1 h. After cooling, the solvent was removed under reduced pressure. To the residue was added water (150 ml) and water layer was washed with Et_2O. Then the Et_2O layer was extracted with 1 N HCl and water layer was combined the above water layer which was washed with Et_2O. Then the water layer was alkalified with saturated $NaHCO_3$ aqueous solution to more than pH 10 and the water layer was concentrated *in vacuo*. Then it was extracted with CH_2Cl_2 and organic layer was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/4–CH_2Cl_2/MeOH=19/1) to afford deprotected compound (13.5 g, 88% yield) as pale yellow oil. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.39—7.26 (5H, m), 5.14 (1H, d, J=12.7 Hz), 5.08 (1H, d, J=12.7 Hz), 4.22 (1H, d, J=13.0 Hz), 4.19 (1H, d, J=18.0 Hz), 4.01 (1H, d, J=11.1 Hz), 3.73 (1H, d, J=18.0 Hz), 3.33 (1H, d, J=9.7 Hz), 3.25 (1H, d, J=9.7 Hz), 3.23 (3H, s), 2.96—2.75 (4H, m), 2.63—2.46 (2H, m), 1.66—1.48 (2H, m), 1.35—1.27 (2H, m).

[Step 2]: To a solution of the deprotected compound (12.0 g) which was afforded in Step 1 in EtOH (200 ml) were added 4-chloropyridine hydrochloride (7.0 g) and *i*-Pr_2NEt (26.9 ml). The mixture was stirred at 150—160 °C in a sealed tube for 4 h then it was concentrated *in vacuo*. The resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=4/1–CH_2Cl_2–CH_2Cl_2/MeOH=99/1) to afford compound **8** (7.27 g, 51% yield) as a pale brown amorphous solid. MALDI-TOF-HR-MS m/z (M+H): Calcd for $C_{25}H_{32}N_5O_4$: 466.2454. Found: 466.2478. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 8.12 (2H, dd, J=1.7, 5.0 Hz), 7.42—7.26 (5H, m), 6.73 (2H, dd, J=1.7, 5.0 Hz), 5.15 (1H, d, J=12.7 Hz), 5.09 (1H, d, J=12.7 Hz), 4.24 (1H, d, J=13.2 Hz), 4.21 (1H, d, J=18.0 Hz), 4.05 (1H, d, J=11.1 Hz), 3.76 (1H, d, J=18.0 Hz), 3.50—3.22 (6H, m), 3.24 (3H, s), 2.96 (1H, d, J=11.1 Hz), 2.85 (1H, d, J=13.2 Hz), 2.78 (1H, s), 1.85—1.65 (2H, m), 1.56—1.46 (2H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.97, 153.69, 153.54, 149.33 (2C), 136.20, 127.78 (2C), 127.27, 126.95 (2C), 107.86 (2C), 76.03, 74.69, 66.19, 58.38, 57.33, 52.29, 48.71, 45.89, 42.99, 42.66, 35.91, 34.62. IR (film) cm^{-1}: 2914, 2848, 1705, 1660, 1595, 1412, 1232, 1120, 987, 733.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (9) [Step 1]: To a solution of compound **8** (1.0 g) in MeOH (20 ml) was added 10% Pd/C (190 mg) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature over night. Then Pd/C was removed by Celite® filtration and the filtrate was concentrated *in vacuo* to obtain a deprotected compound (0.7 g, 98% yield) as a pale yellow amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.25 (2H, dd, J=1.5, 5.1 Hz), 6.67 (2H, dd, J=1.5, 5.1 Hz), 4.32 (1H, d, J=11.7 Hz), 3.67 (1H, d, J=9.4 Hz), 3.62 (1H, d, J=17.8 Hz), 3.55—3.27 (4H, m), 3.48 (1H, d, J=17.8 Hz), 3.41 (3H, s), 3.40 (1H, d, J=9.4 Hz), 3.36 (1H, d, J=12.7 Hz), 2.99 (1H, d, J=11.7 Hz), 2.57 (1H, d, J=12.7 Hz), 1.93—1.73 (2H, m), 1.66—1.53 (2H, m).

[Step 2]: To a solution of the deprotected compound (140 mg) in CH_2Cl_2 (10 ml) which was afforded in Step 1, was added 6-chloronaphthalene-2-sulfonyl chloride (121 mg) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then saturated $NaHCO_3$ aqueous solution and a small amount of 1 N NaOH were added to the reaction mixture at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/3–CH_2Cl_2) to afford compound **9** (148 mg, 63% yield) as a pale brown amorphous solid. MALDI-TOF-HR-MS m/z (M+H): Calcd for $C_{27}H_{30}{}^{35}ClN_5O_4S$: 556.1785. Found: 556.1781. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.34 (1H, s), 8.22 (2H, d, J=6.4 Hz), 8.00—7.90 (3H, m), 7.78 (1H, dd, J=1.5, 8.8 Hz), 7.61 (1H, dd, J=1.8, 8.8 Hz), 6.60 (2H, d, J=6.4 Hz), 4.35 (1H, d, J=16.9 Hz), 4.18 (1H, d, J=11.7 Hz), 4.18 (1H, d, J=11.7 Hz), 3.73 (1H, d, J=9.5 Hz), 3.53—3.11 (4H, m), 3.48 (1H, d, J=9.5Hz), 3.44 (3H, s), 3.31 (1H, d, J=16.9 Hz), 2.97 (1H, d, J=11.7 Hz), 2.48 (1H, brs), 2.25 (1H, d, J=11.7 Hz), 1.91—1.69 (2H, m), 1.47—1.30 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.28, 154.34, 150.29 (2C), 135.66, 135.47, 132.90, 130.81, 130.45, 129.07, 128.95 (2C), 126.82, 123.51, 108.54 (2C), 77.36, 74.62, 59.54, 58.34, 53.13, 51.46, 47.65, 43.85, 43.39, 36.74, 35.30. IR (KBr) cm^{-1}: 3435, 2939, 1662, 1597, 1454, 1421, 1350, 1167.

Tetrahydro-8*a*-(methoxymethyl)-1-methyl-5-oxo-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (10) To a solution of compound **8** (3.0 g) in CH_2Cl_2 (30 ml) was added paraformaldehyde (0.65 g) and $NaBH(OAc)_3$ (4.32 g). The reaction mixture was refluxed for 5 h. Then paraformaldehyde was added to the reaction mixture and it was refluxed for another 10 h. Then 10% HCl–MeOH (5 ml) was added to the mixture and it was refluxed for 1 h. After cooling, the reaction mixture was alkalinized with saturated $NaHCO_3$ aqueous solution and was extracted with CH_2Cl_2. The organic layer was washed with brine and was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford compound **10** (2.85 g, 92% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS m/z (M+H): Calcd for $C_{26}H_{34}N_5O_4$: 480.2611. Found: 480.2583. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 8.13 (2H, dd, J=1.7, 5.1 Hz), 7.42—7.27 (5H, m), 6.74 (2H, dd, J=1.7, 5.1 Hz), 5.13 (2H, s), 4.37 (1H, d, J=12.7 Hz), 4.24 (1H, d, J=11.6 Hz), 4.23 (1H, d, J=17.8 Hz), 3.97—3.80 (2H, m), 3.79 (1H, d, J=17.8 Hz), 3.45 (1H, d, J=10.3 Hz), 3.33 (1H, d, J=10.3 Hz), 3.21 (3H, s), 3.07 (1H, d, J=11.6 Hz), 2.92—2.75 (2H, m), 2.86 (1H, d, J=12.7 Hz), 2.34 (3H, s), 1.97—1.85 (1H, m), 1.80—1.57 (2H, m), 1.28—1.17 (1H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.59, 153.54 (2C), 149.32 (2C), 136.25, 127.78 (2C), 127.26, 126.95 (2C), 107.85 (2C), 76.69, 74.46, 66.21, 59.54, 58.47, 50.06, 47.23, 46.34, 43.74, 43.56, 31.99, 30.98, 26.42. IR (film) cm^{-1}: 2916, 2850, 1705, 1660, 1593, 1414, 1234, 989, 735.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1-methyl-1′-(4-pyridinyl)-(spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (11) [Step 1]: To a solution of compound **10** (1.0 g) in MeOH (20 ml) was added 10 % Pd/C (190 mg) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature over night. Then Pd/C was removed by Celite® filtration and the filtrate was concentrated *in vacuo* to obtain a deprotected compound (0.72 g, quant.) as a pale yellow amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.26 (2H, d, J=6.1 Hz), 6.66 (2H, d, J=6.1 Hz), 4.53 (1H, d, J=11.7 Hz), 3.98—3.82 (2H, m), 3.63—3.55 (1H, m), 3.53 (2H, s), 3.47—3.33 (2H, m), 3.36 (3H, s), 3.05 (1H, d, J=11.7 Hz), 3.02—2.76 (2H, m), 2.65 (1H, d, J=12.8 Hz), 2.34 (3H, s), 2.03—1.92 (1H, m), 1.86—1.73 (1H, m), 1.67—1.57 (1H, m), 1.32—1.22 (1H, m).

[Step 2]: To a solution of the deprotected compound (140 mg) in CH_2Cl_2 (10 ml) which was afforded in Step 1, was added 6-chloronaphthalene-2-sulfonyl chloride (117 mg) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then saturated $NaHCO_3$ aqueous solution was added to the reaction mixture at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/3–CH_2Cl_2) to afford compound **11** (166 mg, 72% yield) as a pale brown amorphous solid. MALDI-TOF-HR-MS m/z (M+H): Calcd for $C_{28}H_{32}{}^{35}ClN_5O_4S$: 570.1942. Found: 570.1948. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.38—8.33 (1H, m),

8.28—8.22 (2H, m), 8.00—7.90 (3H, m), 7.77 (1H, dd, J=1.8, 8.8 Hz), 7.60 (1H, dd, J=2.2, 8.8 Hz), 6.65—6.55 (2H, m), 4.33 (1H, d, J=16.7 Hz), 4.24 (1H, d, J=11.4 Hz), 4.19 (1H, d, J=11.6 Hz), 3.97—3.87 (1H, m), 3.38—3.72 (1H, m), 3.75 (1H, d, J=10.1 Hz), 3.67 (1H, d, J=10.1 Hz), 3.38 (3H, s), 3.34 (1H, d, J=16.7 Hz), 3.22 (1H, d, J=11.6 Hz), 2.87—2.66 (2H, m), 2.37 (3H, s), 2.26 (1H, d, J=11.4 Hz), 1.98—1.81 (2H, m), 1.77—1.58 (1H, m), 1.15—1.05 (1H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.35, 154.20, 150.28 (2C), 135.65, 135.46, 132.79, 130.79, 130.43, 129.06, 128.98, 128.94, 126.81, 123.48, 108.46 (2C), 78.71, 74.42, 60.63, 59.39, 51.46, 50.79, 48.00, 44.87, 44.59, 34.11, 32.81, 28.11. IR (KBr) cm^{-1}: 3446, 2930, 1662, 1597, 1454, 1348, 1167.

8*a*-[(Acetyloxy)methyl]-7-[(6-chloro-2-naphthalenyl)sulfonyl]tetrahydro-1′-(phenylmethyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (13) To a solution of compound **6** (5.26 g) and compound **12**[4] (10.3 g) in toluene (200 ml), was added *p*-toluenesulfonic acid monohydrate (44.2 mg). The reaction mixture was stirred at room temperature for 1 h then was refluxed for 2 h. The mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel flash column chromatography (eluant: AcOEt–AcOEt/MeOH=98/2) to afford compound **13** (7.76 g, 56% yield) as a pale yellow amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{30}H_{34}{}^{35}ClN_4O_5S$: 597.1938. Found: 597.1959. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.37—8.32 (1H, m), 7.97—7.89 (3H, m), 7.77 (1H, dd, J=1.5, 8.8 Hz), 7.59 (1H, dd, J=1.8, 8.8 Hz), 7.35—7.17 (5H, m), 4.36—4.12 (5H, m), 3.45 (2H, s), 3.33 (1H, d, J=16.9 Hz), 2.88 (1H, d, J=11.6 Hz), 2.63—2.40 (2H, m), 2.31 (1H, d, J=12.1Hz), 2.37—1.93 (2H, m), 2.11 (3H, s), 1.80—1.65 (2H, m), 1.40—1.25 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.48, 163.11, 137.92, 135.61, 135.41, 132.66, 130.74, 130.33, 129.05, 129.98 (3C), 128.93, 128.18 (2C), 127.06, 126.77, 123.46, 76.46, 66.06, 62.81, 58.66, 52.98, 51.17, 50.66, 50.38, 47.44, 37.82, 36.72, 20.78. IR (film) cm^{-1}: 2912, 2848, 1747, 1662, 1454, 1419, 1350, 1236, 1167.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(hydroxymethyl)-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (14) [Step 1]: To a solution of compound **13** (0.50 g) in 1,2-dichloroethane (5 ml) was added 1,8-bis(dimethylamino)naphthalene (0.22 g). Then α-chloroethyl chloroformate (0.23 ml) was dropwised into the above solution at 0 °C. The reaction mixture was stirred at ambient temperature for 30 min then was refluxed for 2 h. The reaction mixture was concentrated *in vacuo*. MeOH (5 ml) was added into the resulting residue and the reaction mixture was refluxed for 1 h. After cooling, Et_2O (20 ml) was added into the resulting residue. The residue was tritulated and the solvent was removed by decantation. Then the residue was dissolved in MeOH (5 ml) and 1 N NaOH (10 ml) was added into the mixture. The reaction mixture was stirred at ambient temperature for 1 h and the precipitate was collected by filtration and was washed CH_2Cl_2 (5 ml) to afford deprotected compound (0.20 g, 51% yield) as a pale brown amorphous solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 8.60—8.55 (1H, m), 8.30 (1H, d, J=8.8 Hz), 8.27—8.24 (1H, m), 8.17 (1H, d, J=8.6 Hz), 7.87 (1H, dd, J=1.7, 8.6 Hz), 7.73 (1H, dd, J=2.2, 8.8 Hz), 5.26—5.18 (1H, m), 4.01 (1H, d, J=16.7 Hz), 4.00—3.89 (2H, m), 3.58—3.30 (3H, m), 2.78 (1H, d, J=11.0 Hz), 2.85—2.25 (4H, m), 2.36 (1H, d, J=11.7 Hz), 1.99 (1H, br s), 1.60—1.44 (2H, m), 1.20—1.04 (2H, m).

[Step 2]: To a solution of the deprotected compound (150 mg) which was afforded in Step 1, 4-chloropyridine hydrochloride (73 mg) in EtOH (3 ml), *i*-Pr_2NEt (0.28 ml) was added and the mixture was stirred at 150—160 °C in a sealed tube for 6 h. Then the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: CH_2Cl_2–CH_2Cl_2/MeOH=99/1–98/2–97/3). Then the resulting amorphous solid was suspended and tritulated in Et_2O (5 ml). The precipitate was collected by filtration to afford compound **14** (117 mg, 67% yield) as a pale yellow amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{26}H_{29}{}^{35}ClN_5O_4S$: 542.1629. Found: 542.1613. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.36—8.33 (1H, m), 8.24 (2H, dd, J=1.7, 5.1 Hz), 7.98—7.92 (3H, m), 7.78 (1H, dd, J=1.8, 8.8 Hz), 7.62 (1H, dd, J=1.8, 8.8 Hz), 6.62 (2H, dd, J=1.7, 5.1 Hz), 4.36 (1H, d, J=16.5 Hz), 4.27—4.17 (2H, m), 4.03 (1H, d, J=11.2 Hz), 3.61 (1H, d, J=11.2 Hz), 3.53—3.16 (5H, m), 3.02 (1H, d, J=11.9 Hz), 2.46 (1H, br s), 2.29 (1H, d, J=12.1 Hz), 1.93—1.75 (2H, m), 1.49—1.41 (2H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.26, 154.40, 149.81 (2C), 135.60, 135.43, 132.77, 130.77, 130.37, 129.01, 128.95, 128.88, 126.78, 123.40, 108.46 (2C), 78.32, 64.41, 58.35, 53.31, 50.77, 47.53, 43.71, 43.26, 36.73, 35.33. IR (KBr) cm^{-1}: 3336, 2939, 1657, 1601, 1454, 1421, 1346, 1167.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(hydroxymethyl)-1-methyl-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (15) To a solution of compound **14** (1.00 g) in CH_2Cl_2 (10 ml) was added AcOH (0.42 ml) and paraformaldehyde (0.12 g). The reaction mixture was stirred at room temperature for 30 min and then $NaBH(OAc)_3$ (1.56 g) was added to the reaction mixture. The reaction mixture was refluxed for 8 h. Then H_2O (30 ml) was added to the mixture and the reaction mixture was extracted with CH_2Cl_2 (20 ml, 10 ml×2). The organic layer was washed with brine and was dried with anhydrous Na_2SO_4. Then the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: CH_2Cl_2–CH_2Cl_2/MeOH=99.5/0.5–99/1) to afford a less polar compound and compound **15** (0.45 g).

The above less polar compound was dissolved in 10% HCl–MeOH (2 ml) and the reaction mixture was stirred for 30 min at room temperature. To the reaction mixture was added saturated $NaHCO_3$ aqueous solution for adjusting to pH 10, then the reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure to afford compound **15** (0.35 g). The total yield of compound **15** was 78% (as a pale yellow amorphous solid). MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{27}H_{31}{}^{35}ClN_5O_4S$: 556.1785. Found: 556.1774. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.35 (1H, s), 8.24 (2H, dd, J=1.7, 5.1 Hz), 8.00—7.90 (3H, m), 7.77 (1H, dd, J=2.0, 8.8 Hz), 7.62 (1H, dd, J=2.0, 8.8 Hz), 6.62 (2H, dd, J=1.7, 5.1 Hz), 4.35 (1H, d, J=11.6 Hz), 4.34 (1H, d, J=16.9 Hz), 4.22 (1H, d, J=11.6 Hz), 4.00—3.68 (4H, m), 3.43 (1H, d, J=16.9 Hz), 3.16 (1H, d, J=11.6 Hz), 3.03—2.70 (2H, m), 2.42 (1H, d, J=11.6 Hz), 2.42 (3H, s), 2.10—2.95 (1H, m), 1.84—1.66 (2H, m), 1.15—1.02 (1H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.62, 154.23, 149.75 (2C), 135.70, 135.61, 132.96, 130.82, 130.44, 129.16, 129.08, 128.99, 126.85, 123.31, 108.44 (2C), 79.14, 64.85, 60.83, 51.36, 49.43, 47.81, 44.67, 44.51, 33.06, 30.90, 27.39. IR (film) cm^{-1}: 3444, 2943, 1657, 1599, 1456, 1348, 1167.

***N*-(2,2-Diethoxyethyl)-*N*-[(phenylmethoxy)carbonyl]-glycine Ethyl Ester (17)** Compound **16**[2] (219 g) was dissolved in CH_2Cl_2 (850 ml) and Et_3N (117 ml) was added to this solution. Then benzyl chloroformate (120 ml) was slowly dropwised at 0 °C for 40 min. The reaction mixture was stirred at room temperature over night. The reaction mixture was cooled in ice bath and was acidified with 1 N HCl. The reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (eluant: Hex/AcOEt=5/1–3/1) to afford compound **17** (245 g, 69% yield) as pale yellow oil. EI-MS *m/z*: 353 (M^+), 308, 280, 236, 218, 103. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.42—7.25 (5H, m), 5.24—5.08 (2H, m), 4.62—4.44 (1H, m), 4.23—4.07 (4H, m), 3.78—3.36 (6H, m), 1.30—1.11 (9H, m).

***N*-(2-Oxoethyl)-*N*-[(phenylmethoxy)carbonyl]-glycine Ethyl Ester (18)** To a mixture of water (55 ml) and $CHCl_3$ (55 ml) was added TFA (109 ml) at 0 °C. Then the solution of compound **17** (10 g) in $CHCl_3$ (55 ml) was dropwised into the above mixture for 30 min. Then the reaction mixture was vigorously stirred at room temperature for 2 h. To the reaction mixture was added water (200 ml) and the organic layer was separated. And then water layer was extracted with CH_2Cl_2 (100 ml×2). These extracted organic layers were combined with the above separated organic layer. And the organic layer was washed with 10% K_2CO_3 aqueous solution (200 ml) and with brine (200 ml), respectively. The organic layer was dried with Na_2SO_4. The solvent was removed under reduced pressure to afford compound **18** (8.32 g, quant.). Compound **18** was used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.70—9.59 (1H, m), 7.40—7.26 (5H, m), 5.23—5.11 (2H, m), 4.25—4.01 (6H, m), 1.32—1.18 (3H, m).

Tetrahydro-5-oxo-1′-(phenylmethyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (19) The solution of compound **6** (7.0 g) and compound **18** (7.43 g) in toluene (75 ml) was stirred at room temperature for 1 h. Then the reaction mixture was refluxed for 6 h. After cooling, the reaction mixture was concentrated *in vacuo*. Et_2O (100 ml) was added to the afforded residue and the mixture was stirred at room temperature overnight. Then the precipitate was collected by filtration to afford compound **19** (8.99 g, 78% yield) as a pale brown amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{25}H_{31}N_4O_3$: 435.2396. Found: 435.2394. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.40—7.20 (10H, m), 5.11 (2H, s), 4.51—4.40 (1H, m), 4.28—4.14 (2H, m), 3.67 (1H, d, J=17.6 Hz), 3.48 (2H, s), 3.35 (1H, d, J=11.4 Hz), 3.04 (1H, d, J=11.4 Hz), 2.83 (1H, dd, J=9.9, 12.8 Hz), 2.82—2.72 (1H, m), 2.60—2.45 (2H, m), 2.37—2.23 (2H, m), 1.70—1.50 (4H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.35, 153.60, 138.24, 136.13, 128.09 (2C), 127.82 (2C), 127.46 (2C), 127.30, 127.01 (2C), 126.13, 68.54, 66.28,

61.51, 57.38, 53.15, 49.77, 49.29, 46.44, 45.87, 35.84, 33.96. IR (film) cm^{-1}: 1705, 1653, 1421, 1232, 741, 698.

Tetrahydro-5-oxo-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (20) [Step 1]: To the solution of compound **19** (0.35 g) in 1,2-dichloroethane (7 ml) were added 1,8-bis(dimethylamino)naphthalene (0.21 g) and α-chloroethyl chloroformate (0.22 ml) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in MeOH (7 ml) and the reaction mixture was refluxed for 1 h. After cooling, the solvent was removed under reduced pressure. To the residue was added mixed organic solvent (Hex/Et_2O=1/1, 10 ml). The residue was triturated and precipitate was collected by filtration and washed with mixed organic solvent (Hex/Et_2O=1/1, 5 ml). The afforded precipitate was dissolved in H_2O (15 ml) and the solution was alkalified with K_2CO_3 to more than pH 10. Then it was extracted with CH_2Cl_2 (10 ml, 5 ml×3) and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/4–CH_2Cl_2–CH_2Cl_2/MeOH=97/3) to afford deprotected compound (228 mg, 82% yield) as a pale brown amorphous solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.40—7.30 (5H, m), 5.12 (2H, s), 4.52—4.42 (1H, m), 4.28—4.20 (1H, m), 4.19 (1H, d, J=17.6 Hz), 3.67 (1H, d, J=17.6 Hz), 3.34 (1H, d, J=11.4 Hz), 3.04 (1H, d, J=11.4 Hz), 3.07—2.69 (4H, m), 2.63—2.45 (2H, m), 1.57—1.38 (4H, m).

[Step 2]: To a solution of 4-chloropyridine hydrochloride (131 mg) and the deprotected compound (200 mg) which was afforded in Step 1 in EtOH (4 ml) was added *i*-Pr_2NEt (0.51 ml). The mixture was stirred at 150—160 °C in a sealed tube for 2 h then it was concentrated *in vacuo*. The resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: CH_2Cl_2–CH_2Cl_2/MeOH=99/1–98/2) to afford compound **20** (135 mg, 55% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{23}H_{28}N_5O_3$: 422.2192. Found: 422.2209. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 8.12 (2H, dd, J=1.7, 5.0 Hz), 7.39—7.27 (5H, m), 6.75 (2H, dd, J=1.7, 5.0 Hz), 5.12 (2H, s), 4.58—4.47 (1H, m), 4.30—4.17 (2H, m), 3.70 (1H, d, J=17.6 Hz), 3.48—3.30 (5H, m), 3.11 (1H, d, J=11.4 Hz), 2.88 (1H, dd, J=9.9, 12.8 Hz), 1.79—1.55 (4H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.34, 153.69, 153.60, 149.33 (2C), 136.12, 127.82 (2C), 127.31, 127.02 (2C), 107.83 (2C), 68.67, 66.31, 57.55, 53.38, 46.48, 45.78, 42.83, 42.45, 34.56, 32.80. IR (film) cm^{-1}: 1705, 1653, 1597, 1462, 1232, 719, 669.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (21) [Step 1]: To a solution of compound **20** (120 mg) in MeOH (2.5 ml) was added 10% Pd/C (24 mg) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature for 2 h. Then Pd/C was removed by Celite® filtration and the filtrate was concentrated *in vacuo* to obtain a deprotected compound (78.3 mg, 96%) as a colorless amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.30—8.23 (2H, m), 6.72—6.65 (2H, m), 4.51 (1H, dd, J=4.2, 9.4 Hz), 3.67—3.36 (8H, m), 3.25 (1H, d, J=11.9 Hz), 2.52 (1H, dd, J=9.4, 12.5 Hz), 2.00—1.65 (6H, m).

[Step 2]: To a solution of the deprotected compound (20 mg), which was afforded in Step 1, and Et_3N (10.7 μl) in CH_2Cl_2 (2 ml), was added 6-chloronaphthalene-2-sulfonyl chloride (20 mg) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then saturated $NaHCO_3$ aqueous solution was added to the reaction mixture at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: CH_2Cl_2–CH_2Cl_2/MeOH=99/1) to afford compound **21** (28.3 mg, 79% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{25}H_{27}{}^{35}ClN_5O_3S$: 512.1523. Found: 512.1555. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.38—8.34 (1H, m), 8.27 (2H, dd, J=1.7, 5.0 Hz), 7.99—7.90 (3H, m), 7.79 (1H, dd, J=1.8, 8.8 Hz), 7.61 (1H, dd, J=1.8, 8.8 Hz), 6.65 (2H, dd, J=1.7, 5.0 Hz), 4.80—4.69 (1H, m), 4.40—4.32 (1H, m), 4.32 (1H, d, J=15.8 Hz), 3.55 (1H, d, J=11.7 Hz), 3.55—3.28 (5H, m), 3.20 (1H, d, J=11.7 Hz), 2.35 (1H, dd, J=9.5, 11.6 Hz), 1.85—1.50 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.43, 154.29, 150.33 (2C), 135.69, 135.58, 132.90, 130.79, 130.42, 129.14, 129.12, 128.97, 126.84, 123.55, 108.56 (2C), 69.90, 58.82, 54.11, 48.64, 48.03, 43.64, 43.31, 36.03, 34.09. IR (film) cm^{-1}: 1666, 1593, 1462, 1429, 1331, 1161, 968, 700.

Tetrahydro-1-methyl-5-oxo-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7(1*H*)-carboxylic Acid Phenylmethyl Ester (22) To a solution of compound **20** (1.65 g) in CH_2Cl_2 (23 ml) was added paraformaldehyde (0.26 g). The reaction mixture was stirred at room temperature for 30 min and then $NaBH(OAc)_3$ (2.62 g) was added to the reaction mixture. The reaction mixture was refluxed for 10 h. Then paraformaldehyde (0.13 g) was added to the reaction mixture and was refluxed for another 2 h. After cooling, 10% HCl–MeOH (10 ml) was added to the mixture and the reaction mixture was stirred at room temperature for 30 min. To the reaction mixture was added saturated $NaHCO_3$ aqueous solution to alkalified to pH 10 and then it was extracted with CH_2Cl_2 (20 ml, 10 ml×2). The organic layer was washed with brine and was dried with anhydrous Na_2SO_4. Then the reaction mixture was concentrated *in vacuo*. Since the resulting residue included borane complex, the residue was dissolved in 10% HCl–MeOH (20 ml) and the reaction mixture was stirred for 30 min. Then H_2O (50 ml) was added to the reaction mixture. To the reaction mixture was added Na_2CO_3 to alkalified to pH 10 and then it was extracted with CH_2Cl_2 (50 ml, 20 ml×2). The organic layer was washed with brine and was dried with Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: CH_2Cl_2/MeOH=99/1) to afford compound **22** (1.33 g, 78% yield) as a pale yellow amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{24}H_{30}N_5O_3$: 436.2349. Found: 436.2319. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 8.17—8.10 (2H, m), 7.40—7.25 (5H, m), 6.79—6.73 (2H, m), 5.14 (2H, s), 4.33 (1H, dd, J=3.7, 12.5 Hz), 4.24 (1H, d, J=17.6 Hz), 4.09 (1H, dd, J=3.7, 9.5 Hz), 3.98—3.84 (2H, m), 3.76 (1H, d, J=17.6 Hz), 3.61 (1H, d, J=11.4 Hz), 3.37 (1H, d, J=11.4 Hz), 3.00—2.77 (2H, m), 2.71 (1H, dd, J=9.5, 12.5 Hz), 2.21 (3H, s), 1.93—1.78 (1H, m), 1.76—1.50 (2H, m), 1.48—1.34 (1H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.68, 153.65, 153.55, 149.37 (2C), 136.13, 127.82 (2C), 127.31, 126.97 (2C), 107.89 (2C), 72.39, 66.32, 59.59, 51.01, 46.80, 46.05, 43.72, 42.72, 32.93, 29.29, 24.75. IR (film) cm^{-1}: 1705, 1660, 1595, 1415, 1335, 1232, 1128, 987.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-1-methyl-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (23) [Step 1]: To a solution of compound **22** (1.2 g) in MeOH (24 ml) was added 10% Pd/C (240 mg) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature for 2 h. Then Pd/C was removed by Celite® filtration and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (10 ml) and this solution was concentrated *in vacuo* to obtain a deprotected compound (0.82 g, 99% yield) as a pale yellow amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.31—8.24 (2H, m), 6.72—6.50 (2H, m), 4.08—3.90 (3H, m), 3.75—3.30 (5H, m), 3.00—2.78 (2H, m), 2.51 (1H, dd, J=9.1, 12.1 Hz), 2.25 (3H, s), 2.03 (1H, br s), 2.01—1.88 (1H, m), 1.85—1.70 (1H, m), 1.63—1.44 (2H, m).

[Step 2]: To a CH_2Cl_2 (10 ml) solution of the deprotected compound (120 mg) which was afforded in Step 1, were Et_3N (61 μl) and 6-chloronaphthalene-2-sulfonyl chloride (114 mg) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then saturated $NaHCO_3$ aqueous solution was added to the reaction mixture at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/4–CH_2Cl_2–CH_2Cl_2/MeOH=99.5/0.5) to afford compound **23** (154 mg, 74% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS *m/z* (M+H): Calcd for $C_{26}H_{29}{}^{35}ClN_5O_3S$: 526.1680. Found: 526.1673. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.38—8.33 (1H, m), 8.31—8.24 (2H, m), 7.98—7.89 (3H, m), 7.78 (1H, dd, J=1.8, 9.0 Hz), 7.61 (1H, dd, J=2.0, 9.0 Hz), 6.70—6.62 (2H, m), 4.32 (1H, d, J=17.1 Hz), 4.32—4.22 (2H, m), 4.04—3.85 (2H, m), 3.70 (1H, d, J=11.2 Hz), 3.37 (1H, d, J=11.2 Hz), 3.32 (1H, d, J=17.1 Hz), 2.94—2.70 (2H, m), 2.37—2.25 (1H, m), 2.30 (3H, s), 1.99—1.73 (2H, m), 1.65—1.49 (1H, m), 1.44—1.34 (1H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.90, 154.13, 150.42 (2C), 135.68 (2C), 132.76, 130.78, 130.42, 129.11 (2C), 128.94, 126.85, 123.50, 108.62 (2C), 73.91, 60.64, 51.84, 48.72, 48.34, 44.82, 43.75, 33.79, 30.51, 25.42. IR (KBr) cm^{-1}: 1657, 1595, 1456, 1350, 1165, 698, 600.

Tetrahydro-5-oxo-1′-(phenylmethyl)-spiro[7*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7-carboxylic Acid Phenylmethyl Ester (25) The solution of compound **18** (90.3 g) and compound **24** (71.3 g) in toluene (1 l) was refluxed for 1 h with Dean–Stark apparatus. After cooling, the solvent was removed *in vacuo*. The residue was dissolved in MeOH (1 l) and then a solution of LiOH–H_2O (13.6 g) in H_2O (100 ml) was added into the mixture at 0 °C. The reaction mixture was stirred at room temperature for 1 h and

then it was concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (1 l) and *N*′-(ethylcarbonimidoyl)-*N*,*N*-dimethyl-1,3-propanediamine monohydrochloride (62.2 g) was gently added at 0 °C and then the reaction mixture was stirred at room temperature over night. To the reaction mixture was added saturated $NaHCO_3$ aqueous solution and was extracted with CH_2Cl_2. The organic layer was washed with brine and was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluant: CH_2Cl_2/MeOH=97/3–90/10). Fractions including compound **25** were concentrated under reduced pressure and the resulting residue was further purified by recrystalization (solvent: Hex/Et_2O=1/2) to afford compound **25** (86 g, 61% yield (3 steps)) as colorless crystals. mp 124.5—125.2 °C. MALDI-TOF-HR-MS *m*/*z* (M+H): Calcd for $C_{25}H_{30}N_3O_4$: 436.2236. Found: 436.2263. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.40—7.15 (10H, m), 5.12 (2H, s), 5.00 (1H, dd, *J*=4.2, 8.6 Hz), 4.31 (1H, dd, *J*=4.2, 12.8 Hz), 4.21 (1H, d, *J*=17.6 Hz), 3.76 (1H, d, *J*=17.6 Hz), 3.70 (1H, d, *J*=11.2 Hz), 3.48 (2H, s), 3.10 (1H, d, *J*=11.2 Hz), 3.00—2.88 (1H, m), 2.57—2.32 (4H, m), 1.84—1.55 (4H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.58, 153.65, 138.12, 135.99, 128.08 (2C), 127.81 (2C), 127.47 (2C), 127.33, 127.01 (2C), 126.17, 81.23, 78.92, 66.45, 61.26, 51.20, 49.40, 49.07, 46.43, 45.19, 35.43, 33.39. IR (KBr) cm^{-1}: 1711, 1672, 1462, 1421, 1331, 1228, 1097.

Tetrahydro-5-oxo-1′-(4-pyridinyl)-spiro[7*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4′-piperidine]-7-carboxylic Acid Phenylmethyl Ester (26) [Step 1]: To the solution of compound **25** (50.0 g) in 1,2-dichloroethane (500 ml) was added 1,8-bis(dimethylamino)naphthalene (4.92 g). Then α-chloroethyl chloroformate (31.0 ml) was dropwised into the above solution at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in MeOH (500 ml) and the reaction mixture was refluxed for 1 h. After cooling, the solvent was removed under reduced pressure. The resulting residue was dissolved in H_2O (600 ml) and the water layer was washed Et_2O (200 ml×2) for removing benzyl chloride. Then the water layer was alkalified with K_2CO_3 to more than pH 10 and was extracted with CH_2Cl_2 (500 ml, 250 ml×2). The organic layer was washed with brine and was dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/4–CH_2Cl_2–CH_2Cl_2/MeOH=98/3–95/5–90/10) to afford deprotected compound (26.8 g, 68% yield) as a pale yellow amorphous solid. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 7.38—7.27 (5H, m), 5.12 (2H, s), 5.01 (1H, dd, *J*=4.1, 8.7 Hz), 4.36—4.27 (1H, m), 4.26—4.17 (1H, m), 3.81—3.65 (1H, m), 3.12—3.06 (1H, m), 2.93 (1H, dd, *J*=8.7, 12.8 Hz), 2.90—2.74 (4H, m), 2.64—2.54 (2H, m), 1.67—1.60 (2H, m).1.55—1.47 (2H, m).

[Step 2]: To a EtOH (96 ml) solution of 4-chloropyridine hydrochloride (3.26 g) and the deprotected compound (5 g) which was afforded in Step 1, was added *i*-Pr_2NEt (12.6 ml). The mixture was stirred at 150—160 °C in a sealed tube for 2 h then it was concentrated *in vacuo*. The resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=2/1–1/3–1/5–1/9–CH_2Cl_2–CH_2Cl_2/MeOH=99/1–98/2–95/5–90/10–75/25) to afford compound **26** (3.33 g, 54% yield) as a pale yellow amorphous solid. MALDI-TOF-HR-MS *m*/*z* (M+H): Calcd for $C_{23}H_{27}N_4O_4$: 423.2032. Found: 423.2057. ^{1}H-NMR (300 MHz, DMSO-d_6, 100 °C) δ: 8.13 (2H, dd, *J*=1.7, 4.9 Hz), 7.40—7.25 (5H, m), 6.76 (2H, dd, *J*=1.7, 4.9 Hz), 5.13 (2H, s), 5.07 (1H, dd, *J*=4.3, 8.6 Hz), 4.38–4.28 (1H, m), 4.23 (1H, d, *J*=18.1 Hz), 3.84–3.73 (2H, m), 3.52–3.23 (4H, m), 3.17 (1H, d, *J*=11.2 Hz), 3.04—2.92 (1H, m), 1.90—1.60 (4H, m). ^{13}C-NMR (75 MHz, DMSO-d_6, 100 °C) δ: 162.64, 153.67, 153.55, 149.38 (2C), 135.99, 127.82 (2C), 127.35, 127.04 (2C), 107.94 (2C), 81.45, 78.87, 66.48, 51.39, 46.47, 45.12, 42.60, 42.38, 34.31, 32.28. IR (KBr) cm^{-1}: 1707, 1668, 1595, 1462, 1423, 1232, 1101.

7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-1′-(4-pyridinyl)-spiro[5*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5-one (27) [Step 1]: To a solution of compound **26** (3.2 g) in MeOH (50 ml) was added 10% Pd/C (0.64 g) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature for 3 h. Then Pd/C was removed through Celite® pad and the filtrate was concentrated *in vacuo* to obtain a deprotected compound (2.2 g, quant.) as a colorless amorphous solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.31—8.22 (2H, m), 6.72—6.63 (2H, m), 5.00 (1H, dd, *J*=4.2, 8.1 Hz), 3.96—3.88 (1H, m), 3.65—3.28 (7H, m), 3.19—3.10 (1H, m), 2.66 (1H, dd, *J*=8.1, 12.6 Hz), 2.00—1.55 (4H, m).

[Step 2]: To a CH_2Cl_2 (30 ml) solution of the deprotected compound (1.2 g) which was afforded in Step 1, were added Et_3N (0.67 ml) and 6-chloronaphthalene-2-sulfonyl chloride (1.25 g) at 0 °C. The reaction mixture was stirred at room temperature for 30 min and then H_2O (10 ml) was added to the reaction mixture. Additionally saturated $NaHCO_3$ aqueous solution was added to the reaction mixture. Then the mixture was extracted with CH_2Cl_2 (25 ml×2) and the organic layer was washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was purified by amino-silica gel column chromatography (Fuji Silysia Chemical Ltd., Chromatorex NH®, eluant: Hex/CH_2Cl_2=1/5–CH_2Cl_2–CH_2Cl_2/MeOH=99/1–98/2–97/3–95/5–93/7–80/20) to afford compound **27** (1.98 g, 93% yield) as a colorless amorphous solid. MALDI-TOF-HR-MS *m*/*z* (M+H): Calcd for $C_{25}H_{26}{}^{35}ClN_4O_4S$: 513.1363. Found: 513.1385. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.40—8.33 (1H, m), 8.26 (2H, dd, *J*=1.5, 5.1 Hz), 8.00—7.90 (3H, m), 7.79 (1H, dd, *J*=1.8, 8.8 Hz), 7.61 (1H, dd, *J*=2.0, 8.8 Hz), 6.65 (2H, dd, *J*=1.5, 5.1 Hz), 5.26—5.13 (1H, m), 4.45—4.33 (1H, m), 4.33 (1H, d, *J*=16.7 Hz), 3.75 (1H, d, *J*=11.6 Hz), 3.65—3.47 (2H, m), 3.43—3.22 (2H, m), 3.31 (1H, d, *J*=16.7 Hz), 3.18 (1H, d, *J*=11.6 Hz), 2.45 (1H, dd, *J*=8.8, 11.6 Hz), 2.03—1.88 (1H, m), 1.85—1.60 (3H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 162.43, 154.19, 150.23 (2C), 135.71, 135.61, 132.93, 130.80, 130.43, 129.15, 129.11, 129.03, 126.84, 123.48, 108.54 (2C), 82.73, 79.91, 52.61, 48.14, 47.91, 43.26, 43.08, 35.16, 33.11. IR (KBr) cm^{-1}: 1670, 1595, 1460, 1348, 1165, 968, 698.

(−)-(8*aR*)-7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (M58163) and (+)-(8*aS*)-7-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (30) Compound **9** was optically resolved on HPLC [LC-10A manufactured by Shimadzu Corp.: Column used, Daicel Chiralpak™ AS manufactured by Daicel Chemical Industries, Ltd., 0.46 cm×25 cm: eluent: MeOH (containing 0.1% diethylamine): flow rate, 0.5 ml/min, detection wavelength, 254 nm] to obtain (+)-form (**30**) as a colorless amorphous solid [retention time: 11 min, $[\alpha]_D^{26}$ +113° (*c*=0.330, MeOH), >99% ee], and (−)-form (M58163) as a colorless amorphous solid [retention time: 14 min, $[\alpha]_D^{26}$ −111° (*c*=0.320, MeOH), 98.6% ee], respectively.

(−)-(8*aR*)-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1-methyl-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (M58169) and (+)-(8*aS*)-[(6-Chloro-2-naphthalenyl)sulfonyl]tetrahydro-8*a*-(methoxymethyl)-1-methyl-1′-(4-pyridinyl)-spiro[imidazo[1,2-*a*]pyrazine-2(3*H*),4′-piperidin]-5(1*H*)-one (31) Compound **11** was optically resolved on HPLC [Waters DeltaPrep 4000 manufactured by Waters Inc.: Column used, Daicel Chiralpak™ AS manufactured by Daicel Chemical Industries, Ltd., 2 cm×25 cm: eluent: MeOH: flow rate, 16 ml/min, detection wavelength, 254 nm] to obtain (−)-form (M58169) as colorless crystals [retention time: 22 min, mp 204—205 °C (recrystallized from EtOH), $[\alpha]_D^{29}$ −129° (*c*=0.560, MeOH), >99% ee], and (+)-form (**31**) as a colorless amorphous solid [retention time: 32 min, $[\alpha]_D^{29}$ +129° (*c*=0.545, MeOH), 98.2% ee], respectively.

X-Ray Crystallographic Structure Analysis A colorless single crystal was mounted on Rigaku AFC7R diffractometer. Data collection was performed by using an ω–2θ scan. Determination of the space group was performed by the systematic absences, while the cell constants were refined after data collection with teXan program.[38] The collected intensities were corrected for Lorentz and polarization factors by teXan program.[38] Ψ-scan absorption correction[39] also applied using the teXan program.[38] The structure was dissolved by direct and Fourier methods. The data were refined by full-matrix least squares,[40] minimizing the function $\Sigma w(F_O{}^2-F_C{}^2)^2$. The handedness of structure was tested by refining the Flack parameter.[41,42] The calculations of initial structure were carried out by using SIR92[43] and the refinement was carried out by using teXan programs.[38] The crystallographic data were listed in Table 7.

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