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ENANTIOSELECTIVE SYNTHESIS OF PIPERIDINE DIAMINE DERIVATIVES AS NOVEL fXa INHIBITORS

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Abstract – Previously, we reported that racemic *cis*-piperidine diamine derivatives (±)-**1** showed high anti-fXa, anticoagulation activity and oral activities. To confirm the active enantiomer, (3*R*,4*S*)-piperidine diamine derivatives (-)-**1A** and (-)-**1B** were synthesized enantioselectively from Boc-D-serine. These synthetic routes and intermediates could be utilized for the optimization of these derivatives. From the activities of (-)-**1A** and (-)-**1B**, (3*R*,4*S*)-isomer was confirmed to be the active enantiomer.

INTRODUCTION

Thrombosis-related diseases are major causes of mortality in the industrialized world. Nowadays, safer and more effective orally administrated anticoagulant agents are required in clinical treatment. Among several approaches to address the unmet needs, the inhibition of factor Xa (fXa) is known as one of the most popular.[1] Recently, we discovered promising racemic *cis*-piperidine diamine derivative **1** which showed high anti-fXa, anticoagulation activity and oral activities.[2] Then we took an interest in the stereochemistry of the active enantiomer. In this paper, we report on the enantioselective synthesis of (3*R*,4*S*)-piperidine diamine derivatives **1A**-**B** to determine the active enantiomer. As well, we report on the investigation of the *in vitro* activities of these compounds.

We expected that the stereochemistry of the active enantiomer would be the same as our previous compound (-)-(1R, 2S)-2, which showed two times higher activity than (±)-**2**.[3] Protected piperidine diamine (**I**) was needed to synthesize (3*R*,4*S)*-piperidine diamine derivative **1** and similar derivatives.

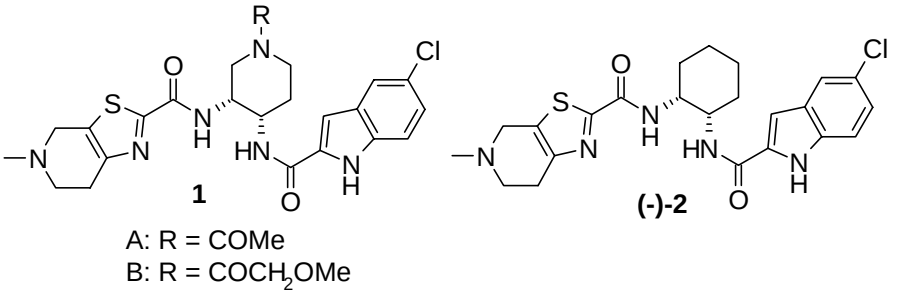
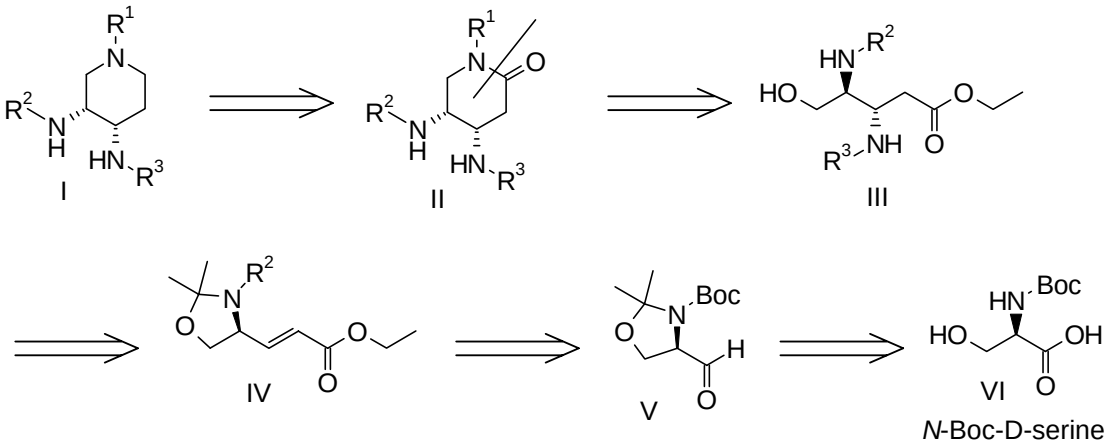


Figure 1. Structures of *cis*-piperidine diamine derivatives (**1)** and cyclohexane diamine derivative (**2**).

We designed retrosynthetic routes of the protected piperidine diamine (**I**) (Scheme 1). The protected piperidine diamine (**I**) would be produced by the reduction of piperidone (**II**), which would be formed by the amination of hydroxyl ester (**III**) and the following cyclization. The R^3-amino group of **III** should be introduced by a Michael addition into α,β-unsaturated ester (**IV**). Ester **(IV)** would be easily synthesized from *N*-Boc-D-serine (**VI**) via Garner aldehyde (**V**). [4]



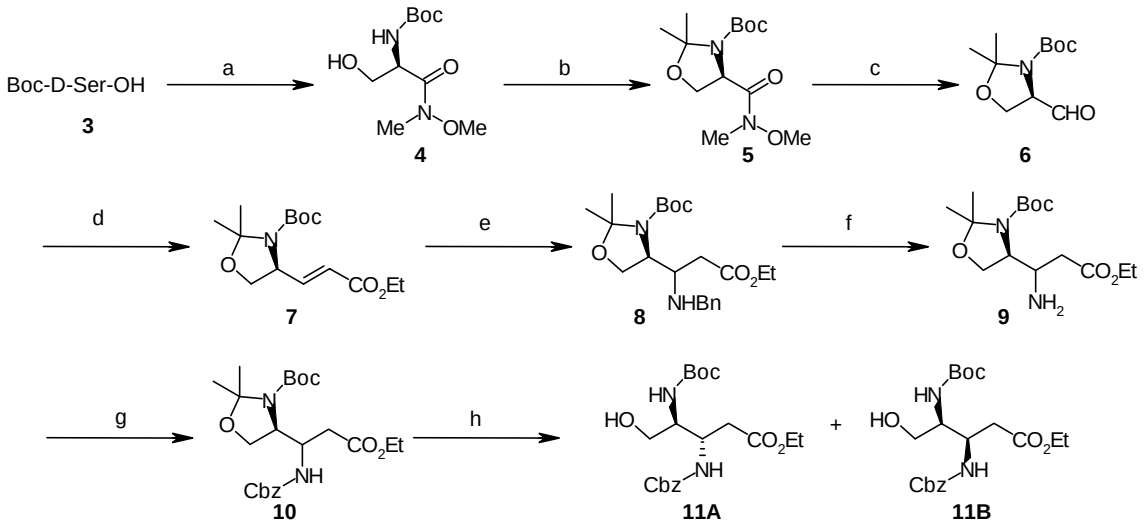
Scheme 1. Retrosynthetic routes of protected piperidine diamine (**I**).

RESULTS AND DISCUSSION

The key intermediate, hydroxyl ester (**III**) was prepared as shown in Scheme 2. The synthesis of (*R*)-Garner aldehyde was referred in Campbell's report.[5] Commercially available Boc-D-serine **3** was condensed with *O,N*-dimethylhydroxylamine to obtain amide **4**. The hydroxyl group and Boc-NH-R group of **4** were protected with dimethyl acetal to obtain protected amide **5**.[5,6] After the reduction of **5** with $LiAlH_4$, the obtained (*R*)-Garner aldehyde **6** was treated with Wittig-Horner reagent to get

α,β-unsaturated ester **7**.[7] Amino group was introduced to ester **7** by treatment with benzylamine. The diastereoselectivity of amino 1,4-addition into **7** was very low, and it was very difficult to separate the diastereoisomers of amine **8** by silica gel chromatography. Therefore, the following synthesis was performed on the diastereomeric mixture for a short time.

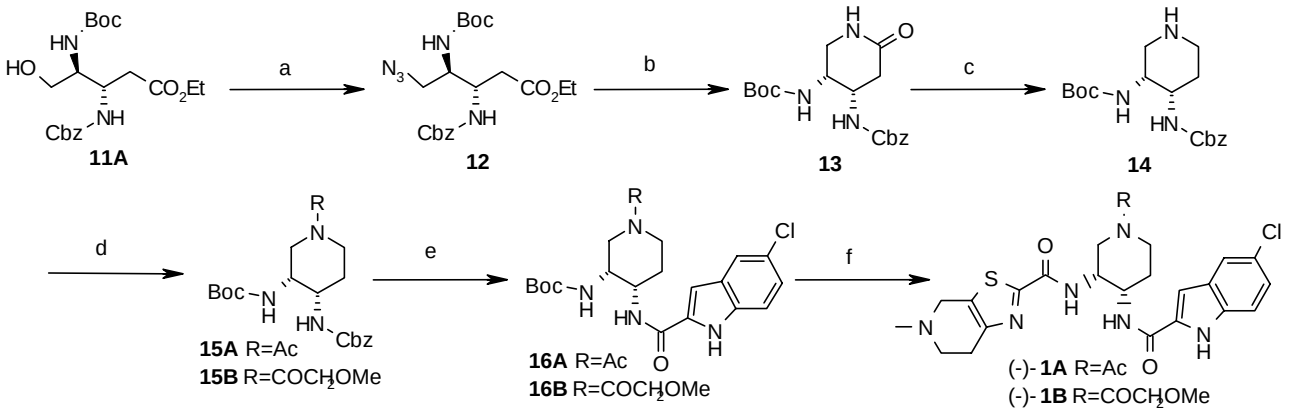
After the change of the *N*-benzyl group into the *N*-benzyloxycarbonyl group, the dimethyl acetal was removed by treatment with *p*-toluenesulfonic acid and the accompanying deprotecting amino moiety was reprotected with a Boc-group to obtain hydroxyl ester **11**. The diastereomeric mixture of **11A** and **11B** could be separated by column chromatography on silica gel and the desired less polar isomer **11A** corresponding to **1** was obtained as a minor product. The stereochemistry of **11A** was confirmed by the synthesis of (-)-**1A** and (-)-**1B**.



Scheme 2. Reagents and conditions: (a) MeN(H)OMe, WSCD, NMM, CH_2Cl_2, -15 ºC, 94%; (b) $Me_2C(OMe)_2$, $BF_3{\cdot}Et_2O$, acetone, rt, quant.; (c) $LiAlH_4$, THF, -78 ºC; (d) Ph_3PCHCO_2Et, toluene, 80 ºC, 2 steps quant.; (e) $BnNH_2$, EtOH, reflux, 80%; (f) H_2, Pd(C), EtOH, rt, 93%; (g) CbzOSu, $NaHCO_3$ aq, dioxane, quant.; (h) i) *p*-TsOH, EtOH, H_2O, reflux, ii) Boc_2O, Et_3N, CH_2Cl_2, rt, 33% (**11A**), 40% (**11B**).

The synthesis of **1** from **11A** is shown in scheme 3. The hydroxyl group of **11A** was transformed into an azide group via mesylate, then the azide group was reduced by hydrogenation with Lindlar catalyst and the resultant amine was treated under basic conditions to form lactame **13** by intramolecular cyclization. Cbz-group was partially eliminated by hydrogenation with Lindlar catalyst and therefore the accompanying amino moiety was protected by the Cbz-group. The amide group of **13** was reduced with borane to obtain piperidine derivative **14**. Compound **14** was treated with acetic anhydride or methoxy acetyl chloride to obtain amide derivatives **15A** and **15B**. After the deprotection of the Cbz-groups by hydrogenation, the resulting amines were condensed with commercially available 5-chloroindole-2-carboxylic acid to yield **16A** and **16B**. These were treated with hydrochloric acid to remove the

Boc-group and the resultant amines were condensed with 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]-pyridine-2-carboxylic acid lithium salt[8] to obtain (3*R*,4*S)*-piperidine diamine derivatives (-)-**1A** and (-)-**1B**. The NMR data of these chiral compounds (-)-**1A** and (-)-**1B** agreed with the corresponding racemic compounds (±)-**1A** and (±)-**1B** respectively.



Scheme 3. Reagents and conditions: (a) i) MsCl, Et_3N, CH_2Cl_2, 0 ºC, ii) NaN_3, DMF, 60 ºC, 93%; (b) i) H_2, Lindlar cat., EtOH, rt, ii) THF, 50 ºC, iii) CbzCl, $NaHCO_3$ aq, THF, rt, 89%; (c) i) BH_3·THF, THF, rt, ii) Et_3N, EtOH, H_2O, reflux, 57%; (d) Ac_2O or $MeOCH_2COCl$, Et_3N, CH_2Cl_2, 0 ºC , **58**% (**15A**) or **82**% (**15B**); (e) (1) H_2, Pd(C), EtOH, rt, (2) 5-Chloroindole-2-carboxylic acid, WSCD, HOBt, DMF, rt, 79% (**16A**), 78% (**16B**); (f) i) HCl, dioxane, rt, ii) Lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylate, WSCD, HOBt, DMF, rt, 44% ((-)-**1A**), 61% ((-)-**1B**).

The Anti-Factor Xa activity (IC_{50}) and anticoagulant activity ($PTCT_2$) of **1A-B** were measured (Table 1).[9] Compounds (-)-**1A** and (-)-**1B** showed very strong inhibition and anticoagulant activity and their activities were about double the strength of their corresponding *cis* racemates. These results imply that (-)-(3*R*,4*S*)-**1** is the active enantiomer.

Table 1. Evaluation of Optically Active Compounds.

	(-)-**1A**	(±)-**1A**	(-)-**1B**	(±)-**1B**
Anti-Factor Xa activity: IC_{50} (nM)	5.6	8.6	2.7	5.8
$PTCT_2$ human (μM)	0.38	0.67	0.34	0.8

To summarize, we have synthesized (3*R*,4*S*)-piperidine diamine derivatives (−)-**1A** and (−)-**1B** from Boc-D-serine, respectively. They were confirmed to be active enantiomers. This enantioselective route and these intermediates can be utilized for synthetic optimization of these derivatives. As well the

improvement of the *in vitro* activity encouraged our further exploration of (3*R*,4*S*)-piperidine diamine derivatives as Factor Xa inhibitor.

EXPERIMENTAL

General. All solvents and reagents were used as acquired from commercial sources without purification. The melting points were determined on a Büchi B-545 or Yanagimoto Micro Melting Point Apparatus and are uncorrected. Column chromatography was performed on Merck silica gel 60 (0.063-0.200 mm). Flash chromatography was performed using a YAMAZEN ULTRA PACK$_{TM}$ column. Thin-layer chromatography (TLC) was performed on a Merck pre-coated TLC glass sheets with silica gel 60 F254. The ^{1}H-NMR spectra were recorded on a JEOL JNM-EX400 spectrometer and chemical shifts are given in ppm (δ) from tetramethylsilane, which was used as the internal standard. The ESI mass spectra were recorded on a SCIEX API-150EX spectrometer, an Agilent Technologies Agilent 1100 series LC/MSD or a Thermoquest FINNING AQA. The FAB mass spectra were recorded on a JEOL JMS-HX110 spectrometer. The HR-ESI mass spectra were recorded on JMS-T100LP AccuTOF LC-plus. The IR spectra were recorded on a Hitachi 270-30 spectrometer. Optical rotations were determined on a HORIBA SEPA-300 high sensitive polarimeter.

***tert*-Butyl (4*R*)-4-[methoxymethylcarbamoyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (5)**

(i) To the solution of Boc-D-serine (150 g, 731 mmol) in CH_2Cl_2 (1.80 L), *N*,*O*-dimethylhydroxylamine hydrochloride（72.6 g, 744 mmol), *N*-methylmorpholine (83.0 mL, 755 mmol) and CH_2Cl_2 (600 mL) were added. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (145 g, 754 mmol) was added gradually under cooling at -15 ºC, and the resultant mixture was stirred at -15 to -9 ºC for 2 h. After adding 1M hydrochloric acid, the organics were extracted with CH_2Cl_2 twice. The organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give N^2-(*tert*-butoxycarbonyl)-*N*-methoxy-*N*-methyl-D-serinamide (**4**) (171 g, 94%) as a white solid. This compound was used directly in the next steps without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.51-2.74 (1H, m), 3.24 (3H, s), 3.78 (3H, s), 3.79-3.87 (2H, m), 4.71-4.89 (1H, m), 5.50-5.69 (1H, m). MS (ESI) *m/z*: 149 (M - Boc)$^+$, 193 (M – tBu).

(ii) Boron trifluoride diethyl etherate (2.00 mL, 15.92 mmol) was added to the mixture of compound **4** (171 g, 690 mmol) and 2,2-dimethoxypropane (500 mL, 4.09 mol) in acetone (1.00 L) at rt. After stirring at rt for 1.5 h, triethylamine (5.60 mL) was added. The resultant mixture was concentrated *in vacuo*, and EtOAc and 10% aqueous citric acid were added to the residue. After extracting with EtOAc, the organic layer was combined and washed with 10% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After adding hexane to the residue, the title compound was precipitated and collected by filtration (193 g) as a white

solid. Furthermore the title compound (7.33 g) was obtained from filtrate by column chromatography on silica gel (hexane / EtOAc = 4 / 1 → 2 / 1). In total the title compound (200 g, quant.) was obtained. mp 67-68 ºC (lit., mp 66.5-67.5 ºC [5], 65.7-67.5 ºC [6]). $[\alpha]_D^{25}$ +39.4 (c 1.00, $CHCl_3$). (lit., $[\alpha]_D$ +35.8[5], 37.1[6] (c 2.36, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (4.5H, s), 1.50 (4.5H, s), 1.53 (1.5H, s), 1.57 (1.5H, s), 1.68 (1.5H, s), 1.71 (1.5H, s), 3.22 (3H, s), 3.70 (1.5H, s), 3.75 (1.5H, s), 3.93 (0.5H, dd, *J* = 9.2, 3.5 Hz), 3.97 (0.5H, dd, *J* = 9.2, 2.9 Hz), 4.15-4.24 (1H, m), 4.73 (0.5H, dd, *J* = 7.1, 3.7 Hz), 4.81 (0.5H, dd, *J* = 7.1, 2.9 Hz). MS (ESI) *m/z*: 189 (M - Boc)$^+$, 311 (M + Na)$^+$, 599 (2M + Na)$^+$.

tert-Butyl (4*S*)-4-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (7)

(i) To the solution of compound **5** (200 g, 694 mmol) in THF (1.00 L), 1.0 M lithium aluminum hydride THF solution (347 mL, 347 mmol) was added gradually over 30 min under ice cooling. The reaction mixture was stirred for 30 min under ice cooling. The reaction was stopped by cautiously adding saturated aqueous $KHSO_3$ solution (900 mL). After diluting with Et_2O (2.00 L), the mixture was stirred for 20 min. The insoluble substance was eliminated through a Celite pad and the filtrate was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give *tert*-butyl (4*R*)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (**6**) (180.58 g) as a colorless oil. This compound was used directly in the next steps without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.39-1.71 (15H, m), 3.94 (0.5H, dd, *J* = 9.2, 5.5 Hz), 3.99-4.28 (2H, m), 4.28-4.39 (0.5H, m), 9.55 and 9.61 (total 1H, each s).

(ii) To the solution of compound **6** (181 g) in toluene (600 mL) was added ethyl (triphenylphosphoranylidene)acetate (275 g, 789.2 mmol) in toluene solution (400 mL), and the reaction mixture was stirred at 80 °C for 14 h. After concentration *in vacuo*, mixed solvent (hexane / EtOAc = 8 / 1) was added to the residue. The insoluble substances were eliminated by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane / EtOAc = 9 / 1 → 8 / 1 → 7 / 1) to give the title compound (207 g, quant. from **5**) containing a slight amount of *Z*-isomer as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, *J* = 6.5 Hz), 1.35-1.69 (15H, m), 3.80 (1H, dd, *J* = 9.1, 2.5 Hz), 4.09 (1H, dd, *J* = 9.1, 6.9 Hz), 4.14-4.26 (2H, m), 4.34-4.47 (1H, m), 4.49-4.62 (1H, m), 5.79-6.00 (1H, m), 6.75-6.93 (1H, m). MS (ESI) *m/z*: 200 (M - Boc)$^+$, 244 (M - tBu)$^+$, 322 (M + Na)$^+$.

tert-Butyl (4*S*)-4-[1-(benzylamino)-3-ethoxy-3-oxopropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (8)

To the solution of compound **7** (202 g, 674 mmol) in EtOH (1.00 L) was added benzylamine (37.5 mL, 343 mmol) and the reaction mixture was refluxed for 16 h. After adding benzylamine (37.5 mL, 343 mmol) to the reaction mixture, the reaction mixture was refluxed for another 2 days. After cooling the mixture, the solvent was distilled off *in vacuo*. The residue was purified by chromatography on silica gel

(hexane / EtOAc = 10 / 1 → 9 / 1 → 8 / 1 → 0 / 1) to give the title compound (220 g, 80%) as a pale green oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20-1.29 (3H, m), 1.38-1.67 (16H, m), 2.20-2.71 (2H, m), 3.20-3.45 (0.5H, br), 3.46-3.55 (0.5H, m), 3.73-3.96 (3H, m), 3.98-4.26 (4H, m), 7.18-7.34 (5H, m). MS (ESI) *m/z*: 407 $(M + H)^+$.

***tert*-Butyl (4*S*)-4-(1-amino-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (9)**

To the solution of compound **8** (220 g, 541 mmol) in EtOH (3.00 L) was added wet 10% palladium-on-carbon (40.8 g). The reaction mixture was stirred under a hydrogen atmosphere for 6.5 h. The catalyst was eliminated through a Celite pad and the filtrate was concentrated *in vacuo* to give the title compound (158 g, 93%) as a light grey oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J = 7.1 Hz), 1.42-1.52 (15H, m), 1.60 (2H, s), 2.17-2.33 (1H, m), 2.39-2.51 (0.5H, m), 2.52-2.64 (0.5H, m), 3.43-3.60 (1H, m), 3.68-4.00 (2H, m), 4.04 (1H, d, J = 7.8 Hz), 4.16 (2H, q, J = 7.1 Hz). MS (ESI) *m/z*: 317 $(M + H)^+$.

***tert*-Butyl (4*S*)-4-(1-{[(benzyloxy)carbonyl]amino}-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (10)**

To the solution of compound **9** (159 g, 502 mmol) in dioxane (220 mL) was added 9% aqueous $NaHCO_3$ solution (1.40 L). *N*-(Benzyloxycarbonyloxy)succinimide (134 g, 539 mmol) was added to the mixture for 15 min under ice cooling. The mixture was stirred for 14 h while it slowly returned to rt. EtOAc and water were added to the mixture. After extracting with EtOAc, the organic layer was combined and washed with water, 10% aqueous citric acid solution and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane / EtOAc = 10 / 1 → 8 / 1 → 6 / 1 → 2 / 1) to give the title compound (228 g, quant.) as a light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (1.5H, t, J = 7.1 Hz), 1.24 (1.5H, t, J = 7.1 Hz), 1.36-1.64 (15H, m), 2.37-2.73 (2H, m), 3.78-4.00 (2H, m), 4.00-4.48 (4H, m), 5.09 (2H, s), 5.30-5.45 (0.25H, br), 5.52-5.70 (0.25H, br), 5.80-6.00 (0.25H, br), 6.10-6.32 (0.25H, br), 7.26-7.39 (5H, m). MS (ESI) *m/z*: 351 $(M - Boc)^+$, 473 $(M + Na)^+$. HRMS (ESI) Calcd for $C_{23}H_{35}N_2O_7$: 451.24443. Found: 451.24494.

Ethyl (3*S*,4*S*)-3-{[(benzyloxy)carbonyl]amino}-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate (11A) and ethyl (3*R*,4*S*)-3-{[(benzyloxy)carbonyl]amino}-4-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-pentanoate (11B)

p-Toluenesulfonic acid hydrate (96.2 g, 505 mmol) was added to the solution of compound **10** (228 g, 507 mmol) in a mixed solution of EtOH (1.20 L) and water (60 mL), and the mixture was refluxed for 20 min. p-Toluenesulfonic acid hydrate (5.00 g, 26.3 mmol) was added, and the mixture was refluxed for another 20 min. After cooling to rt, the solvent was distilled off *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.30 L), and triethylamine (92 mL) and di-*tert*-butyl dicarbonate (112 g, 511 mmol) were added to the solution. After stirring for 18 h at rt, CH_2Cl_2 and water were added to the mixture. After extracting with CH_2Cl_2, the organic layer was combined and washed with 10% aqueous citric acid solution,

saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane / EtOAc = 8 / 1 → 6 / 1 → 4 / 1 → 2 / 1). Comparatively high purity fractions of each isomer were concentrated and the residues were stirred in combined solvent (hexane – EtOAc) respectively. Each of the chiral isomers were filtrated as white solids. The filtrate was combined and purified by flash chromatography on silica gel (hexane / EtOAc = 4 / 1). In total (**11A**; less polar isomer) (68.9 g, 33%) and (**11B**; higher polar isomer) (82.5 g, 40%) were respectively obtained as white solids.

(3*S*,4*S*)-isomer (**11A**; less polar isomer): mp 106-108 °C. $[\alpha]_D^{25}$ -5.67 (c 1.00, $CHCl_3$). IR (ATR) cm^{-1}: 3504, 3349, 1732, 1680, 1527, 1300, 1240, 1269, 1211, 1169, 1082, 1039, 1026. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, *J* = 7.1 Hz), 1.42 (9H, s), 2.57-2.71 (2H, m), 3.35-3.56 (1H, m), 3.65 (1H, t, *J* = 9.9 Hz), 3.70-3.80 (2H, m), 3.86-3.99 (1H, m), 4.05-4.25 (2H, m), 5.10 (1H, d, *J* = 12.4 Hz), 5.14 (1H, d, *J* = 12.4 Hz), 5.16-5.26 (1H, m), 5.90-6.08 (1H, m), 7.30-7.40 (5H, m). MS (ESI) *m/z*: 311 $(M - Boc)^+$, 355 $(M - tBu)^+$, 433 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{30}ClN_2O_7$: C, 58.52; H, 7.37; N, 6.32. Found: C, 58.50; H, 7.34; N, 6.60.

(3*R*,4*S*)-isomer (**11B**; higher polar isomer): mp 89-90 °C. $[\alpha]_D^{25}$ +31.7 (c 1.00, $CHCl_3$). IR (ATR) cm^{-1}: 3352, 1716, 1676, 1531, 1234, 1184, 1053. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, *J* = 7.2 Hz), 1.41 (9H, s), 2.48-2.72 (2H, m), 3.19-3.53 (2H, m), 3.53-3.70 (1H, m), 3.70-3.85 (1H, m), 4.05-4.20 (2H, m), 4.24-4.45 (1H, m), 4.72-4.88 (1H, m), 5.08 (1H, d, *J* = 12.4 Hz), 5.12 (1H, d, *J* = 12.4 Hz), 5.52-5.83 (1H, m), 7.28-7.39 (5H, m). MS (ESI) *m/z*: 311 $(M - Boc)^+$, 355 $(M - tBu)^+$, 411 $(M + H)^+$, 433 $(M + Na)^+$. Anal. Calcd for $C_{20}H_{30}ClN_2O_7$: C, 58.52; H, 7.37; N, 6.32. Found: C, 58.45; H, 7.38; N, 6.70.

Benzyl [(4*S*,5*R*)-5-(*tert*-butoxycarbonyl)amino-2-oxopiperidin-4-yl]carbamate (13)

(i) Triethylamine (40.0 mL, 287 mmol) and methanesulfonyl chloride (13.0 mL, 168.0 mmol) were sequentially added to the solution of compound **11A** (58.5 g, 143 mmol) in CH_2Cl_2 (700 mL) under ice cooling and the mixture was stirred for 1 h under ice cooling. After adding water, the mixture was stirred for 10 min. 10% aqueous citric acid solution and CH_2Cl_2 were added to the mixture. After extracting with CH_2Cl_2, the organic layer was combined and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain crude mesylate (75.0 g). DMF (700 mL) and sodium azide were added to the crude mesylate and the mixture was stirred for 6 h at 60 °C. After cooling to rt, the mixture was diluted with EtOAc and water. After extracting with EtOAc, the organic layer was combined and washed with brine and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was stirred in combined solvent (hexane / EtOAc = 10 / 1) and filtrated to obtain ethyl (3*S*,4*R*)-5-azide-3-{[(benzyloxy)carbonyl]amino}-4-[(*tert*-butoxy-carbonyl)amino]pentanoate (**12**) (57.5 g, 93%) as a white solid. This compound was used directly in the next steps without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, *J* = 7.1 Hz), 1.43 (9H, s),

2.56-2.68 (2H, m), 3.48-3.60 (2H, m), 3.88-3.97 (1H, m), 4.04-4.97 (1H, br), 5.10 (2H, s), 5.60-5.75 (1H, br), 7.30-7.40 (5H, m). MS (ESI) *m/z*: 336 $(M - Boc)^+$, 436 $(M + H)^+$, 458 $(M + Na)^+$.

(ii) Lindlar catalyst (8.73 g) and EtOH (200 mL) were added to the suspension of compound **12** (57.4 g, 132 mmol) in THF (700 mL). The mixture was stirred for 20 h under a hydrogen atmosphere. The catalyst was removed through a Celite pad and washed with THF (300 mL). The filtrate was stirred for 17 h at 50 °C. After cooling to rt, the solvent was distilled off *in vacuo*. THF (400 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and benzyloxycarbonyl chloride (5.0 mL) were added to the residue, and the mixture was stirred for 3 h at rt. The mixture was diluted with EtOAc and water. After extracting with EtOAc, the organic layer was combined and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH = 50 / 1 → 40 / 1 → 30 / 1) to obtain the title compound (46.3 g, 89%) as a white solid. mp 69-72 °C. $[\alpha]_D^{25}$ -30.0 (c 0.40, $CHCl_3$). IR (ATR) cm^{-1}: 3315, 1695, 1655, 1529, 1496, 1365, 1333, 1238, 1163, 1043. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 2.25-2.50 (1H, m), 2.61-2.93 (1H, m), 3.13-3.33 (1H, m), 3.38-3.66 (1H, m), 4.01-4.24 (2H, m), 5.11 (2H, s), 5.32-5.51 (1H, br), 5.53-5.82 (1H, br), 6.03-6.32 (1H, br), 7.28-7.40 (5H, m). MS (ESI) *m/z*: 364 $(M + H)^+$. Anal. Calcd for $C_{18}H_{25}ClN_3O_5$: C, 58.76; H, 6.99; N, 11.42. Found: C, 58.73; H, 7.00; N, 11.43.

Benzyl {(3*R*,4*S*)-3-[(*tert*-butoxycarbonyl)amino]piperidin-4-yl}carbamate (14)

To the solution of compound **13** (45.0 g, 124 mmol) in THF (250 mL) was added borane-THF complex (1M THF solution) (480 mL, 480 mmol) and the mixture was stirred for 13.5 h at rt. The reaction was stopped by adding dropwisely MeOH (300 mL), and the resultant mixture was concentrated *in vacuo*. Ethanol (675 mL), water (75 mL) and triethylamine (150 mL) were added to the residue, and the mixture was refluxed for 24 h. After removing the solvent *in vacuo*, the residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH = 50 / 1 → 30 / 1 → 20 / 1 → 10 / 1 → 8 / 1) to obtain the title compound (24.9 g, 57%) as a white solid. mp 103-105 °C. $[\alpha]_D^{25}$ -39.2 (c 1.00, $CHCl_3$). IR (ATR) cm^{-1}: 3330, 1716, 1668, 1514, 1344, 1246, 1169, 1078, 1066. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.46-2.01 (3H, m), 2.60-2.71 (1H, m), 2.81 (1H, br d, *J* = 12.2 Hz), 2.87-3.07 (2H, m), 3.57-3.76 (1H, m), 3.86-4.00 (1H, m), 5.07 (1H, d, *J* = 12.4 Hz), 5.12 (1H, d, *J* = 12.4 Hz), 5.31-5.60 (2H, m), 7.27-7.39 (5H, m). MS (ESI) *m/z*: 294 $(M - tBu)^+$, 350 $(M + H)^+$. Anal. Calcd for $C_{18}H_{27}N_3O_4 \cdot 0.6H_2O$: C, 60.01; H, 7.89; N, 11.66. Found: C, 59.98; H, 7.74; N, 11.68.

Benzyl {[(3*R*,4*S*)-1-Acetyl-3-[(*tert*-butoxycarbonyl)amino]piperidin-4-yl)carbamate (15A)

Triethylamine (5.0 mL) and acetic anhydride (250 μL, 2.65 mmol) were successively added to the solution of compound **14** (807 mg, 2.31 mmol) in CH_2Cl_2 (50 mL) under ice cooling. The mixture was stirred for 3.5 h while it slowly returned to rt. After adding ice, the mixture was stirred for 10 min. 10%

aqueous citric acid solution and EtOAc were added, the oganic layer was washed with saturated aqueous $NaHCO_3$ solution and brine. After drying with Na_2SO_4, the solvent was distilled off. The residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH = 25 / 1) to obtain the title compound (250 mg, 58%) as a white powder. mp 63-66 °C. IR (ATR) cm^{-1}: 1704, 1620, 1511, 1453, 1365, 1304, 1243, 1160, 1043, 1001. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.85-2.15 (2H, m), 2.07 (1.5H, s), 2.14 (1.5H, s), 2.75-2.90 (1H, m), 3.10-3.20 (0.5H, m), 3.25-3.35 (0.5H, br d, *J* = 14.2 Hz), 3.65-4.05 (3H, m), 3.65-4.05 (3H, m), 4.38-4.47 (0.5H, br d, *J* = 13.0 Hz), 4.54-4.63 (0.5H, m), 4.69-4.83 (1H, br), 4.98-5.20 (2.5H, m), 5.90-6.05 (0.5H, br), 7.30-7.40 (5H, m). MS (ESI) *m/z*: 392 $(M + H)^+$. Anal. Calcd for $C_{20}H_{29}N_3O_5$: C, 60.53; H, 7.52; N, 10.59. Found: C, 60.54; H, 7.53; N, 10.33.

***tert*-Butyl [(3*R*,4*S*)-1-acetyl-4-{[(5-chloroindol-2-yl)carbonyl]amino}piperidin-3-yl]carbamate (16A)**

To the solution of compound **15A** (745 mg, 1.90 mmol) in EtOH (50 mL) was added 10% palladium-on-carbon (532 mg) and the mixture was stirred for 16 h under a hydrogen atmosphere. The catalyst was eliminated through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was dissolved in DMF (15.0 mL), and triethylamine (400 μL, 2.87 mmol), 5-chloroindole-2-carboxylic acid (467 mg, 2.39 mmol), 1-hydroxybenzotriazole (311 mg, 2.30 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (550 mg, 2.87 mmol) were added to the solution. After stirring for 5 h at rt, the mixture was diluted with CH_2Cl_2 and 10% aqueous citric acid solution was added. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine. After drying with Na_2SO_4, the solvent was distilled off. The residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH = 50 / 1) to obtain the title compound (650 mg, 79%) as a pale yellow solid. mp 228-231 °C (decomp). IR (ATR) cm^{-1}: 3266, 1625, 1544, 1365, 1250, 1159, 990. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.60-1.80 (2H, m), 2.12 (1H, s), 2.16 (2H, s), 2.30-2.45 (0.5H, m), 2.67-2.82 (0.3H, m), 2.89 (0.7H, d, *J* = 13.7 Hz), 3.23 (0.7H, t, *J* = 12.9 Hz), 3.37 (0.3H, d, *J* = 13.7 Hz), 3.81-3.95 (1H, m), 4.05-4.33 (2H, m), 4.62-4.72 (0.3H, br), 4.77 (0.7H, d, *J* = 13.7 Hz), 5.10-5.27 (1H, m), 6.81 (0.3H, br s), 6.85 (0.7H, s), 7.21 (1H, br d, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 8.8 Hz), 7.57 (0.3H, br s), 7.61 (0.7H, s), 8.55-8.65 (0.5H, br), 9.43-9.53 (0.7H, br), 9.60-9.70 (0.3H, br). MS (ESI) *m/z*: 435 $(M + H)^+$. Anal. Calcd for $C_{21}H_{27}ClN_4O_4 \cdot 0.5H_2O$: C, 56.52; H, 6.36; Cl, 7.99; N, 12.62. Found: C, 56.70; H, 6.38; Cl, 8.09; N, 12.59.

***N*-[(3*R*,4*S*)-1-Acetyl-4-{[(5-chloroindol-2-yl)carbonyl]amino}piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxamide hydrochloride ((-)-1A)**

To the solution of compound **16A** (630 mg, 1.45 mmol) in dioxane (15 mL) was added 4M hydrochloric acid dioxane solution (7.0 mL, 28 mmol). After stirring for 1 h at rt, the mixture was concentrated *in vacuo*. The resultant yellow solid was dissolved in DMF (20 mL) and lithium (5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)carboxylate (379 mg, 1.86 mmol), 1-hydroxybenzotriazole (250 mg,

1.86 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (370 mg, 1.93 mmol) and triethylamine (300 μL, 2.15 mmol) were added. After stirring for 3 days at rt, the mixture was diluted with CH_2Cl_2 and 10% aqueous citric acid solution was added. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine. After drying with Na_2SO_4, the solvent was distilled off. The residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH = 20 / 1) and preparative thin layer chromatography on silica gel ($CHCl_3$ / MeOH = 10 / 1) to obtain the free form of the title compound (330 mg, 44%) as a white solid. ^{1}H-NMR (DMSO-d_6) δ: 1.65-1.85 (1H, m), 1.87 and 2.06 (total 3H, each s), 1.88-2.10 (1H, m), 2.37 (3H, s), 2.65-2.77 (2H, m), 2.79-2.89 (2H, m), 2.99-3.09 (0.5H, m), 3.30-3.52 (2H, m), 3.64 (2H, s), 3.70-3.80 (0.5H, m), 3.96-4.21 (2H, m), 4.27 (1H, br s), 4.35-4.48 (1H, m), 7.07 and 7.11 (total 1H, each s), 7.18 (1H, d, J = 8.8 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.71 (1H, s), 8.16-8.22 (1H, m), 8.37 and 8.46 (total 1H, each d, J = 7.8 Hz), 11.81 and 11.83 (total 1H, each s).

To the solution of the free form of the title compound (200 mg) in a mixed solvent of EtOH (20 mL) and $CHCl_3$ (0.5 mL) was added 1M hydrochloric acid solution in EtOH (1.0 mL) and the mixture was concentrated *in vacuo*. Diethyl ether was added to the residue and the precipitate was filtrated and dried *in vacuuo* to obtain the title compound (178 mg) as a white powder. mp 202-222 °C (decomp). $[\alpha]_D^{25}$ -56.0 (c 0.500, MeOH). IR (KBr) cm^{-1}: 1631, 1547, 1442, 1421, 1319, 1242, 1061, 991. ^{1}H-NMR (DMSO-d_6) δ: 1.66-1.85 (1H, m), 1.88 and 2.06 (total 3H, each s), 1.89-2.10 (1H, m), 2.92 (3H, s), 3.05-3.30 (2H, m), 3.30-3.55 (2.5H, m), 3.62-3.82 (1.5H, m), 3.96-4.18 (2H, m), 4.20-4.34 (1H, m), 4.35-4.50 (2H, m), 4.65-4.77 (1H, m), 7.08 and 7.12 (total 1H, each s), 7.18 (1H, d, J = 8.8 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.71 (1H, s), 8.22-8.52 (2H, m), 11.15-11.50 (1H, br), 11.86 (1H, br s). MS (ESI) *m/z*: 515 $(M + H)^+$. Anal. Calcd for $C_{24}H_{27}ClN_6O_3S \cdot HCl \cdot 2H_2O$: C, 49.06; H, 5.49; Cl, 12.07; N, 14.30; S, 5.46. Found: C, 49.21; H, 5.37; Cl, 12.10; N, 14.31; S, 5.17.

Benzyl {[(3*R*,4*S*)-3-[(*tert*-butoxycarbonyl)amino]-1-(2-methoxyacetyl)piperidin-4-yl)carbamate (15B)

Compound **14** (825 mg, 2.36 mmol), methoxyacetyl chloride (0.26 mL, 2.83 mmol), triethylamine (6.50 mL, 47.2 mmol) and CH_2Cl_2 (40 mL) were treated as described for **15A**, to give the title compound (818 mg, 82%) as a white solid. mp 56-59 °C. IR (ATR) cm^{-1}: 1704, 1643, 1511, 1453, 1245, 1161, 1043, 1002. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.71-2.12 (2H, m), 2.66-2.85 (0.75H, m), 2.93 (0.25H, br d, J = 13.3 Hz), 3.03-3.16 (0.25H, m), 3.22 (0.75H, br d, J = 13.7 Hz), 3.41 (3H, s), 3.70-4.23 (5H, m), 4.35-4.58 (1H, m), 4.71-4.96 (0.25H, br), 5.08 (1H, d, J = 12.5 Hz), 5.12 (1H, d, J = 12.5 Hz), 5.25-5.43 (0.75H, br), 5.55-5.76 (0.75H, br), 5.83-6.00 (0.25H, br), 7.28-7.40 (5H, m). MS (ESI) *m/z* 322 $(M - Boc)^+$, 388 $(M + H)^+$, 444 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{31}N_3O_6 \cdot 0.25H_2O$: C, 59.21; H, 7.45; N, 9.86. Found: C, 59.13; H, 7.48; N, 9.72.

tert-Butyl [(3*R*,4*S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(methoxyacetyl)piperidin-3-yl]carbamate (16B)

Compound **15B** (812 mg, 1.93 mmol), 10% palladium-on-carbon (812 mg) and EtOH (80 mL) were treated as described for **16A** to give crude *tert*-butyl {[(3*R*,4*S*)-4-amino-1-(2-methoxyacetyl)piperidin-3-yl)carbamate. This crude amine, 5-chloroindole-2-carboxylic acid (701 mg, 3.59 mmol), 1-hydroxybenzoriazole (291 mg, 2.15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (688 mg, 3.59 mmol) and DMF (30 mL) were treated as described for **16A** to give the title compound (652 mg, 73%) as a white solid. mp 130-133 °C. IR (ATR) cm^{-1}: 1634, 1545, 1365, 1252, 1158. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.60-1.80 (1H, m), 2.20-2.40 (1H, m), 2.70-2.80 (0.6H, m), 2.90-3.00 (0.4H, m), 3.15-3.30 (0.4H, m), 3.32-3.40 (0.6H, m), 3.46 and 3.49 (total 3H, each s), 3.85-4.30 (5H, m), 4.55-4.80 (1H, m), 5.11 (0.4H, br s), 6.05 (0.6H, br s), 6.86 (1H, s), 7.20 (1H, dd, J = 8.7, 2.0 Hz), 7.33 (1H, d, J = 8.7 Hz), 7.61 (1H, s), 8.40-8.60 (1H, m), 9.41 (1H, br s). MS (FAB) *m/z*: 465 $(M + H)^+$. HRMS (ESI) Calcd for $C_{22}H_{29}{}^{35}ClN_4NaO_5$: 487.16973. Found: 487.16961.

***N*-[(3*R*,4*S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxamide hydrochloride ((-)-1B)**

Compound **16B** (646 mg 1.39 mmol), 4M hydrochloric acid dioxane solution (20 mL) and dioxane (10 mL) were treated as described for **1A** to give crude *N*-[(3*R*,4*S*)-3-amino-1-(2-methoxyacetyl)piperidin-4-yl]-5-chloroindole-2-carboxamide. This crude amine, lithium (5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-*c*]pyridin-2-yl)carboxylate (343 mg, 1.68 mmol), 1-hydroxybenzoriazole (262 mg, 1.94 mmol), triethylamine (1.25 mL, 9.03 mmol), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (495 mg, 2.58 mmol) and DMF (40 mL) were treated as described for **1A**, to give the title compound (178 mg, 39%) as a pale yellow solid.

(Free foam): ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.85 (2H, m), 2.20-2.50 (1H, m), 2.52 (3H, s), 2.70-3.00 (4H, m), 3.30-3.85 (7H, m), 3.95-4.35 (3H, m), 4.40-4.50 (1H, m), 4.60-4.90 (1H, m), 6.90 (1H, s), 7.18-7.35 (2H, m), 7.64 (1H, s), 7.67 and 8.19 (total 1H, each br s), 9.18 (1H, s).

(HCl salt): mp 207-220 °C (decomp). $[\alpha]_D^{25}$ -53.4 (c 0.515, MeOH). IR (ATR) cm^{-1}: 3255, 2935, 2884, 2823, 1643, 1546, 1463, 1442, 1417, 1369, 1319, 1257. ^{1}H-NMR (DMSO-d_6) δ: 1.70-1.80 (1H, m), 1.85-2.05 (1H, m), 2.90 (3H, s), 3.00-3.20 (2H, m), 3.16 (3H, s), 3.22-3.82 (7H, m), 3.88-4.80 (5H, m), 7.09 (1H, d, J = 9.0 Hz), 7.17 (1H, dd, J = 8.8, 1.9 Hz), 7.42 (1H, d, J = 8.8 Hz), 7.70 (1H, d, J = 1.9 Hz), 8.29 (1H, br s), 8.40-8.50 (1H, m), 11.20-11.50 (1H, m), 11.85 (1H, s). MS (ESI) *m/z*: 545 $(M + H)^+$. Anal. Calcd for $C_{25}H_{29}ClN_6O_4S{\cdot}HCl{\cdot}H_2O$: C, 50.08; H, 5.38; Cl, 11.83; N, 14.02; S, 5.35. Found: C, 49.94; H, 5.28; Cl, 11.58; N, 13.87; S, 5.54.

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