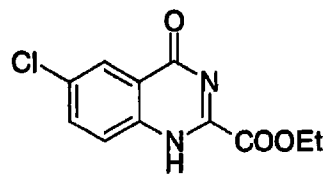
346 was dissolved in tetrahydrofuran (30 ml), and n-butyllithium (1.59 N hexane solution, 4.46 ml) was added dropwise at -78°C under an argon atmosphere. The temperature of the reaction mixture was allowed to raise to room temperature and stirred for 1 hour. The reaction mixture was cooled again to -78°C, stirred for 2 minutes under a carbon dioxide atmosphere and then warmed to room temperature. After the reaction mixture was concentrated under reduced pressure, saturated aqueous solution of sodium chloride and ethyl acetate were added to the residue to conduct liquid separation. 3N Hydrochloric acid was added to the resultant water layer to acidify it, and extraction was conducted with ethyl acetate. The resultant organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain the title compound (453 mg).

^{1}H-NMR (DMSO-d_6) δ: 7.55(2H,d,J=8.5Hz), 7.66(2H,d,J=8.5Hz), 13.90(1H,br.s).

MS (EI) m/z: 180(M^+).

[Referential Example 348]

Ethyl 6-chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylate:



Ethyl chlorooxoacetate (2.0 ml) was added to a solution of 2-amino-5-chlorobenzamide (2.50 g) in pyridine

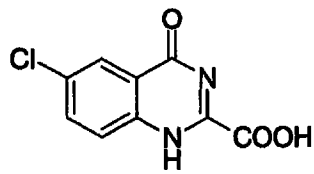
(15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in acetic acid (50 ml). Acetic anhydride (5.0 ml) was added to the solution, and the mixture was heated under reflux for 16 hours. The solvent was distilled off under reduced pressure, and ethanol was added to the residue. Crystals deposited were collected by filtration and washed to obtain the title compound (2.71 g).

^{1}H-NMR (DMSO-d_6) δ: 1.35(3H,t,J=7.1Hz), 4.38(2H,q,J=7.1Hz), 7.85(1H,d,J=8.6Hz), 7.91(1H,dd,J=8.6,2.3Hz), 8.10(1H,d,J=2.3Hz), 12.85(1H,br.s).

MS (ESI) m/z: 253$(M+H)^+$.

[Referential Example 349]

6-Chloro-4-oxo-1,4-dihydroquinazoline-2-carboxylic acid:



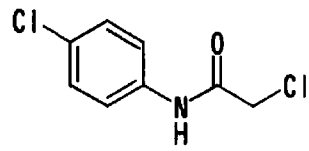
Lithium hydroxide (263 mg) was added to a solution of the compound (1.26 g) obtained in Referential Example 348 in a mixed solvent of water (5 ml) and tetrahydrofuran (15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized with 1N hydrochloric acid (11 ml) under ice cooling and stirred for 1 hour. Crystals deposited were collected by filtration and washed with water to obtain the title compound (0.96 g).

^{1}H-NMR (DMSO-d_6) δ: 7.50-8.20(3H,m), 12.44(1H,br.s).

MS (ESI) m/z: 265$(M+H+CH_3CN)^+$.

[Referential Example 350]

2-Chloro-N-(4-chlorophenyl)acetamide:

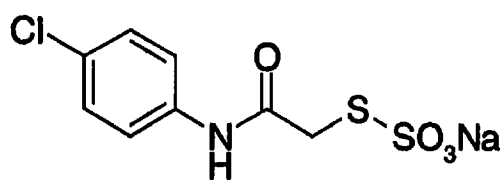


p-Chloroaniline (3.82 g) was dissolved in ethyl acetate (30 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 3.5 hours, crystals deposited were collected by filtration to obtain the title compound (4.78 g). The filtrate was concentrated to about 1/4, and crystals deposited were collected by filtration to obtain the title compound (1.01 g).

^{1}H-NMR ($CDCl_3$) δ: 4.19(2H,s), 7.33(2H,d,J=9.0Hz), 7.51(2H,d,J=9.0Hz), 8.22(1H,br.s).

[Referential Example 351]

Sodium S-[2-(4-chloroanilino)-2-oxoethyl]thiosulfate:



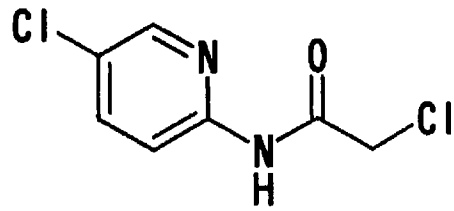
The compound (5.79 g) obtained in Referential Example

350 was dissolved in ethanol (140 ml), and an aqueous solution (140 ml) of sodium thiosulfate pentahydrate (7.04 g) was added at a time at 70°C to heat the mixture under reflux for 1.5 hours. The reaction mixture was concentrated to about 1/10, and crystals deposited were collected by filtration to obtain the title compound (8.20 g).

^{1}H-NMR (DMSO-d_6) δ: 3.73(2H,s), 7.35(2H,d,J=8.8Hz), 7.57(2H,d,J=8.8Hz), 10.30(1H,s).

[Referential Example 352]

2-Chloro-N-(5-chloropyridin-2-yl)acetamide hydrochloride:

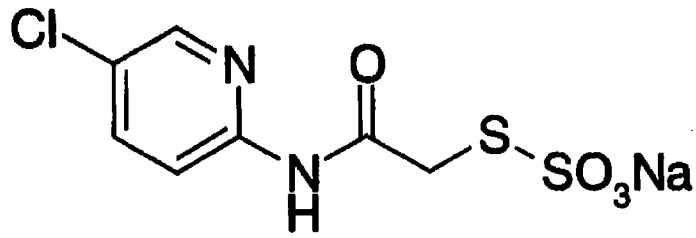


2-Amino-5-chloropyridine (3.85 g) was dissolved in ethyl acetate (60 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 30 minutes, chloroacetyl chloride (0.5 ml) was additionally added, and the mixture was stirred at 60°C for additional 1 hour. Powder deposited was collected by filtration to obtain the title compound (6.18 g).

^{1}H-NMR (DMSO-d_6) δ: 4.36(2H,s), 7.94(1H,dd,J=8.8,2.7Hz), 8.09(1H,d,J=8.8Hz), 8.40(1H,d,J=2.7Hz), 11.03(1H,s).

[Referential Example 353]

Sodium S-{2-[(5-chloropyridin-2-yl)amino]-2-oxoethyl}thiosulfate:



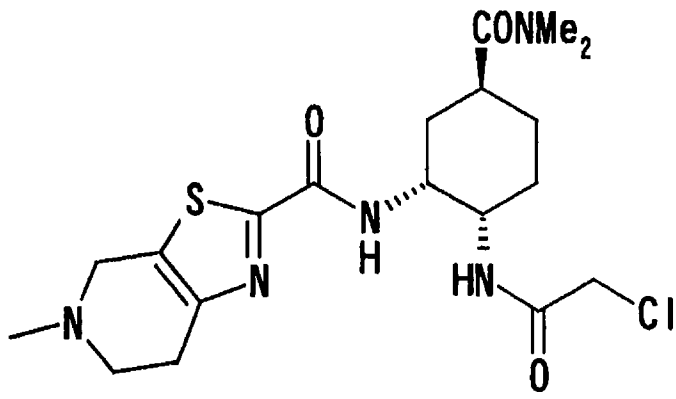
An aqueous solution (130 ml) with sodium thiosulfate pentahydrate (6.35 g) and sodium hydrogencarbonate (2.15 g) dissolved therein was added to a solution with the compound (6.18 g) obtained in Referential Example 352 dissolved in

ethanol (130 ml) at a time at 80°C under stirring, and the mixture was heated under reflux at 110°C for 2 hours. The reaction mixture was concentrated to solids under reduced pressure, and ethanol (500 ml) was added to the residue. The resultant mixture was heated and extracted twice. The extract was concentrated to about 1/20, and diethyl ether was added. Insoluble matter deposited was collected by filtration to obtain the title compound (6.65 g).

^{1}H-NMR (DMSO-d_6) δ: 3.77(2H,s), 7.89(1H,dd,J=9.0,2.7Hz), 8.09(1H,d,J=9.0Hz), 8.34(1H,d,J=2.7Hz), 10.57(1H,s).

[Referential Example 354]

N-{(1R,2S,5S)-2-[(2-chloroacetyl)amino]-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrathiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (100 mg) obtained in Referential Example 253 was disslved in ethyl acetate (10 ml), and chloroacetyl chloride (21.6 μl) was added to heat and stir the mixture at 60°C for 30 minutes. After allowing the reaction mixture to cool, insoluble matter was collected

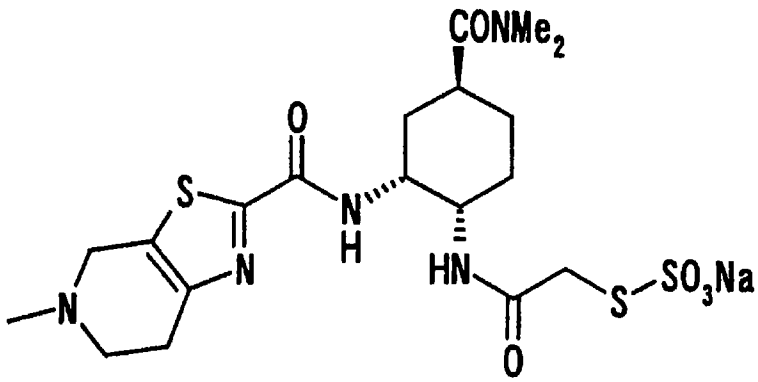
by filtration and dissolved in methylene chloride-methanol, and the solvent was distilled off under reduced pressure to obtain the crude title compound (112 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(1H,m), 1.55-2.00(5H,m), 2.78(3H,s), 2.98(3H,s), 3.00-3.25(5H,m), 3.17(3H,s), 3.80-3.90(1H, m), 3.96(1H,d,J=12.9Hz), 4.00-4.15(1H,m), 4.02(1H,d,J=12.9Hz), 4.45-4,70(2H,m), 7.85-8.00(1H,br), 8.12(1H,d,J=7.3Hz), 8.35(1H,d,J=8.3Hz).

MS (ESI) m/z: 442$(M+H)^+$.

[Referential Example 355]

Sodium S-{2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrathiazolo[5,4-c]pyridine-2-yl)-carbonyl]amino}cyclohexyl)amino]-2-oxoethyl}thiosulfate:



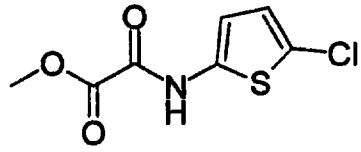
The compound (106 mg) obtained in Referential Example 354 was dissolved in ethanol (1.5 ml), and an aqueous solution (1.5 ml) of sodium thiosulfate pentahydrate (55 mg) and sodium hydrogencarbonate (18.6 mg) dissolved therein was added at a time at 90°C under stirring. The resultant mixture was heated under reflux for 1 hour. The

reaction mixture was concentrated to solids under reduced pressure, and ethanol (10 ml) was added to the residue. The resultant mixture was heated and extracted. The extract was concentrated to about 1/2, and isopropyl ether (10 ml) was added. Insoluble matter deposited was collected by filtration to obtain the title compound (72 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(1H,m), 1.55-1.90(5H,m), 2.40(3H,s), 2.78(3H,s), 2.80-3.10(5H,m), 2.96(3H,s), 3.44(1H,d,J=14.2Hz), 3.50(1H,d,J=14.2Hz), 3.68(2H,s), 3.75-3.90(1H,m), 4.45-4.50(1H,m), 8.01(1H,d,J=7.4Hz), 8.15(1H,d,J=8.3Hz).

[Referential Example 356]

Methyl 2-[(5-chlorothien-2-yl)amino]-2-oxoacetate:



Triethylamine (1.25 ml) and diphenylphosphoryl azide (1.55 ml) were added to a suspension of 5-chlorothiophene-2-carboxylic acid (0.99 g) in toluene (20 ml), and the mixture was stirred at 80°C for 1 hour. After the reaction mixture was cooled to room temperature, tert-butanol (2 ml) was added, and the mixture was heated under reflux for 19 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride (200 ml) was added to the resultant residue. The resultant mixture was

successively washed with distilled water, a 10% aqueous solution of citric acid, distilled water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain tert-butyl 5-chloro-2-thienylcarbamate (1.05 g).

^{1}H-NMR ($CDCl_3$) δ: 1.51(9H,s), 6.21(1H,d,J=3.1Hz), 6.60(1H,d,J=3.1Hz), 6.91(1H,br.s).

MS (ESI) m/z: 234$(M+H)^+$.

After the product (1.87 g) obtained above was added to a 4N dioxane solution (40 ml) of hydrochloric acid, and the mixture was stirred at room temperature for 4 hours, the solvent was distilled off under reduced pressure. The residue was suspended in tetrahydrofuran (50 ml), and sodium hydrogencarbonate (2.02 g) and methyl chlorooxoacetate (0.883 ml) were added under ice cooling to stir the mixture at room temperature for 18 hours. After the solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation, the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel

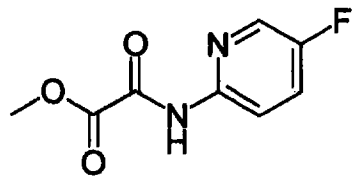
(hexane:ethyl acetate = 3:1), and the solvent was distilled off to obtain the title compound (1.44 g).

^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 6.61(1H,d,J=4.2Hz), 6.75(1H,d,J=4.2Hz), 9.42(1H,br.s).

MS (FAB) m/z: 220$(M+H)^+$.

[Referential Example 357]

Methyl 2-[(5-fluoropyridin-2-yl)amino]-2-oxoacetate:



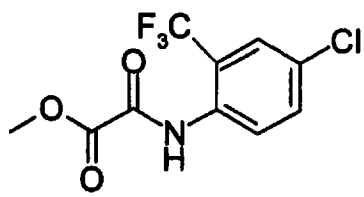
The title compound was obtained from 2-amino-5-fluoropyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.48-7.53(1H,m), 8.21(1H,d,J=2.9Hz), 8.27-8.31(1H,m), 9.41(1H,br.s).

MS (FAB) m/z: 198$(M+H)^+$.

[Referential Example 358]

Methyl 2-[4-chloro-2-(trifluoromethyl)anilino]-2-oxoacetate:



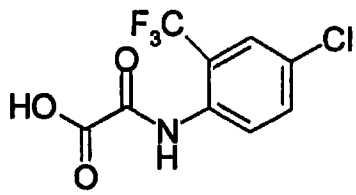
The title compound was obtained from 4-chloro-2-trifluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 4.01(3H,s), 7.58(1H,dd, J=8.8,2.2Hz), 7.65(1H,d,J=2.2Hz), 8.34(1H,d,J=8.8Hz), 9.30(1H,br.s).

MS (EI) m/z: 281$(M+H)^+$.

[Referential Example 359]

2-[4-Chloro-2-(trifluoromethyl)anilino]-2-oxoacetic acid:



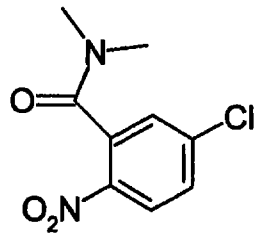
Lithium hydroxide (28 mg) was added to a solution of the compound (297 mg) obtained in Referential Example 358 in a mixed solvent of tetrahydrofuran (7ml) and water (3 ml), and the mixture was stirred at room temperature for 2 hours. 1N Hydrochloric acid (8 ml) and methylene chloride (20 ml) were added to the reaction mixture to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was dried to obtain the title compound (291 mg).

^{1}H-NMR ($CDCl_3$) δ: 7.61(1H,dd,J=8.8,2.5Hz), 7.68(1H,d,J=2.5Hz), 8.26(1H,d,J=8.8Hz), 9.36(1H,br.s).

MS (ESI, anion) m/z: 267$(M-H)^-$

[Referential Example 360]

5-Chloro-N,N-dimethyl-2-nitrobenzamide:

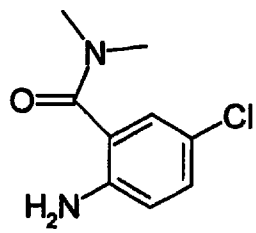


The title compound was obtained by condensing 5-chloro-2-nitrobenzoic acid with dimethylamine in a similar manner to the process described in Referential Example 143.

^{1}H-NMR ($CDCl_3$) δ: 2.86(3H,s), 3.16(3H,s), 7.38(1H,d,J=2.2Hz), 7.51(1H,dd,J=8.8,2.2Hz), 8.15(1H,d,J=8.8Hz).

[Referential Example 361]

2-Amino-5-chloro-N,N-dimethylbenzamide:



Iron(III) chloride hexahydrate (9.93 g) and zinc powder (8.01 g) were added to a solution of the compound (2.8 g) obtained in Referential Example 360 in a mixed solvent of N,N-dimethylformamide (80 ml) and water (40 ml), and the mixture was heated under reflux for 20 minutes. The reaction mixture was filtered through Celite 545, and ethyl acetate (200 ml) was added to the filtrate to conduct liquid separation. The resultant water layer was washed with ethyl acetate (100 ml x 2), and organic layers

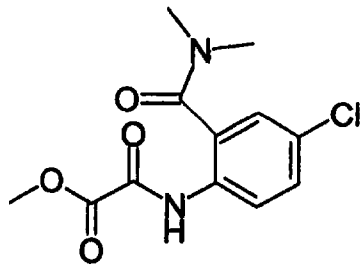
were combined, washed with distilled water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was subjected to column chromatography on silica gel (methylene chloride:hexane = 1:1 → 1:0 → methanol:methylene chloride = 1:100) to obtain the title compound (2.41 g).

^{1}H-NMR ($CDCl_3$) δ: 3.13(6H,s), 4.33(2H,br), 6.65(1H,d,J=8.5Hz), 7.07(1H,d,J=2.2Hz), 7.11(1H,dd,J=8.5,2.2Hz).

MS (ESI) m/z: 240$(M+MeCN)^+$.

[Referential Example 362]

Methyl 2-{4-chloro-2-[(dimethylamino)carbonyl]anilino}-2-oxoacetate:

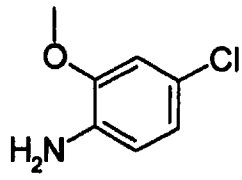


The title compound was obtained from the compound obtained in Referential Example 361 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.09(6H,br), 3.96(3H,s), 7.30(1H,d,J=2.4Hz), 7.41(1H,d,J=8.8,2.4Hz), 8.34(1H,d,J=8.8Hz), 10.46(1H,br).

MS (ESI) m/z: 285$(M+H)^+$.

[Referential Example 363] 4-Chloro-2-methoxyaniline:



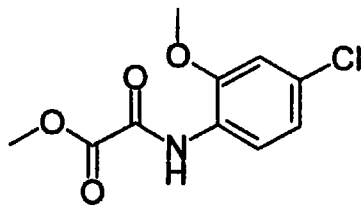
The title compound was obtained from 5-chloro-2-nitroanisole in a similar manner to the process described in Referential Example 361.

^{1}H-NMR ($CDCl_3$) δ: 3.65-3.95(2H,br), 3.87(3H,s), 6.61(1H,d,J=8.8Hz), 6.74-6.78(2H,m).

MS (ESI) m/z: 199$(M+MeCN+H)^+$.

[Referential Example 364]

Methyl 2-(4-chloro-2-methoxyanilino)-2-oxoacetate:



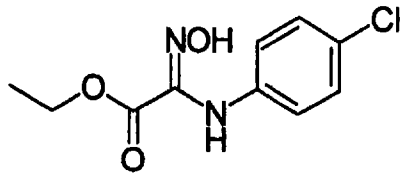
The title compound was obtained from the compound obtained in Referential Example 363 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.92(3H,s), 3.97(3H,s), 6.90(1H,d,J=2.2Hz), 6.98(1H,dd,J=8.8,2.2Hz), 8.35(1H,d,J=8.8Hz), 9.33-9.44(1H,br).

MS (ESI) m/z: 244$(M+H)^+$.

[Referential Example 365]

Ethyl 2-(4-chloroanilino)-2-(hydroxyimino)-acetate:



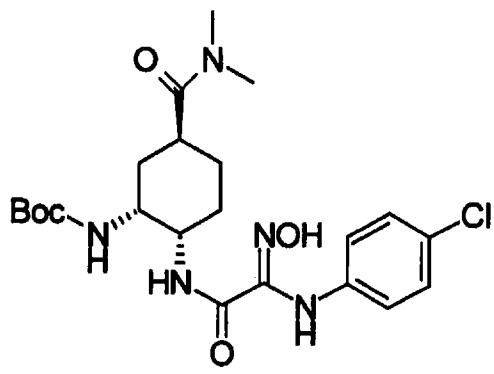
The title compound was obtained from 4-chloroaniline (3.03 g) and ethyl 2-chloro-2-hydroxyiminoacetate in a similar manner to the process described in literature (Gilchrist, T. L.; Peek, M. E.; Rees, C. W.; J. Chem. Soc. Chem. Commun., 1975, 913).

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.60-1.80(1H,br), 4.28(2H,q,J=7.1Hz), 6.85(2H,d,J=8.6Hz), 7.24(2H,d,J=8.6Hz), 8.15-8.45(1H,br).

MS (ESI) m/z: 243$(M+H)^+$.

[Referential Example 366]

tert-Butyl (1R,2S,5S)-2-{[2-(4-chloroanilino)-2-(hydroxyimino)acetyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:



The compound (597 mg) obtained in Referential Example 144 was added to a solution of the compound (350 mg) obtained in Referential Example 365 in ethanol (5.0 ml),

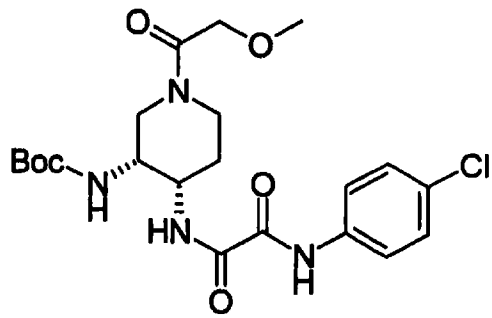
and the mixture was stirred at 70°C for 3 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (180 mg).

^{1}H-NMR (CD_3OD) δ: 1.46(9H,s), 1.47-1.84(6H,m), 1.88-1.95(1H,m), 2.90(3H,s), 3.08(3H,s), 3.90-3.97(1H,m), 4.11-4.17(1H,m), 6.84(2H,d,J=8.8Hz), 7.18(2H,d,J=8.8Hz).

MS (ESI) m/z: 504$(M+Na)^+$.

[Referential Example 367]

tert-Butyl (3R,4S)-4-{[2-(4-chloroanilino)-2-oxoacetyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



The title compound was obtained from the compound obtained in Referential Example 374 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

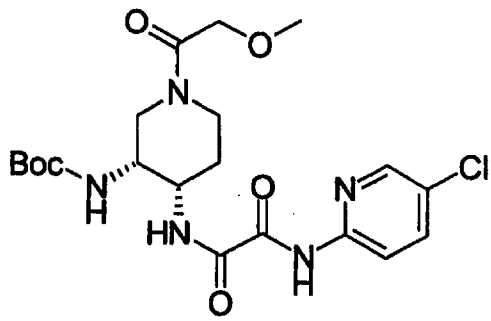
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.94-2.07(1H,br), 2.70-3.00(1H,m), 3.10-3.37(1H,m), 3.44(3H,s), 3.88-4.22(4H,m), 4.55-4.69(1H,br), 4.80-4.90(0.5H,br), 5.36-5.48(0.5H,br), 7.20-7.30(1H,br), 7.32(2H,d,J=8.8Hz),

7.62(2H,d,J=8.8Hz), 8.20-8.40(1H,br), 9.15-9.25(1H,br).

MS (ESI) m/z: 469$(M+H)^+$.

[Referential Example 368]

tert-Butyl (3R,4S)-4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



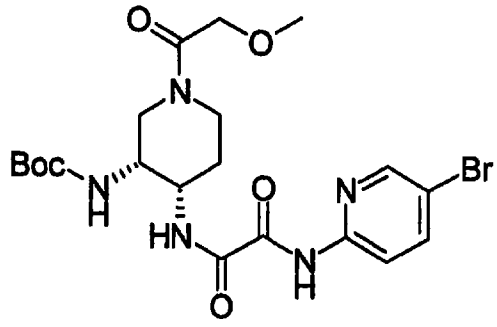
The title compound was obtained from the compound obtained in Referential Example 266 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.65-2.30(2H,br), 2.68-3.02(1H,m), 3.10-3.35(1H,m), 3.44(3H,s), 3.80-4.25(4H,m), 4.45-4.70(1H,m), 5.05-5.20(0.5H,m), 5.80-5.93(0.5H,m), 7.30-7.40(1H,br), 7.71(1H,br d,J=8.7Hz), 7.95-8.05(0.3H,br), 8.19(1H,br d,J=8.8 Hz), 8.31(1H,br.s), 8.38-8.53(0.7H,br), 9.74-9.84(1H,br).

MS (ESI) m/z: 470$(M+H)^+$.

[Referential Example 369]

tert-Butyl (3R,4S)-4-({2-[(5-bromopyridin-2-yl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:

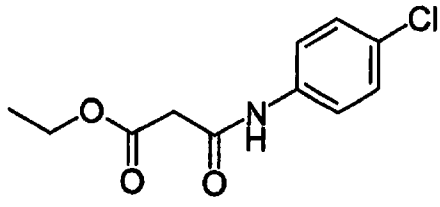


The title compound was obtained from the compound obtained in Referential Example 375 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.50-1.75(1H,m), 1.95-2.13(1H,br), 2.70-2.98(1H,m), 3.05-3.36(1H,m), 3.45(3H,s),3.80-4.24(4H,m), 4.57-4.73(1H,br), 4.85-4.95(0.25H,br), 5.10-5.15(0.25H,br), 5.45-5.58(0.5H,br), 7.30-7.38(1H,m), 7.84(1H,dd,J=8.8,2.2Hz), 8.16(1H,d,J=8.8Hz), 8.30-8.55(1H,br), 8.40(1H,d,J=2.2Hz), 9.68(1H,br.s).

[Referential Example 370]

Ethyl 3-(4-chloroanilino)-3-oxopropionate:



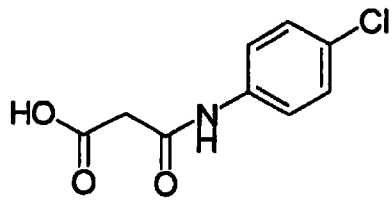
Potassium ethyl malonate (3.2 g), 1-hydroxybenzotriazole (2.1 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.5 g) were successively added to a solution of 4-chloroaniline (2.0 g) in N,N-

dimethylformamide (20 ml) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of sodium hydrogencarbonate, a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (4.0 g).

^{1}H-NMR ($CDCl_3$) δ: 1.33(3H,t,J=7.3Hz), 3.47(2H,s), 4.26(2H,q,J=7.3Hz), 7.29(2H,d,J=8.8Hz), 7.51(2H,d,J=8.8Hz), 9.32(1H,br.s).

[Referential Example 371]

3-(4-Chloroanilino)-3-oxopropionic acid:



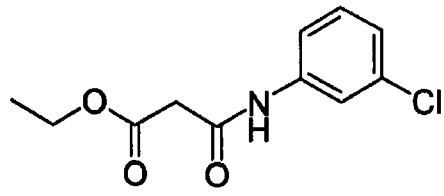
A 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to a solution of the compound (1.0 g) obtained in Referential Example 370 in ethanol (10 ml) at room temperature, and the mixture was stirred for 2 hours. 1N Hydrochloric acid (10 ml) was added to the reaction mixture, the mixture was stirred, and insoluble matter deposited was then collected by filtration to obtain the title compound (0.5 g).

^{1}H-NMR (DMSO-d_6) δ: 3.34(2H,s), 7.35(2H,d,J=8.8Hz),

7.59(2H,d,J=8.8Hz), 10.26(1H,s), 12.66(1H,br.s).

[Referential Example 372]

Ethyl 3-(3-chloroanilino)-3-oxopropionate:

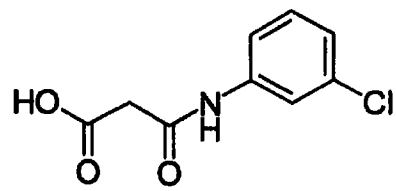


The title compound was obtained by condensing 3-chloroaniline with potassium ethyl malonate in a similar manner to the process described in Referential Example 370.

^{1}H-NMR ($CDCl_3$) δ: 1.33(3H,t,J=7.3Hz), 3.47(2H,s), 4.26(2H,q,J=7.3Hz), 7.09(1H,d,J=8.8Hz), 7.22-7.26(1H,m), 7.39(1H,d,J=8.8Hz), 7.69(1H,s), 9.35(1H,br.s).

[Referential Example 373]

3-(3-Chloroanilino)-3-oxopropionic acid:

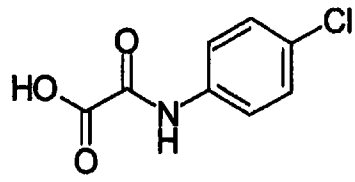


The title compound was obtained from the compound obtained in Referential Example 372 in a similar manner to the process described in Referential Example 371.

^{1}H-NMR (DMSO-d_6) δ: 3.35(2H,s), 7.11(1H,d,J=8.8Hz), 7.33(1H,t,J=8.8Hz), 7.39(1H,d,J=8.8Hz), 7.78(1H,s), 10.31(1H,s), 12.67(1H,br.s).

[Referential Example 374]

2-(4-Chloroanilino)-2-oxoacetic acid:

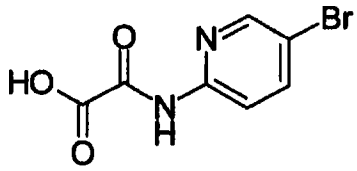


The title compound was obtained from the compound obtained in Referential Example 242 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 7.37(2H,d,J=8.8Hz), 7.79(2H,d,J=8.8Hz), 10.66(1H,s).

[Referential Example 375]

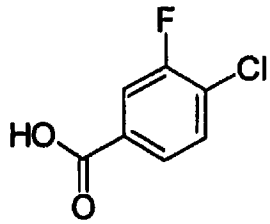
2-[(5-Bromopyridin-2-yl)amino]-2-oxoacetic acid:



The title compound was obtained from the compound obtained in Referential Example 262 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 7.95-8.00(1H,m), 8.08(1H,dd,J=8.8,2.0Hz), 8.50(1H,d,J=2.0Hz), 10.74(1H,s).

[Referential Example 376] 4-Chloro-3-fluorobenzoic acid:



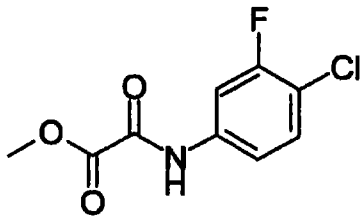
Sodium chlorite (17 g) was added portionwise to a mixture solution composed of 4-chloro-3-fluorobenzaldehyde

(10 g), amidosulfuric acid (18 g), tert-butyl alcohol (50 ml) and water (50 ml) under ice cooling, and the mixture was stirred for 4 days while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, 1N hydrochloric acid and saturated aqueous solution of sodium chloride. After the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure, the resultant residue was recrystallized from a mixed solvent of diisopropyl ether and hexane to obtain the title compound (11.2 g).

^{1}H-NMR (DMSO-d_6) δ: 7.72(1H,dt,J=8.3,1.5Hz), 7.77(1H,dt,J=8.3,1.6Hz), 7.82(1H,dt,J=9.7,1.5Hz), 13.45(1H,s).

[Referential Example 377]

Methyl 2-(4-chloro-3-fluoroanilino)-2-oxoacetate:



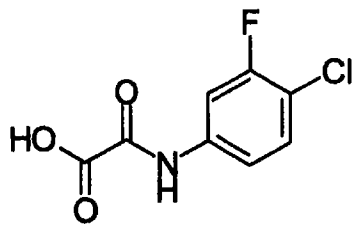
The title compound was obtained by subjecting the compound obtained in Referential Example 376 to Curtius rearrangement reaction and then condensing this product with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 356.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.25-7.27(1H,m),

7.39(1H,t,J=8.5Hz), 7.72(1H,dd,J=10.4,2.4Hz),
8.90(1H,br.s).

[Referential Example 378]

2-(4-Chloro-3-fluoroanilino)-2-oxoacetic acid:

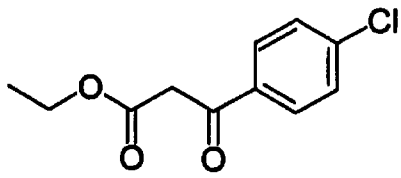


The title compound was obtained from the compound obtained in Referential Example 377 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 7.52(1H,t,J=8.8Hz),
7.63(1H,dd,J=8.8,2.2Hz), 7.88(1H,dd,J=12.0,2.2Hz),
10.83(1H,br.s).

[Referential Example 379]

Ethyl 3-(4-chlorophenyl)-3-oxopropionate:



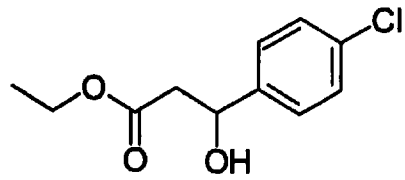
Triethylamine (17 ml) and magnesium chloride (5.5 g) were added to a suspension of potassium ethyl malonate (8.2 g) in ethyl acetate (100 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. On the other hand, a suspension composed of 4-chlorobenzoic acid (5.0 g), thionyl chloride (12 ml), N,N-

dimethylformamide (one drop) and toluene (100 ml) was heated under reflux for 1 hour, and the reaction mixture was then concentrated. The resultant residue was dissolved in ethyl acetate, and the solution was added dropwise to the reaction mixture previously prepared under ice cooling. The resultant mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the mixture was stirred for 30 minutes to separate the resultant organic layer. The organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (6.4 g).

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.3Hz), 3.96(2H,s), 4.21(2H,q,J=7.3Hz), 7.46(2H,d,J=8.8Hz), 7.89(2H,d,J=8.8Hz).

[Referential Example 380]

Ethyl 3-(4-chlorophenyl)-3-hydroxypropionate:



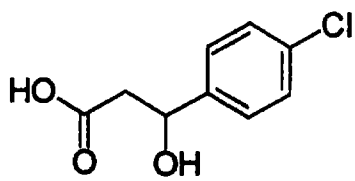
Sodium borohydride (0.2 g) was added portionwise under ice cooling to a solution of the compound (1.0 g) obtained in Referential Example 379 in tetrahydrofuran (10

ml), and the mixture was stirred for 2 hours while the temperature of the system was gradually raised to room temperature. A 10% aqueous solution of citric acid was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was isolated and purified by column chromatography on silica gel (chloroform) to obtain the title compound (0.56 g).

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.3Hz), 2.70(1H,d,J=7.8Hz), 2.71(1H,d,J=3.4Hz), 3.37(1H,d,J=3.4Hz), 4.18(2H,q,J=7.3Hz), 5.09-5.13(1H,m), 7.30-7.35(5H,m).

[Referential Example 381]

3-(4-Chlorophenyl)-3-hydroxypropionic acid:



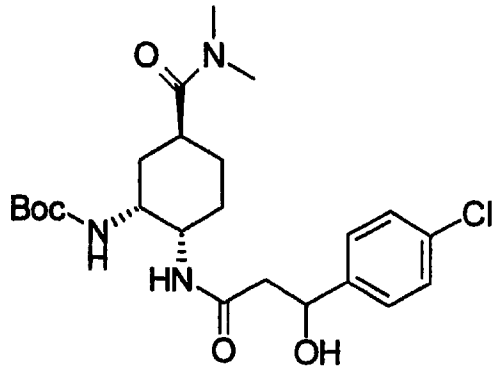
The title compound was obtained from the compound obtained in Referential Example 380 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 3.25-3.32(1H,m), 4.89-4.95(1H,m), 5.45-5.53(1H,m), 7.35-7.36(5H,m), 12.11-12.18(1H,m).

MS (ESI,anion) m/z: 198$(M-H)^-$.

[Referential Example 382]

tert-Butyl (1R,2S,5S)-2-{[3-(4-chlorophenyl)-3-hydroxypropanoyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:



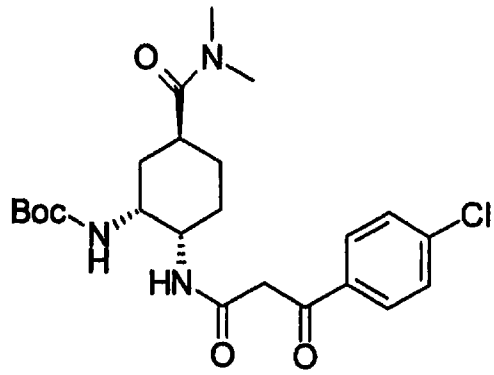
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 381 in a similar manner to the process described in Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.44(2H,m), 1.46(9H,s), 1.76-1.92(2H,m), 1.95-2.10(2H,m), 2.40-2.55(2H,m), 2.55-2.68(1H,m), 2.94(3H,s), 3.05(3H,s), 3.82-3.96(1H,m), 4.02-4.17(1H,m), 4.65-4.80(2H,m), 5.03-5.13(1H,m), 7.28-7.33(5H,m).

MS (ESI) m/z: 468$(M+H)^+$.

[Referential Example 383]

tert-Butyl (1R,2S,5S)-2-{[3-(4-chlorophenyl)-3-oxopropanoyl]amino}-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:



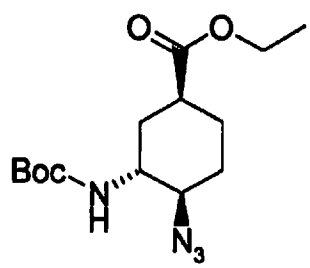
Manganese dioxide (0.47 g) was added to a solution of the compound (0.5 g) obtained in Referential Example 382 in 1,4-dioxane (20 ml) at room temperature, and the mixture was stirred for 4 days. Insoluble matter was removed by filtration through Celite pad, and the resultant filtrate was concentrated under reduced pressure to obtain the title compound (0.46 g).

^{1}H-NMR (DMSO-d_6) δ: 1.28-1.39(1H,m), 1.40(9H,s), 1.41-1.63(3H,m), 2.25-2.42(2H,m), 2.76(3H,s), 2.90-2.97(1H,m), 2.98(3H,s), 3.56(2H,s), 3.89-3.97(1H,m), 4.88-4.98(1H,m), 6.65-6.70(1H,m), 7.30-7.35(4H,m), 7.33(1H,dd,J=2.9,1.7Hz).

MS (ESI,anion) m/z: 464(M-H)$^-$.

[Referential Example 384]

Ethyl (1S,3R,4R)-4-azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:



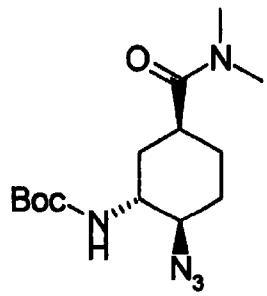
The title compound was obtained from the compound obtained in Referential Example 248 in a similar manner to the process described in Referential Example 249.

$[\alpha]_D^{25}$ +62° (c=1, chloroform)

^{1}H-NMR ($CDCl_3$) δ: 1.27(3H,t,J=7.1Hz), 1.46(9H,s), 1.61(1H,s), 1.61-1.71(2H,m), 1.81-1.90(1H,m), 1.97-2.03(1H,m), 2.22-2.28(1H,m), 2.56-2.60(1H,m), 3.54(1H,br.s), 3.63-3.68(1H,m), 4.16(2H,q,J=7.1Hz), 4.58(1H,br.s).

[Referential Example 385]

tert-Butyl (1R,2R,5S)-2-azido-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



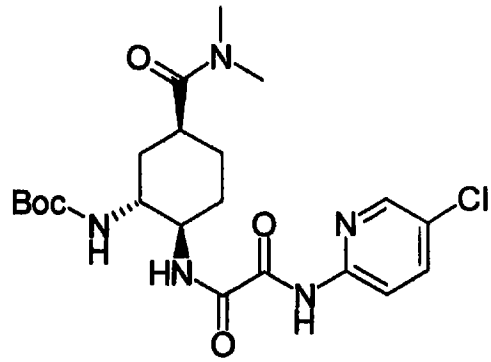
The title compound was obtained from the compound obtained in Referential Example 384 in similar manners to Referential Examples 250 and 251.

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.40-2.20(6H,m), 2.70-2.80(1H,m), 2.93(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 3.83-3.95(1H,m), 4.65(1H,d,J=7.2Hz).

[Referential Example 386]

tert-Butyl (1R,2R,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexyl-

carbamate:



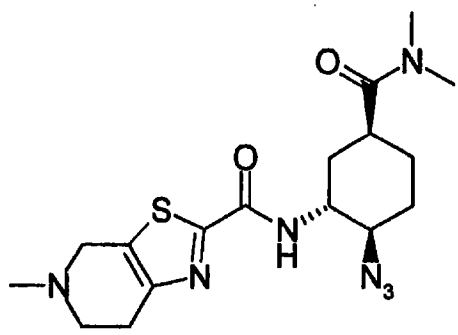
The title compound was obtained by converting the azide group of the compound obtained in Referential Example 385 into an amino group in a similar manner to the process described in Referential Example 90 and then condensing this product with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.13-2.25(16H,m), 2.94(3H,s), 3.03(3H,s), 3.60-3.78(1H,m), 4.13-4.31(1H,m), 4.45-4.65(1H,m), 7.80(1H,dd,J=8.8,2.4Hz), 8.03(1H,br.s), 8.21(1H,d,J=8.8Hz), 8.29(1H,d,J=2.4Hz), 9.71(1H,s).

MS (ESI) m/z: 468$(M+H)^+$.

[Referential Example 387]

N-{(1R,2R,5S)-2-Azido-5-[(dimethylamino)carbonyl]-cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:



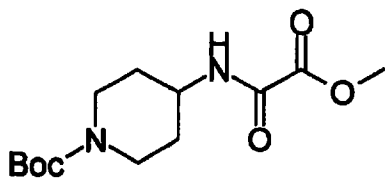
The title compound was obtained from the compound obtained in Referential Example 385 and the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.

^{1}H-NMR ($CDCl_3$) δ: 1.75-2.08(6H,m), 2.20-2.32(1H,m), 2.51(3H,s), 2.75-2.97(4H,m), 2.95(3H,s), 3.04(3H,s), 3.65-3.80(3H,m), 4.27-4.39(1H,m), 7.17-7.28(1H,m).

MS (ESI) m/z: 392$(M+H)^+$.

[Referential Example 388]

tert-Butyl 4-[(2-methoxy-2-oxoacetyl)amino]piperidine-1-carboxylate:



The title compound was obtained from (4-amino-N-tert-butoxycarbonyl)piperidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

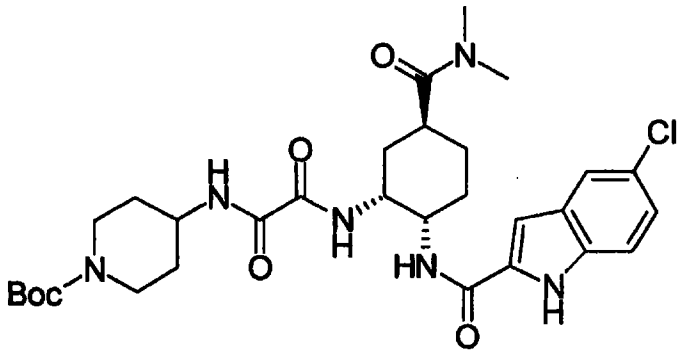
^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 1.34-1.51(2H,m), 1.89-

1.98(2H,m), 2.82-2.96(2H,m), 3.91(3H,s), 3.88-4.14(3H,m), 6.96-7.07(1H,m).

MS (FAB) m/z: 287$(M+H)^+$.

[Referential Example 389]

tert-Butyl 4-{[2-({(1R,2S,5S)-2-{[(5-chloroindol-2-yl)-carbonyl]amino}-5-[(dimethylamino)carboyl]cyclohexyl}-amino)-2-oxoacetyl]amino}piperidine-1-carboxylate:



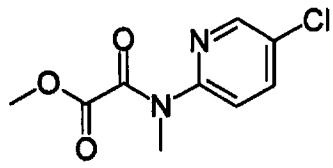
The title compound was obtained from the compound obtained in Referential Example 310 and the compound obtained in Referential Example 388 in a similar manner to the process described in Referential Example 191.

^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 1.35-2.28(11H,m), 2.70-3.18(9H,m), 3.80-4.57(4H,m), 6.78(1H,s), 7.15-8.12(6H,m), 9.45(1H,s).

MS (FAB) m/z: 617$(M+H)^+$.

[Referential Example 390]

Methyl 2-[(5-chloropyridin-2-yl)(methyl)amino]-2-oxoacetate:



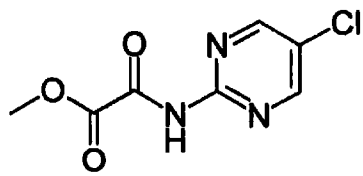
The title compound was obtained from 5-chloro-N-methyl-2-pyridineamine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.43(3H,s), 3.81(3H,s), 7.08(1H,br.s), 7.68-7.78(1H,m), 8.27(1H,br.s).

MS (ESI) m/z: 229$(M+H)^+$.

[Referential Example 391]

Methyl 2-[(5-chloropyrimidin-2-yl)amino]-2-oxoacetate:



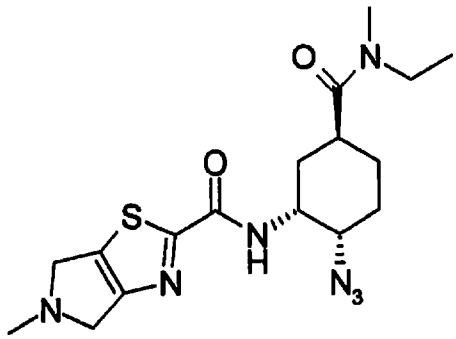
The title compound was obtained from 2-amino-5-chloropyrimidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 4.00(3H,s), 8.63(2H,s), 9.58(1H,br.s).

MS (ESI) m/z: 215$(M+H)^+$.

[Referential Example 392]

N-((1R,2S,5S)-2-Azido-5-{[ethyl(methyl)amino]carbonyl}-cyclohexyl)-5-methyl-5,6-dihydro-4H-pyrrolo[3,4-d]-thiazole-2-carboxamide:



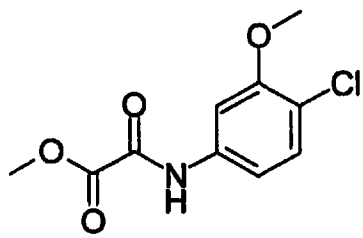
The title compound was obtained from the compound obtained in Referential Example 323 and the compound obtained in Referential Example 293 in a similar manner to the process described in Referential Example 252.

^{1}H-NMR ($CDCl_3$) δ: 1.08,1.15(3H,each t,J=7.1Hz), 1.74-1.88(4H,m), 2.12-2.22(2H,m), 2.67(3H,s), 2.81-2.86(1H,m), 2.89,2.96(3H,each s), 3.28-3.43(2H,m), 3.91-4.10(5H,m), 4.60-4.62(1H,m), 7.21(1H,d,J=7.6Hz).

MS (ESI) m/z: 392$(M+H)^+$.

[Referential Example 393]

Methyl 2-(4-chloro-3-methoxyanilino)-2-oxoacetate:



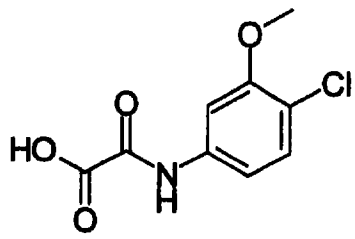
The title compound was obtained by reducing 2-chloro-5-nitroanisole in a similar manner to the process described in Referential Example 361 into an amino derivative and then condensing the amino derivative with

methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.93(3H,s), 3.98(3H,s), 7.00(1H,dd,J=8.5,2.4Hz), 7.33(1H,d,J=8.5Hz), 7.57(1H,d,J=2.4Hz), 8.89(1H,br.s).

[Referential Example 394]

2-(4-Chloro-3-methoxyanilino)-2-oxoacetic acid:



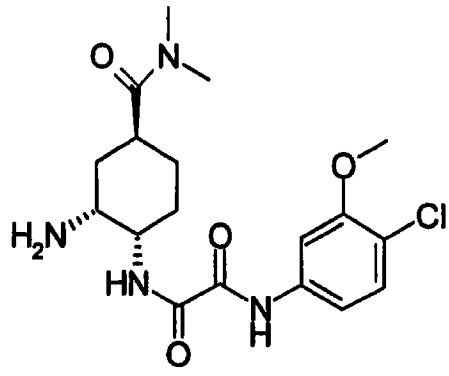
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 393 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 3.81(3H,s), 7.36(1H,d,J=8.7Hz), 7.43(1H,d,J=8.7Hz), 7.65(1H,d,J=2.2Hz), 10.79(1H,s).

MS (ESI, anion) m/z: 228$(M-H)^-$.

[Referential Example 395]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(4-chloro-3-methoxyphenyl)ethanediamide:



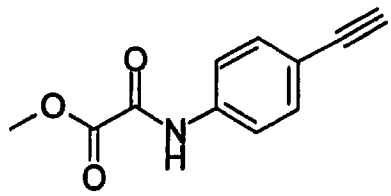
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 394 in a similar manner to the process described in Referential Example 97, treating this product with hydrochloric acid in a similar manner to the process described in Referential Example 69 and then neutralizing it with a 1N aqueous solution of sodium hydroxide.

^{1}H-NMR ($CDCl_3$) δ: 1.48-2.00(8H,m), 2.84-2.93(1H,m), 2.95(3H,s), 3.08(3H,s), 3.33-3.35(1H,m), 3.89-3.94(4H,m), 7.06(1H,dd,J=8.5,2.2Hz), 7.32(1H,d,J=8.5Hz), 7.56(1H,d,J=2.2Hz), 8.05(1H,d,J=8.5Hz), 9.43(1H,br.s).

MS (ESI) m/z: 397(M^+).

[Referential Example 396]

Methyl 2-(4-ethynylanilino)-2-oxoacetate:



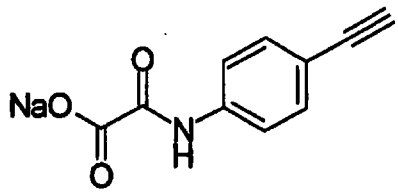
The title compound was obtained from 4-ethynylaniline

and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.09(1H,s), 3.98(3H,s), 7.50(2H,d,J=8.4Hz), 7.62(2H,d,J=8.4Hz), 8.89(1H,br.s).

[Referential Example 397]

Sodium 2-(4-ethynylanilino)-2-oxoacetate:

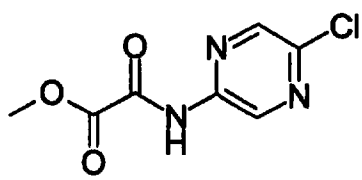


The title compound was obtained by hydrolyzing the compound obtained in Referential Example 396 with sodium hydroxide in a similar manner to the process described in Referential Example 266.

^{1}H-NMR (DMSO-d_6) δ: 4.06(1H,s), 7.39(2H,d,J=8.4Hz), 7.80(2H,d,J=8.4Hz), 10.33(1H,br.s).

[Referential Example 398]

Methyl 2-[(5-chloropyrazin-2-yl)amino]-2-oxoacetate:



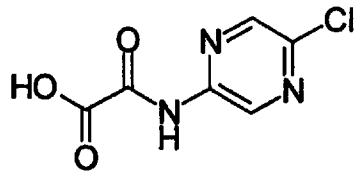
The title compound was obtained from 2-amino-5-chloropyrazine synthesized in accordance with literature (Sato, Nobuhiro et al., J. Heterocycl. Chem., 1982, 19(3), 673-4) and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 4.02(3H,s), 8.35(1H,d,J=1.5Hz), 9.37(1H,d,J=1.5Hz), 9.41(1H,br.s).

MS (FAB) m/z: 216$(M+H)^+$.

[Referential Example 399]

2-[(5-Chloropyrazin-2-yl)amino]-2-oxoacetic acid:



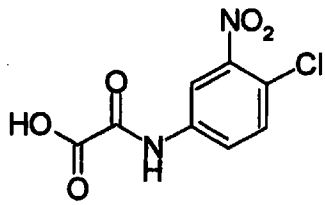
The title compound was obtained from the compound obtained in Referential Example 398 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR (DMSO-d_6) δ: 8.62(1H,s), 9.02(1H,br.s), 11.30(1H,s).

MS (EI) m/z: 201 M^+.

[Referential Example 400]

2-(4-Chloro-3-nitroanilino)-2-oxoacetic acid:



The title compound was obtained by condensing 4-chloro-3-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242 and then hydrolyzing this product in a similar manner to the process described in Referential Example 359.

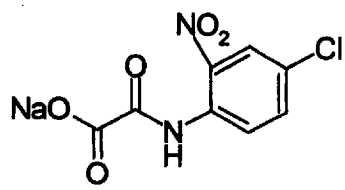
^{1}H-NMR (DMSO-d_6) δ: 7.76(1H,dd,J=8.8Hz), 8.04(1H,dd,J=8.8,2.4Hz), 8.55(1H,d,J=2.4Hz), 11.24(1H,s).

No proton attributable to the carboxylic acid was observed.

MS (EI) m/z: 244 M^+.

[Referential Example 401]

Sodium 2-(4-chloro-2-nitroanilino)-2-oxoacetate:

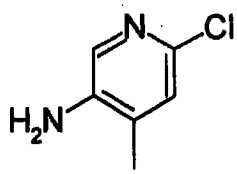


The title compound was obtained by condensing 4-chloro-2-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242, hydrolyzing this product in a similar manner to the process described in Referential Example 266, dissolvig the resultant residue in methanol, adding a 1N aqueous solution of sodium hydroxide and collecting precipitate formed by filtration.

^{1}H-NMR (DMSO-d_6) δ: 7.84(1H,dd,J=9.0,2.5Hz), 8.20(1H,d,J=2.5Hz), 8.67(1H,d,J=9.0Hz), 11.89(1H,s).

[Referential Example 402]

6-Chloro-4-methyl-3-pyridineamine:



2-Chloro-4-methyl-5-nitropyridine (173 mg) was dissolved in ethanol (5 ml), and a catalytic amount of Raney nickel catalyst was added to stir the mixture at

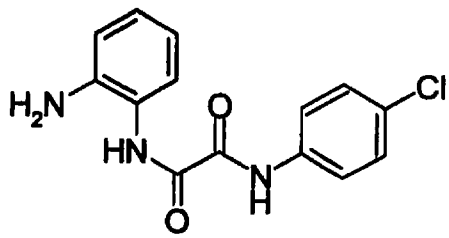
room temperature for 9 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:2) to obtain the title compound (113 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.13(3H,s), 3.85(2H,br.s), 6.96(1H,s), 7.74(1H,s).

MS (EI) m/z: 142 M^+.

[Referential Example 403]

N^1-(2-Aminophenyl)-N^2-(4-chlorophenyl)ethanamide:



The title compound was obtained by condensing 1,2-benzenediamine with the compound obtained in Referential Example 374 in a similar manner to the process described in Referential Example 59.

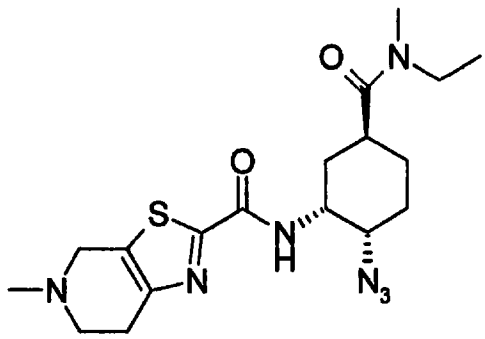
^{1}H-NMR (DMSO-d_6) δ: 5.00(2H,s), 6.59-6.63(1H,m), 6.78(1H,dd,J=8.1,1.2Hz), 6.96-7.01(1H,m), 7.25(1H,dd,J=7.8,1.2Hz), 7.44(2H,d,J=8.8Hz), 7.91(2H,d,J=8.8Hz), 10.04(1H,s),10.91(1H,s).

MS (FAB): 290$(M+H)^+$.

[Referential Example 404]

N-((1R,2S,5S)-2-Azido-5-{[ethyl(methyl)amino]carbonyl}-

cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

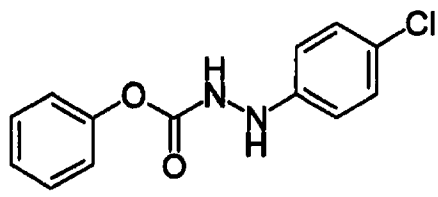


The title compound was obtained by treating the compound obtained in Referential Example 323 with hydrochloric acid, performing deprotection and then condensing this product with the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.

^{1}H-NMR ($CDCl_3$) δ: 1.08(1/2 of 3H,t,J=7.2Hz), 1.14(1/2 of 3H,t,J=7.2Hz), 1.70-1.90(4H,m), 2.10-2.25(2H,m), 2.52(3H,s), 2.78-3.00(8H,m), 3.25-3.45(2H,m), 3.69(1H,d,J=13.4Hz), 3.73(1H,d,J=13.4Hz), 3.87-3.95(1H,m), 4.55-4.62(1H,m), 7.26(1H,d,J=7.6Hz).

[Referential Example 405]

Phenyl 2-(4-chlorophenyl)-1-hydrazinecarboxylate:



(4-Chlorophenyl)hydrazine hydrochloride (3.00 g) was dissolved in tetrahydrofuran (50 ml), diethyl ether (50

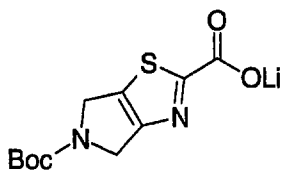
ml) and a saturated aqueous solution of sodium hydrogencarbonate. An organic layer was separated, dried over anhydrous sodium sulfate and then concentrated, giving (4-chlorophenyl)hydrazine as a brown solid. This product was dissolved in benzene (15 ml), and the solution was heated under reflux, to which a solution of diphenyl carbonate (5.22 g) in benzene (8.0 ml) was added dropwise over at least 30 minutes. After refluxing for 19 hours, the reaction mixture was allowed to cool and concentrated. Benzene (15 ml) was then added to the residue. The mixture was subjected to ultrasonic treatment, giving a suspension. After hexane (50 ml) was added to the suspension, and the mixture was stirred for 30 minutes, insoluble matter was collected by filtration and dried to obtain the title compound (1.05 g).

^{1}H-NMR ($CDCl_3$) δ: 5.86(1H,br.s), 6.83-6.92(3H,m), 7.17(1H,br.s), 7.20-7.32(4H,m), 7.37(2H,t,J=7.7Hz).

MS (ESI) m/z: 263$(M+H)^+$.

[Referential Example 406]

Lithium 5-tert-butoxycarbonyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole-2-carboxylate:

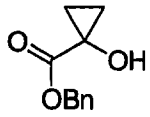


The title compound was obtained from the compound obtained in Referential Example 33 in a similar manner to the process described in Referential Example 10.

^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 4.30-4.70(4H,m).

[Referential Example 407]

Benzyl 1-hydroxycyclopropanecarboxylate:



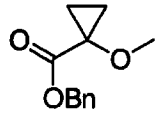
Triethylamine (1.0 ml) and benzyl bromide (650 µl) were added to a solution of 1-hydroxycyclopropanecarboxylic acid (409 mg) in tetrahydrofuran (3.0 ml), and the mixture was stirred at room temperature for 23 hours. Methylene chloride and 1N hydrochloric acid were added to the reaction mixture to separate the mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (607 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.16(2H,dd,J=7.9,4.9Hz), 1.32(2H,dd,J=7.9,4.9Hz), 3.09(0.5H,s), 3.11(0.5H,s), 5.17(2H,s), 7.30-7.39(5H,m).

MS (FAB) m/z: 192$(M+H)^+$.

[Referential Example 408]

Benzyl 1-methoxycyclopropanecarboxylate:



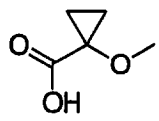
60% Sodium hydride in oil (345 mg) and methyl iodide (900 µl) were added to a solution of the compound (600 mg) obtained in Referential Example 407 in tetrahydrofuran (5.0 ml), and the mixture was heated under reflux for 28 hours. Ethyl acetate and a saturated aqueous solution of ammonium chloride were added to the reaction mixture to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. A crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to obtain the title compound (340 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.16(2H,dd,J=7.9,4.8Hz), 1.31(2H,dd,J=7.9,4.8Hz), 3.42(3H,s), 5.18(2H,s), 7.30-7.39(5H,m).

MS (FAB) m/z: 207$(M+H)^+$.

[Referential Example 409]

1-Methoxycyclopropanecarboxylic acid:

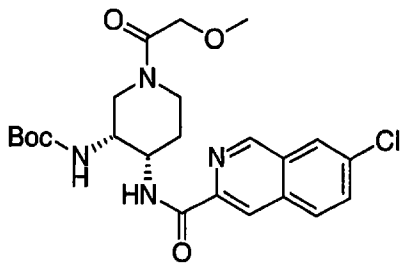


The title compound was obtained from the compound obtained in Referential Example 408 in a similar manner to the process described in Referential Example 152.

^{1}H-NMR ($CDCl_3$) δ: 1.23(2H,dd,J=8.0,4.9Hz), 1.38(2H,dd,J=8.0,4.9Hz), 3.45(3H,s), 8.80-9.00(1H,br).

[Referential Example 410]

tert-Butyl (3R,4S)-4-({7-chloroisoquinolin-3-yl}carbonyl)-amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:



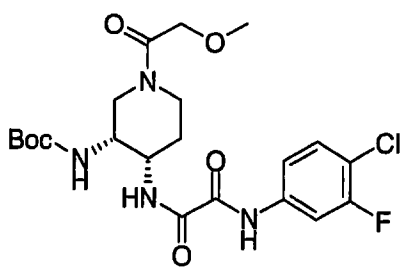
The title compound was obtained from the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,br s), 1.62-1.80(1H,m), 2.04-2.22(1H,m), 2.95-3.32(1H,m), 3.38-3.53(1H,m), 3.46(3H,s), 3.84-3.95(1H,m), 4.02-4.27(3H,m), 4.30-4.65(2H,m), 4.87-4.98(0.5H,br), 5.32-5.43(0.5H,br), 7.71(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.02(1H,s), 8.55-8.66(0.7H,br), 8.58(1H,s), 8.73-8.85(0.3H,br), 9.14(1H,br s).

MS (ESI) m/z: 477$(M+H)^+$.

[Referential Example 411]

tert-Butyl (3R,4S)-4-{[2-(4-chloro-3-fluoroanilino)-2-oxoacetyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



The title compound was obtained by condensing the

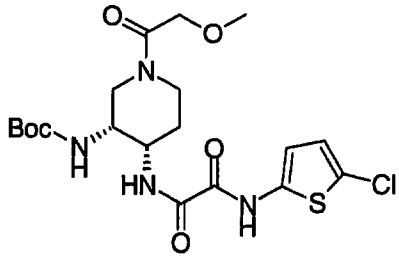
compound obtained in Referential Example 220 with the compound obtained in Referential Example 337 in a similar manner to the process described in Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.60-1.75(1H,m), 1.92-2.08(1H,m), 2.68-2.80(0.5H,m), 2.88-3.03(0.5H,m), 3.06-3.24(0.5H,m), 3.27-3.36(0.5H,m), 3.45(3H,s), 3.90-4.22(5H,m), 4.56-4.71(1H,m), 4.80-4.92(0.3H,br), 5.44-5.54(0.7H,br), 7.24(1H,d,J=12.9Hz), 7.35(1H,t,J=8.3Hz), 7.72(1H,dd,J=8.3,2.3Hz), 8.20-8.42(1H,br), 9.18-9.28(1H,br).

MS (ESI) m/z: 487$(M+H)^+$.

[Referential Example 412]

tert-Butyl (3R,4S)-4-({2-[(5-chloro-2-thienyl)amino]-2-oxoacetyl}amino)-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the compound obtained in Referential Example 356 in a similar manner to the process described in Referential Example 214.

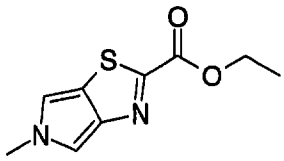
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.90-2.10(1H,br), 2.68-2.80(0.7H,m), 2.90-3.03(0.3H,br), 3.07-

3.22(0.3H,br), 3.25-3.35(0.7H,br), 3.45(3H,s), 3.83-4.22(5H,m), 4.55-4.70(1H,br), 4.80-4.90(0.2H,br), 5.07-5.14(0.2H,br), 5.44-5.55(0.6H,br), 6.58-6.64(1H,br), 6.73(1H,d,J=3.9Hz), 8.05-8.27(1H,br), 9.65-9.88(1H,br).

MS (FAB) m/z: 475$(M+H)^+$.

[Referential Example 413]

Ethyl 5-methyl-5H-pyrrolo[3,4-d]thiazolo-2-carboxylate:



1) Ethyl 2-thioxoacetate (26.75 g) was added to a solution of 3-bromo-2-butanone (26.36 g) in ethanol (250 ml), and the mixture was heated under reflux for 14 hours. After cooling the reaction mixture, it was concentrated, and ethyl acetate and saturated aqueous solution of sodium chloride were added to separate the mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain ethyl 4,5-dimethylthiazole-2-carboxylate (19.53 g).

^{1}H-NMR ($CDCl_3$) δ: 1.42(3H,t,J=7.1Hz), 2.42(3H,s), 2.44(3H,s), 4.45(2H,q,J=7.1Hz).

2) N-Bromosuccinimide (62.42 g) and 2,2'-azobis-

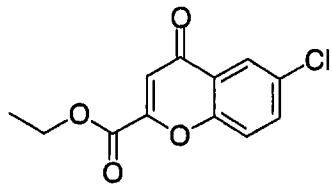
isobutyronitrile (227 mg) were added to a solution of the above-described product (19.53 g) in 1,2-dichloroethane (500 ml), and the mixture was refluxed for 42 hours. After cooling the reaction mixture, water and methylene chloride were added to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then concentrated under reduced pressure to obtain a crude product (40.54 g) as a dark brown oil. Triethylamine (8.0 ml) and a 2 M tetrahydrofuran solution (11.0 ml) of methylamine were added to the crude product (8.41 g), and the mixture was stirred at room temperature for 3 days. After the reaction mixture was concentrated under reduced pressure, methylene chloride and saturated aqueous solution of sodium chloride were added to the residue to separate the mixture into two layers. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (270 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.1Hz), 3.91(3H,s), 4.48(2H,q,J=7.1Hz), 6.73(1H,d,J=1.7Hz), 7.30(1H,d,J=1.7Hz).

MS (ESI) m/z: 211$(M+H)^+$.

[Referential Example 414]

Ethyl 6-chloro-4-oxo-4H-chromene-2-carboxylate:



About 60% sodium hydride in oil (1.68 g) was added to ethanol (10 ml) under purging with argon, and the mixture was stirred at room temperature for 10 minutes. After diethyl oxalate (3.36 ml) was added, an ethanol solution (20 ml) of 5'-chloro-2'-hydroxyacetophenone (2.82 g) was added dropwise. Ethanol (40 ml) was additionally added, and the mixture was refluxed for 1.5 hours and stirred at 50°C for 14 hours. Concentrated sulfuric acid (1.5 ml) and ethanol (10 ml) were added to the reaction mixture, and the resultant mixture was refluxed for 4 hours. After cooling, the solvent was decreased to a half by concentration under reduced pressure. Toluene and a 1N aqueous solution (15 ml) of sodium hydroxide were added to the concentrated the reaction mixture. Extraction was conducted with ethyl acetate, and the resultant organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:1), the resultant solids were washed with hexane to obtain the title compound (1.20 g).

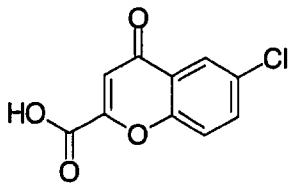
^{1}H-NMR ($CDCl_3$) δ: 1.44(3H,t,J=7.1Hz), 4.47(2H,q,J=7.1Hz), 7.12(1H,s), 7.58(1H,d,J=9.0Hz), 7.69(1H,dd,J=9.0,2.7Hz),

8.16(1H,d,J=2.7Hz).

MS (ESI) m/z: 293(M+MeCN+H)$^+$.

[Referential Example 415]

6-Chloro-4-oxo-4H-chromene-2-carboxylic acid:



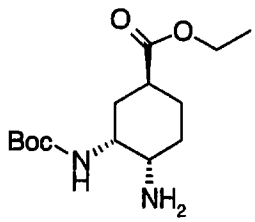
The title compound was obtained from the compound obtained in Referential Example 414 in a similar manner to the process described in Referential Example 359.

^{1}H-NMR ($CDCl_3$) δ: 7.12(1H,s), 7.60(1H,d,J=8.8Hz), 7.69(1H,dd,J=8.8,2.7Hz), 8.15(1H,d,J=2.7Hz).

MS (FAB) m/z: 225(M+H)$^+$.

[Referential Example 416]

Ethyl (1S,3R,4S)-4-amino-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylate:

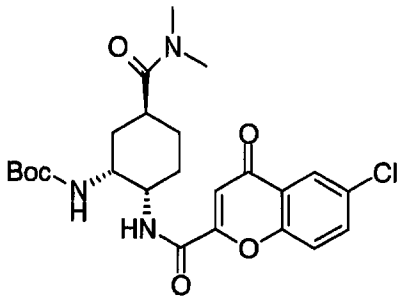


The title compound was obtained from the compound obtained in Referential Example 249 in a similar manner to the process described in Referential Example 90.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.80(4H,m), 1.25(3H,t,J=7.3Hz), 1.46(9H,s), 1.85-2.00(1H,m), 2.10-2.20(1H,m), 2.30-2.45(1H,m), 2.90-3.00(1H,m), 3.84(1H,br s), 4.12(2H,q,J=7.3Hz), 4.75(1H,br s).

[Referential Example 417]

tert-Butyl (1R,2S,5S)-2-{[(6-chloro-4-oxo-4H-chromen-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



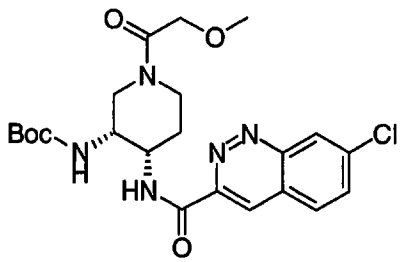
N,N-Dimethylformamide (0.02 ml) was added to a solution of the compound (213 mg) obtained in Referential Example 415 in thionyl chloride (2.0 ml), and the mixture was refluxed for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (4.0 ml). To the solution were added triethylamine (500 µl) and the compound (294 mg) obtained in Referential Example 144, and the mixture was stirred at room temperature for 15 minutes. Ethyl acetate and a 10% aqueous solution of citric acid to separate the reaction mixture into two layers. An organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (230 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.33-1.77(3H,m), 1.50(9H,s), 1.81-2.34(3H,m), 2.63-2.80(1H,m), 2.95(3H,s), 3.10(3H,s), 3.90-4.04(1H,br), 4.18-4.31(1H,br), 4.93-5.12(1H,br), 7.13(1H,s), 7.55(1H,d,J=8.8Hz), 7.66(1H,dd,J=8.8,2.4Hz), 8.14(1H,d,J=2.4Hz), 8.77-8.92(1H,br).

MS (ESI) m/z: 492$(M+H)^+$.

[Referential Example 418]

tert-Butyl (3R,4S)-4-{[(7-chlorocinnolin-3-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl-carbamate:



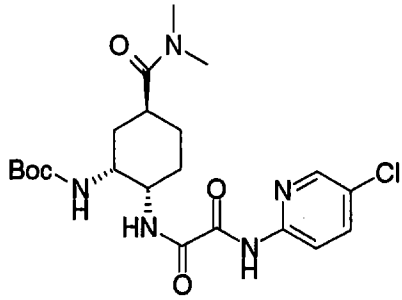
The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the ester described in Referential Example 297 in a similar manner to the process described in Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.38(9H,s), 1.65-1.90(1H,m), 1.90-2.15(1H,m), 2.80-3.00(0.6H,m), 3.00-3.15(0.4H,m), 3.20-3.50(1H,m), 3.46(3H,s), 3.80-4.70(6H,m), 4.87(0.4H,br s), 5.30(0.6H,br s), 7.78(1H,d,J=8.8Hz), 7.97(1H,d,J=8.8Hz), 8.61(1H,s), 8.62-8.90(1H,br), 8.73(1H,s).

MS (ESI) m/z: 478$(M+H)^+$.

[Referential Example 419]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



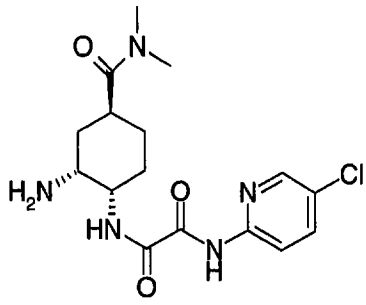
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 68.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.65(1H,m), 1.45(9H,s), 1.65-1.89(2H,m), 1.90-2.10(3H,m), 2.56-2.74(1H,br), 2.95(3H,s), 3.06(3H,s), 3.94-4.01(1H,m), 4.18-4.27(1H,m), 4.70-4.90(0.7H,br), 5.80-6.20(0.3H,br), 7.68(1H,dd,J=8.9,2.6Hz) ,7.83(1H,br s), 8.14(1H,br d,J=7.8Hz), 8.30(1H,s), 9.72(1H,s).

MS (ESI) m/z: 468$(M+H)^+$.

[Referential Example 420]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethanediamide hydrochloride:



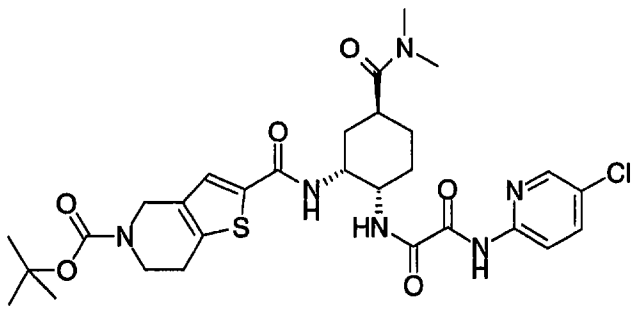
The title compound was obtained from the compound obtained in Referential Example 419 in a similar manner to the process described in Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.38-1.51(1H,m), 1.65-1.85(3H,m), 1.96-2.10(2H, m), 2.81(3H,s), 3.07(3H,s), 3.23-3.33(1H,m), 3.74(1H,br s), 3.84-3.92(1H,m), 8.02(1H,dd,J=9.0,2.5Hz), 8.07(1H,d,J=9.0Hz), 8.34(3H,br s), 8.46(1H,d,J=2.5Hz), 8.96(1H,d,J=6.6Hz), 10.34(1H,s).

MS (ESI) m/z: 368$(M+H)^+$.

[Referential Example 421]

tert-Butyl 2-[({(1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}amino)carbonyl]-6,7-dihydrothieno[3,2-c]-pyridine-5(4H)-carboxylate:



The title compound was obtained by condensing the compound obtained in Referential Example 420 with 5-(tert-

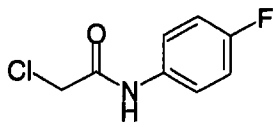
butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599).

^{1}H-NMR ($CDCl_3$) δ: 1.50(9H,s), 1.73-1.95(3H,m), 1.95-2.06(1H,m), 2.08-2.20(2H,m), 2.82(3H,br s), 2.94(3H,s), 3.03(3H,s), 3.60-3.80(2H,m), 3.96-4.08(1H,m), 4.44(2H,br s), 4.66(1H,br s), 6.74(1H,br s), 7.20-7.32(1H,m), 7.66(1H,dd,J=9.0,2.4Hz), 8.13(1H,d,J=9.0Hz), 8.13-8.25(1H,m), 8.28(1H,d,J=2.4Hz), 9.75(1H,s).

MS (ESI) m/z: 633$(M+H)^+$.

[Referential Example 422]

2-Chloro-N-(4-fluorophenyl)acetamide:

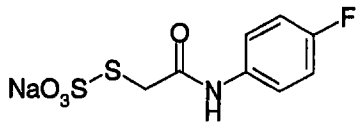


The title compound was obtained from p-fluoroaniline in a similar manner to the process described in Referential Example 350.

^{1}H-NMR ($CDCl_3$) δ: 4.19(2H,s), 7.05(2H,t,J=8.6Hz), 7.51(2H,dd,J=9.1,4.7Hz), 8.19(1H,br s).

[Referential Example 423]

Sodium S-[2-(4-fluoroanilino)-2-oxoethyl]thiosulfate:

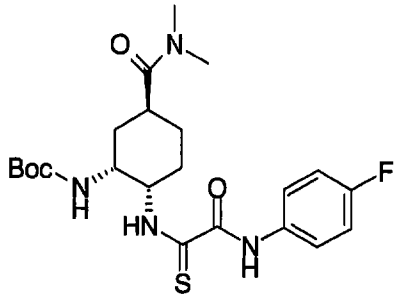


The title compound was obtained from the compound obtained in Referential Example 422 in a similar manner to the process described in Referential Example 351.

^{1}H-NMR (DMSO-d_6) δ: 3.72(2H,s), 7.14(2H,t,J=9.0Hz), 7.56(2H,dd,J=9.0,5.1Hz), 10.21(1H,s).

[Referential Example 424]

tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-{[2-(4-fluoroanilino)-2-oxoethanethioyl]amino}cyclohexylcarbamate:



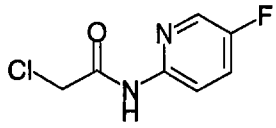
The compound (1.1 g) obtained in Referential Example 144 and the compound (1.2 g) obtained in Referential Example 423 were dissolved in N-methylmorpholine (20 ml), and the temperature of a bath was raised from room temperature to 140°C over 15 minutes to heat and stir the mixture for 15 minutes at the same temperature. After allowing to cool, ice water was added to the reaction mixture to collect insoluble matter by filtration. This product was purified by column chromatography on silica gel (methylene chloride:methanol = 200:1 → 197:3) to obtain the title compound (1.43 g).

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.70-2.10(5H,m), 2.10-2.30(1H,m), 2.60-2.80(1H,m), 2.96(3H,s), 3.07(3H,s), 4.30-4.50(2H,m), 4.65-4.85(1H,m), 7.06(2H,t,J=8.5Hz), 7.50-7.70(2H,m), 9.75-9.95(1H,m), 10.13(1H,s).

MS (ESI) m/z: 467$(M+H)^+$.

[Referential Example 425]

2-Chloro-N-(5-fluoropyridin-2-yl)acetamide hydrochloride:



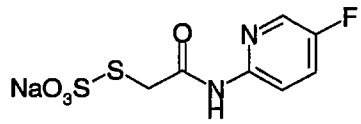
The title compound was obtained from 2-amino-5-fluoropyridine in a similar manner to the process described in Referential Example 352.

^{1}H-NMR (DMSO-d_6) δ: 4.35(2H,s), 7.74-7.82(1H,m), 8.10(1H,dd,J=9.0,4.2Hz), 8.36(1H,d,J=2.9Hz), (1H,br s).

MS (ESI) m/z: 188$(M+H)^+$.

[Referential Example 426]

Sodium S-{2-[(5-fluoropyridin-2-yl)amino]-2-oxoethyl}thiosulfate:

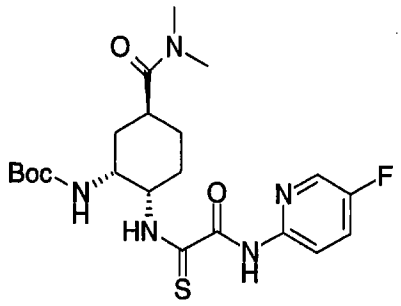


The title compound was obtained from the compound obtained in Referential Example 425 in a similar manner to the process described in Referential Example 353.

^{1}H-NMR (DMSO-d_6) δ: 3.75(2H,s), 7.67-7.77(1H,m), 8.07(1H,dd,J=9.2,4.2Hz), 8.28(1H,d,J=2.9Hz), 10.48(1H,s).

[Referential Example 427]

tert-Butyl (1R,2S,5S)-5-[(dimethylamino)carbonyl]-2-({2-[(5-fluoropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-cyclohexylcarbamate:



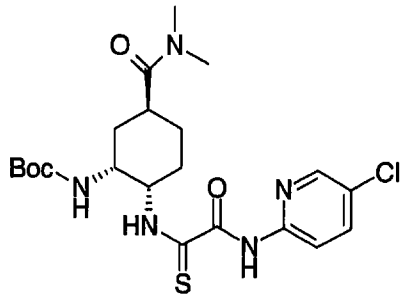
A solution of the compound (1.20 g) obtained in Referential Example 144 in pyridine (70 ml) was heated to 120°C, and the compound (2.42 g) obtained in Referential Example 426 was added. After stirring the mixture for 30 minutes, the reaction mixture was allowed to cool to room temperature, and the solvent was distilled off under reduced pressure. Methylene chloride (100 ml), a saturated aqueous solution (100 ml) of sodium hydrogencarbonate and water (50 ml) were added to the resultant residue to conduct liquid separation. A water layer was then extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:tetrahydrofuran = 1:1). After the resultant solids were slurried for 1 hour in isopropyl ether (40 ml), they were collected by filtration and dried to obtain the title compound (920 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.70-2.10(5H,m), 2.27(1H,br s), 2.70(1H,br s), 2.96(3H,s), 3.08(3H,s), 4.34-4.44(2H,m), 4.77(1H,br s), 7.44-7.51(1H,m), 8.18-8.27(2H,m), 9.90(1H,br s), 10.57(1H,s).

MS (ESI) m/z: 468(M+H)$^+$.

[Referential Example 428]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:

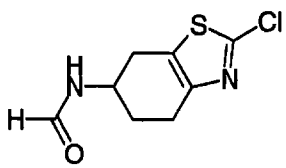


The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 353 in a similar manner to the process described in Referential Example 427.

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.65-2.35(6H,m), 2.70(1H,br s), 2.95(3H,s), 3.09(3H,s), 4.30-4.60(2H,m), 4.87(1/2H,br s), 6.92(1/2H,br s), 7.69(1H,dd,J=8.9,2.6Hz), 7.95-8.20(1H,br), 8.29(1H,s), 9.67(1/2H,br s), 9.93(1/2H,br s), 10.54(1H,br s).

[Referential Example 429]

2-Chloro-4,5,6,7-tetrahydrobenzothiazol-6-ylformamide:



Ammonium acetate (18.58 g) and sodium cyanoborohydride (10.68 g) were added to a solution of 2-chloro-5-oxo-4,5,6,7-tetrahydrobenzo[d]thiazole (Helv. Cim.

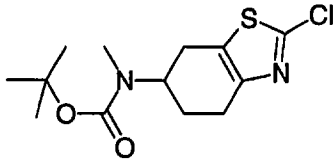
Acta., 1994, Vol. 77, p. 1256) (4.53 g) in methanol (200 ml), and the mixture was heated under reflux. After 19 hours, hydrochloric acid was added to decompose excessive reagents before the reaction mixture was concentrated under reduced pressure. After the residue was alkalified with a 1N aqueous solution of sodium hydroxide, methylene chloride was added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was subjected to column chromatography on silica gel (methylene chloride:methanol = 20:1), and the solvent was distilled off to obtain a pale yellow oil (2.42 g). This oil was dissolved in methylene chloride (100 ml), and formic acid (530 µl), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.68 g), 1-hydroxybenzotriazole (2.60 g) and N-methylmorpholine (3.88 g) were added to stir the mixture at room temperature. After 20 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, the solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (2.21 g).

^{1}H-NMR ($CDCl_3$) δ: 1.93-2.11(2H,m), 2.63-2.69(1H,m), 2.83-

2.89(2H,m), 3.13(1H,dd,J=16.2,4.4Hz), 4.46-4.48(1H,m), 5.76(1H,br s), 8.17(1H,s).

[Referential Example 430]

tert-Butyl N-(2-chloro-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-methylcarbamate:



A 1 M tetrahydrofuran solution (14.6 ml) of borane-tetrahydrofuran complex was added to a solution of the compound (2.11 g) obtained in Referential Example 429 in tetrahydrofuran (50 ml), and the mixture was heated under reflux. After 15 hours, a 1 M tetrahydrofuran solution (6.0 ml) of borane-tetrahydrofuran complex was additionally added to heat the mixture under reflux. After 4 hours, ethanol (10 ml) and 1N hydrochloric acid (15 ml) were added to heat the mixture under reflux. After 3 hours, the reaction mixture was concentrated under reduced pressure. A 1N aqueous solution of sodium hydroxide and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was dissolved in methylene chloride (50 ml), and triethylamine (1.28 g) and di-tert-butyl dicarbonate (2.21 g) were added to stir the mixture at room temperature. After 30 minutes, methylene chloride and 1N hydrochloric

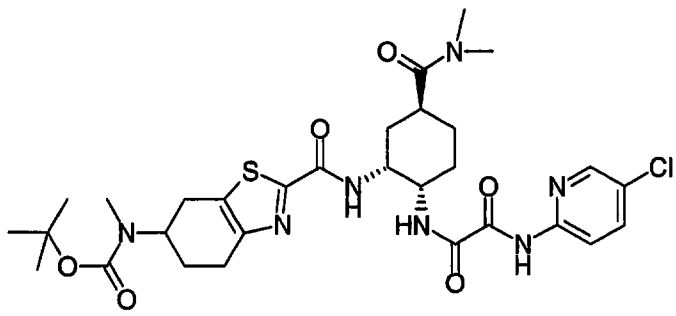
acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (2.26 g).

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.96-1.98(2H,m), 2.80-2.96(7H,m), 4.40-4.50(1H,m).

MS (FAB) m/z: 303$(M+H)^+$.

[Referential Example 431]

tert-Butyl N-(2-[({(1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexyl}amino)carbonyl]-4,5,6,7-tetrahydrobenzothiazol-6-yl)-N-methylcarbamate:



After a solution of the compound (1.0 g) obtained in Referential Example 430 in diethyl ether (10 ml)-tetrahydrofuran (5 ml) was cooled -78°C, a 1.6N pentane solution (3.1 ml) of tert-butyllithium was added, and the mixture was stirred for 20 minutes. Carbon dioxide was then introduced for 20 minutes. The reaction mixture was warmed to room temperature and concentrated under reduced

pressure, giving lithium 6-[(tert-butoxycarbonyl)(methyl)-amino]-4,5,6,7-tetrahydrobenzothiazole-2-carboxylate.

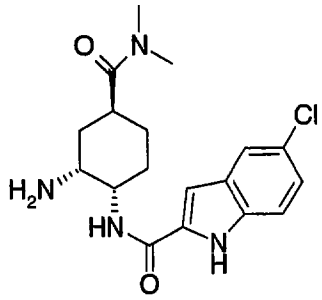
The lithium salt (350.2 mg) of the carboxylic acid obtained by the above-described reaction, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (287.6 mg), 1-hydroxybenzotriazole (202.7 mg) and N-methylmorpholine (0.319 ml) were added to a solution of the compound (490.5 mg) obtained in Referential Example 420 in N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 4 days. The solvent was distilled off under reduced pressure, and water and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was then successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (methylene chloride:methanol = 40:1 → 20:1) to obtain the title compound (323.9 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.48,1.49(total 9H,each s), 1.60-1.92(4H,m), 1.95-2.20(6H,m), 2.78-3.10(3H,m), 2.83(3H,s), 2.95(3H,s), 3.06, 3.07(total 3H,each s), 4.05-4.15(1H,m), 4.20-4.60(1H,m), 4.63-4.73(1H,m), 7.39(1H,d,J=8.6Hz), 7.68(1H,dt,J=8.8,2.6Hz), 7.95-8.10(1H,m), 8.13-8.22(1H,m), 8.30-8.35(1H,m), 9.72(1H,brs).

MS (ESI) m/z: 662$(M+H)^+$.

[Referential Example 432]

N-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-5-chloroindole-2-carboxamide hydrochloride:

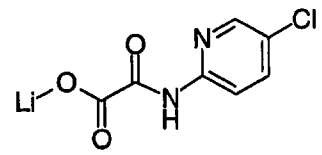


The title compound was obtained by deprotecting the compound obtained in Referential Example 310 in a similar manner to the process described in Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.43-1.56(0.5H,m), 1.72-1.97(4.5H,m), 2.82(3H,s), 3.06(3H,s), 3.11-3.26(1H,m), 3.75-3.84(1H,m), 4.07-4.14(1H,m), 4.22-4.41(1H,m), 7.19(1H,dd,J=2.0,8.8Hz), 7.29(1H,d,J=2.0Hz), 7.45(1H,d,J=8.8Hz), 7.72(1H,s), 8.07(3H,br), 8.47(1H,m), 11.85(1H,br).

[Referential Example 433]

Lithium 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate:



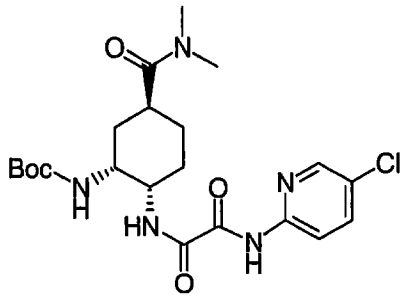
Methyl chlorooxoacetate (78.7 ml) was added dropwise to a suspension of 2-amino-5-chloropyridine (100 g) and sodium hydrogencarbonate (78.4 g) in tetrahydrofuran (2000 ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. After the reaction mixture was added to a mixture of diethyl ether (2000 ml), ammonium chloride

(62.4 g) and water (1000 ml), liquid separation was performed. The resultant water layer was extracted with methylene chloride. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain methyl 2-[(5-chloropyridin-2-yl)amino]-2-oxoacetate (162 g). Water (450 ml) and lithium hydroxide (18.2 g) were added to a solution of this ester (160 g) in tetrahydrofuran (1800 ml). After the mixture was stirred at room temperature for 2 hours, the solvent was distilled off under reduced pressure, and hexane (3000 ml) was added to the resultant residue to stir the mixture for 3 hours. Solids were collected by filtration and dried. Acetonitrile (1000 ml) was added to the solids (190 g), and the mixture was stirred for 1 hour. Solids formed were collected by filtration, washed with diethyl ether (500 ml) and then dried to obtain the title compound (158 g).

^{1}H-NMR (DMSO-d_6) δ: 7.92(1H,dd,J=9.1,2.7Hz), 8.13(1H,dd,J=9.1,0.5Hz), 8.36(1H,dd,J=2.7,0.5Hz), 10.19(1H,s).

[Referential Example 434]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}amino)-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



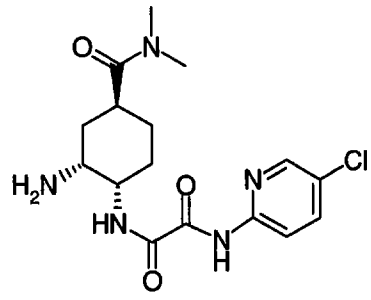
The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 433 in a similar manner to Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.25-1.55(1H,m), 1.45(9H,s), 1.60-2.15(5H,m), 2.56-2.74(1H,br), 2.95(3H,s), 3.06(3H,s), 3.90-4.01(1H,m), 4.18-4.27(1H,m), 4.70-4.85(0.7H,br), 5.70-6.00(0.3H,br), 7.70(1H,dd,J=8.8,2.4Hz), 7.75-8.00(1H,br), 8.16(1H,br d,J=8.8Hz), 8.30(1H,d,J=2.4Hz), 9.73(1H,s).

MS (ESI) m/z: 468$(M+H)^+$.

[Referential Example 435]

N^1-{(1S,2R,4S)-2-Amino-4-[(dimethylamino)carbonyl]-cyclohexyl}-N^2-(5-chloropyridin-2-yl)ethanediamide hydrochloride:



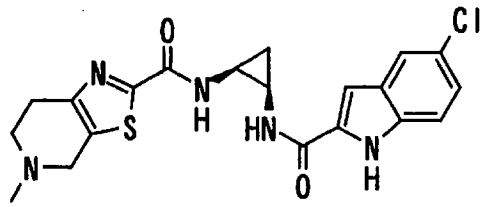
The title compound was obtained from the compound obtained in Referential Example 434 in a similar manner to

Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.38-1.51(1H,m), 1.65-1.85(3H,m), 1.92-2.09(2H,m), 2.80(3H,s), 3.06(3H,s), 3.20-3.32(1H,m), 3.55-4.40(2H,br), 8.02(1H,dd,J=9.1,2.5Hz), 8.07(1H,d,J=9.1Hz), 8.15-8.40(3H,br), 8.45(1H,d,J=2.5Hz), 8.96(1H,d,J=6.6Hz), 10.33(1H,s).

[Example 1]

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



1-Hydroxybenzotriazole monohydrate (71 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg) were added to a solution with the compound (108 mg) obtained in Referential Example 59 and the compound (124 mg) obtained in Referential Example 10 dissolved in N,N-dimethylformamide (3 ml) at room temperature, and the mixture was stirred for 8 days. After concentrating the reaction mixture under reduced pressure using a vacuum pump, water (50 ml) and a saturated aqueous solution (50 ml) of sodium hydrogencarbonate were added to the residue to conduct extraction with methylene chloride. The

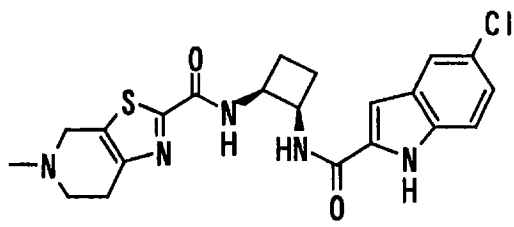
resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 10:1). After 1N hydrochloric acid, methylene chloride and methanol were added to the thus-obtained amorphous substance, the mixture was concentrated to obtain the title compound (72 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.35(2H,m), 2.88(3H,s), 2.95-3.25(4H,m), 3.35-3.75(2H,m), 4.32-4.45(1H,m), 4.68(1H,br,J=15.4Hz), 7.08(1H,s), 7.17(1H,dd,J=8.6,2.1Hz), 7.41(1H,d,J=8.6Hz), 7.70(1H,s), 8.50(1H,br,J=11.0Hz), 8.56(1H,br.s), 11.56(1H,br,J=19.3Hz), 11.86(1H,s).

MS (FAB) m/z: 430$(M+H)^+$.

[Example 2]

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



The compound (136 mg) obtained in Referential Example 10, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (255 mg) and 1-hydroxybenzotriazole

monohydrate (90 mg) were added to a solution with the compound (117 mg) obtained in Referential Example 60 dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred overnight at room temperature. The solvent was then distilled off under reduced pressure using a vacuum pump, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). After ethyl acetate and a 1N ethanol solution of hydrochloric acid were added to the thus-obtained compound to acidify it, and the solvent was distilled off under reduced pressure. Ethyl acetate was added again, and precipitate formed was collected by filtration and dried to obtain the title compound (56 mg).

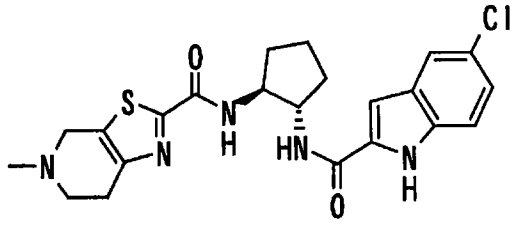
^{1}H-NMR (DMSO-d_6) δ: 2.00-2.35(4H,m), 2.88(3H,m), 3.10(2H,br.s), 3.20-3.75(3H,m), 4.20-4.85(3H,m), 7.09(1H,s), 7.16(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.71(1H,s), 8.63(1H,d,J=8.3Hz), 8.85(1H,d,J=8.6Hz), 10.85-11.20(1H,br), 11.81(1H,s).

MS (FAB) m/z: 444$(M+H)^+$.

[Example 3]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-

cyclopentyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



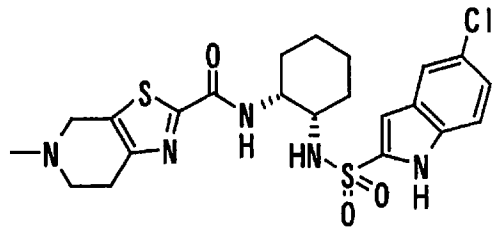
5-Chloroindole-2-carboxylic acid (80 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg), 1-hydroxybenzotriazole monohydrate (23 mg) and triethylamine (141 µl) were added to a solution with the compound (120 mg) obtained in Referential Example 62 dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7). After methylene chloride (5 ml) and a 1N ethanol solution (282 µl) of hydrochloric acid were added to the thus-obtained pale yellow solid, ethyl acetate was added, and precipitate formed was collected by filtration to obtain the title compound (109 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.64-1.74(4H,m), 1.98-2.02(2H,m), 2.89(3H,s), 3.14(2H,br.s), 3.47-3.65(2H,m), 4.29-4.63(4H,m), 7.10(1H,d,J=1.5Hz), 7.14(1H,dd,J=8.5,2.0Hz), 7.38(1H,d,J=8.5Hz), 7.68(1H,d,J=2.0Hz), 8.55(1H,d,J=8.5Hz), 8.91(1H,d,J=8.5Hz), 11.49(1H,br.s), 11.76(1H,s).

MS (ESI) m/z: 458$(M+H)^+$.

[Example 4]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)sulfonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The compound (400 mg) obtained in Referential Example 67 was suspended in methylene chloride (10 ml), triethylamine (0.514 ml) and (5-chloro-1-phenylsulfonylindole-2-sulfonyl chloride (Japanese Patent Application Laid-Open No. 2000-119253) (319 mg) were added, and the mixture was stirred at room temperature for 15 minutes. After water was added to the reaction mixture to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene

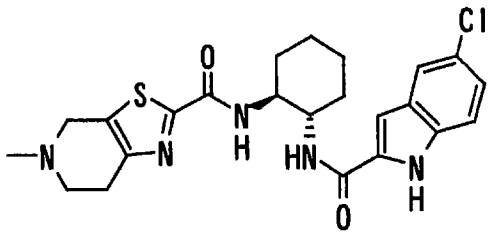
chloride:methanol = 100:3) to obtain a pale yellow foamy substance. This substance was dissolved in tetrahydrofuran (3 ml), and methanol (2 ml) and a 1N aqueous solution (1.5 ml) of sodium hydroxide were added to heat the mixture under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and methylene chloride and 1N hydrochloric acid were added to the residue to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3). 1N Hydrochloric acid (1 ml) was added to the resultant product, and the mixture was concentrated under reduced pressure to obtain the title compound (108 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.78(8H,m), 2.94(3H,s), 3.13(2H,br.s), 3.22-3.40(1H,m), 3.44-3.70(3H,m), 3.83-3.95(1H,m), 4.20-4.70(1H,m), 6.78(1H,s), 7.18-7.30(2H,m), 7.44(1H,s), 7.69(1H,br.s), 8.09(1H,br.s), 11.92(1H,s).

MS (FAB) m/z: 508$(M+H)^+$.

[Example 5]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



5-Chloroindole-2-carboxylic acid (109 mg), 1-hydroxybenzotriazole monohydrate (9 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (321 mg) and triethylamine (0.232 ml) were added to a solution with the compound (300 mg) obtained in Referential Example 65 dissolved in N,N-dimethylformamide (20 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure using a vacuum pump, and methylene chloride and water were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 25:1) to obtain a colorless foamy substance. This substance was suspended in 1N hydrochloric acid (1 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (203 mg).

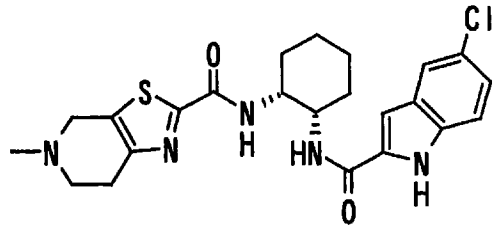
^{1}H-NMR (DMSO-d_6) δ: 1.25-1.40(2H,m), 1.46-1.81(4H,m), 1.88-1.98(2H,m), 2.89(3H,s), 3.00-3.76(5H,m), 3.86-3.97(1H,m), 4.00-4.10(1H,m), 4.25-4.72(1H,m), 7.03(1H,s), 7.12(1H,dd,J=8.5,1.2Hz), 7.38(1H,d,J=8.5Hz), 7.64(1H,s),

8.28(1H,d,J=8.5Hz), 8.54(1H,d,J=8.5Hz), 11.70(1H,s).

MS (FAB) m/z: 472$(M+H)^+$.

[Example 6]

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



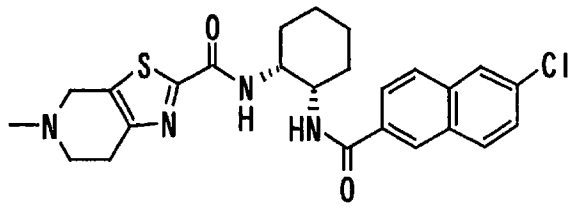
The title compound was obtained from the compound obtained in Referential Example 67 and 5-chloroindole-2-carboxylic acid in a similar manner to Example 5.

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.70(6H,m), 1.80-2.06(2H,m), 2.89(3H,s), 3.00-3.27(2H,m), 3.35-3.51(1H,m), 3.57-3.82(1H,m), 4.15-4.30(2H,m), 4.32-4.48(1H,m), 4.60-4.74(1H,m), 7.15(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.6Hz), 7.70(1H,d,J=2.0Hz), 8.14(1H,br.s), 8.36-8.48(1H,m), 11.51(1H,br.s), 11.86(1H,s).

MS (FAB) m/z: 472$(M+H)^+$.

[Example 7]

N-{(1R*,2S*)-2-[(6-Chloro-2-naphthoyl)amino]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



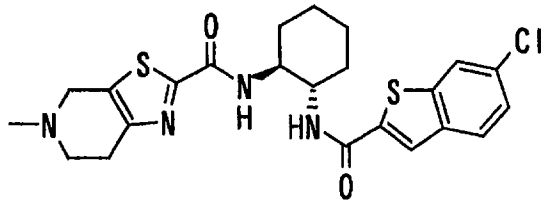
The title compound (186 mg) was obtained by dissolving the compound (275 mg) obtained in Referential Example 67, 6-chloronaphthalene-2-carboxylic acid (Eur. J. Chem. Chim. Ther., 1984, Vol. 19, pp. 205-214) (148 mg), triethylamine (0.298 ml) and 1-hydroxybenzotriazole monohydrate (11 mg) in N,N-dimethylformamide (20 ml) and causing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (412 mg) to react in a similar manner to Example 5.

^{1}H-NMR (DMSO-d_6) δ: 1.40-1.56(2H,m), 1.57-1.77(4H,m), 1.90-2.10(2H,m), 2.90(3H,s), 3.13(2H,br.s), 3.28-3.74(2H,m), 4.26(2H,br.s), 4.30-4.74(2H,m), 7.59(1H,d,J=8.6Hz), 7.90(1H,d,J=8.6Hz), 7.98(1H,d,J=8.3Hz), 8.03-8.11(2H,m), 8.25-8.58(3H,m), 11.52(1H,br.s).

MS (FAB) m/z: 483$(M+H)^+$.

[Example 8]

N-((1R*,2R*)-2-{[(6-Chloro-1-benzothiophen-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



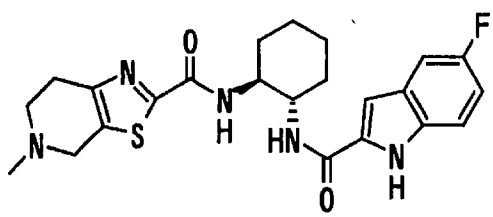
The title compound (239 mg) was obtained by dissolving the compound (255 mg) obtained in Referential Example 65, 6-chlorobenzo[b]thiophene-2-carboxylic acid (Japanese Patent Application Laid-Open No. 2000-119253) (141 mg), triethylamine (0.276 ml) and 1-hydroxybenzotriazole monohydrate (10 mg) in N,N-dimethylformamide (20 ml) and causing 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (382 mg) to react in a similar manner to Example 5.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.98(8H,m), 2.88(3H,s), 3.00-3.72(4H,m), 3.84-4.09(2H,m), 4.20-4.75(2H,m), 7.41(1H,dd,J=8.6,1.7Hz), 7.91(1H,d,J=8.6Hz), 7.99(1H,s), 8.12(1H,s), 8.54-8.67(2H,m), 11.53(1H,br.s).

MS (FAB) m/z: 489$(M+H)^+$.

[Example 9]

N-((1R*,2R*)-2-{[(5-Fluoroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



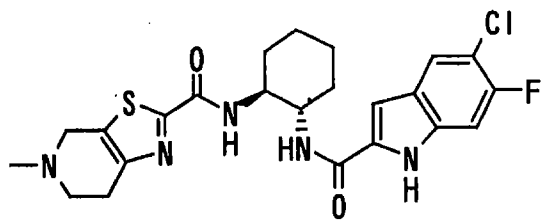
The title compound was obtained from the compound obtained in Referential Example 65 and 5-fluoroindole-2-carboxylic acid in a similar manner to Example 5.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.38(2H,m), 1.40-1.57(1H,m), 1.54-1.68(1H,m), 1.71(2H,d,J=7.3Hz), 1.88(2H,d,J=12.0Hz), 2.86(3H,s), 2.95-3.24(2H,m), 3.40(1H,br.s), 3.63(1H,br.s), 3.90(1H,br.s), 3.97-4.10(1H,m), 4.20-4.44(1H,m), 4.53-4.70(1H,m), 6.98(1H,dd,J=9.2,2.3Hz), 7.01(1H,s), 7.31-7.39(2H,m), 8.26(1H,d,J=8.6Hz), 8.59(1H,d,J=8.4Hz), 11.21(1/2H,br.s), 11.42(1/2H,br.s), 11.60(1H,s).

MS (ESI) m/z: 456$(M+H)^+$.

[Example 10]

N-((1R*,2R*)-2-{[(5-Chloro-6-fluoroindol-2-yl)carbonyl]-amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride



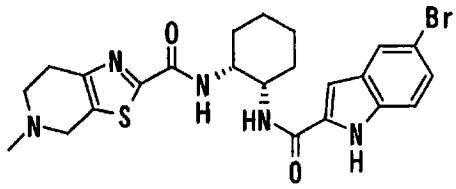
The title compound was obtained from the compound obtained in Referential Example 65 and the compound obtained in Referential Example 23 in a similar manner to Example 5.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.40(2H,m), 1.40-1.80(4H,m), 1.80-2.00(2H,m), 2.87(3H,s), 3.01(2H,br.s), 3.30-3.80(2H,m), 3.81-3.97(2H,m), 4.20-4.80(2H,m), 7.06(1H,s),

7.28(1H,d,J=10.0Hz), 7.86(1H,d,J=7.3Hz),
8.32(1H,d,J=8.5Hz), 8.59(1H,d,J=8.5Hz), 11.77(1H,s).
MS (FAB) m/z: 490$(M+H)^+$.

[Example 11]

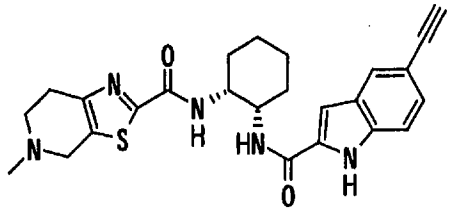
N-((1R*,2S*)-2-{[(5-Bromoindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 67 and 5-bromoindole-2-carboxylic acid in a similar manner to Example 5.
^{1}H-NMR (DMSO-d_6) δ: 1.43(2H,br.s), 1.61(4H,br.s),
1.80-2.10(2H,m), 2.88(3H,s), 3.00-3.26(2H,m),
3.40(1H,br.s), 3.65(1H,br.s), 4.22(1H,br.s), 4.26(1H,br.s),
4.41(1H,br.s), 4.67(1H,d,J=15.6Hz), 7.14(1H,s),
7.28(1H,d,J=8.7Hz), 7.37(1H,d,J=8.7Hz), 7.84(1H,s),
8.13(1H,br.s), 8.33-8.52(1H,m), 11.51(1H,br.s),
11.86(1H,s).
MS (ESI) m/z: 515(M^+).

[Example 12]

N-((1R*,2S*)-2-{[(5-Ethynylindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



Triethylamine (6 ml), N,N-dimethylformamide (5 ml), trimethylsilylacetylene (0.250 ml) and palladium acetate (20 mg) were added to a tetrahydrofuran solution (2 ml) of the compound (300 mg) obtained in Example 11 and triphenylphosphine (70 mg) at room temperature. After stirring at 90°C for 2 hours, the reaction mixture was allowed to cool to room temperature, and methylene chloride (20 ml) and a saturated aqueous solution (30 ml) of sodium hydrogencarbonate were added to conduct liquid separation. The resultant water layer was extracted with methylene chloride (3 x 10 ml), the organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain residue. The resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:acetone:methanol = 10:10:1) to obtain colorless solids. This product was dissolved in methanol (6 ml), potassium carbonate (120 mg) was added, and the mixture was stirred for 1 hour. Methylene chloride (20 ml) and water (20 ml) were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted with methylene chloride (2 x 15 ml), the organic layers were combined and dried over anhydrous sodium

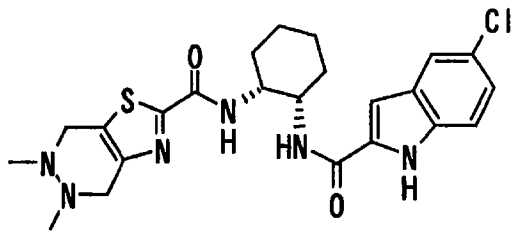
sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:acetone:methanol = 10:10:1) and dissolved in water-methanol-methylene chloride. The resultant solution was then concentrated to obtain the title compound (72 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.50-2.25(8H,m), 2.53(3H,s), 2.85(2H,br.s), 2.93(2H,br.s), 3.01(1H,s), 3.74(1H,d,J=14.1Hz), 3.77(1H,d,J=14.1Hz), 4.21(1H,br.s), 4.45(1H,br.s), 6.91(1H,s), 7.25-7.42(2H,m), 7.61(1H,br.s), 7.80-7.97(2H,m), 9.72(1H,s).

MS (FAB) m/z: 462$(M+H)^+$.

[Example 13]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5,6-dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-d]pyridazine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 51 in a similar manner to Example 2.

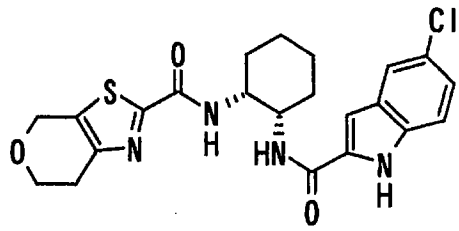
^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(2H,m), 1.50-1.75(4H,m), 1.80-2.10(2H,m), 2.70(3H,br.s), 2.79(3H,br.s),

4.10-4.70(6H,m), 7.10-7.27(2H,m), 7.41(1H,d,J=8.8Hz), 7.70(1H,s), 8.12(1H,d,J=6.8Hz), 8.47(1H,d,J=7.6Hz), 11.85(1H,s).

MS (FAB) m/z: 487$(M+H)^+$.

[Example 14]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-6,7-dihydro-4H-pyrano[4,3-d]thiazole-2-carboxamide:



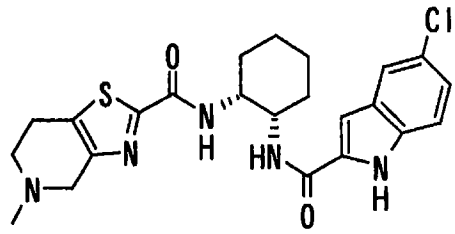
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 26 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.36-1.72(6H,m), 1.90-2.10(2H,m), 2.80-2.87(2H,m), 3.93(2H,t,J=5.6Hz), 4.20-4.32(2H,m), 4.81(2H,s), 7.12(1H,s), 7.15(1H,dd, J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.67(1H,d,J=1.7Hz), 8.11(1H,d,J=6.6Hz), 8.36(1H,d,J=8.3Hz), 11.78(1H,s).

MS (FAB) m/z: 459$(M+H)^+$.

[Example 15]

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



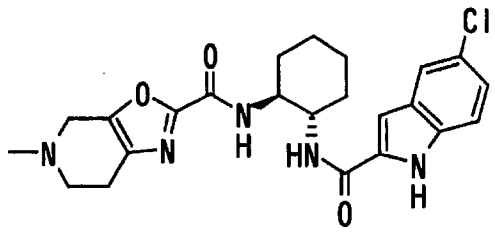
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 29 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.32-1.74(6H,m), 1.82-2.10(2H,m), 2.92(3H,s), 3.12-3.50(3H,m), 3.69(1H,br.s), 4.13-4.39(3H,m), 4.51(1H,br.s), 7.10-7.19(2H,m), 7.41(1H,d,J=8.6Hz), 7.68(1H,s), 8.10(1H,br.s), 8.40(1H,br.s), 11.41(1H,br.s), 11.87(1H,s).

MS (FAB) m/z: 472$(M+H)^+$.

[Example 16]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-methyl-4,5,6,7-tetrahydrooxazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 69 and the compound obtained in Referential Example 21 in a similar manner to

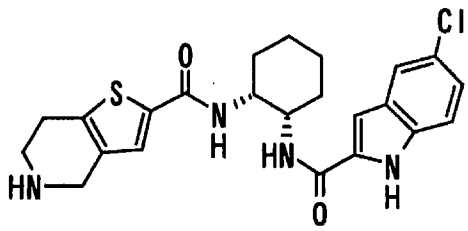
Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.23-1.39(2H,m), 1.40-1.81(4H,m), 1.82-1.98(2H,m), 2.60-3.00(5H,m), 3.20-3.70(2H,m), 3.87-3.96(1H,m), 3.98-4.10(1H,m), 4.12-4.70(2H,m), 7.04(1H,d,J=1.5Hz), 7.12(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.65(1H,d,J=2.0Hz), 8.33(1H,d,J=8.6Hz), 8.72(1H,d,J=8.6Hz), 11.61(1H,br.s), 11.72(1H,s).

MS (FAB) m/z: 456$(M+H)^+$.

[Example 17]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained by condensing the compound obtained in Referential Example 71 with 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-carboxylic acid (WO94/21599) and treating the formed product with hydrochloric acid to deprotect in a similar manner to Example 2.

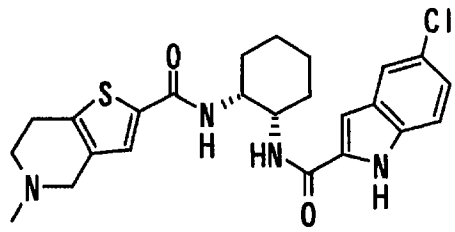
^{1}H-NMR (DMSO-d_6) δ: 1.42(2H,br.s), 1.56-1.76(4H,m), 1.98-2.11(2H,m), 3.04(2H,br.s), 3.32-3.45(2H,m), 4.15(3H,br.s), 4.26(1H,br.s), 7.14(1H,dd,J=8.8,2.0Hz), 7.23(1H,s), 7.41(1H,d,J=8.8Hz), 7.62(1H,s), 7.77(1H,s),

8.18-8.30(2H,m), 9.42(2H,br.s), 11.92(1H,s).

MS (FAB) m/z: 457$(M+H)^+$.

[Example 18]

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



The compound (171 mg) obtained in Example 17 was suspended in methylene chloride (10 ml), and triethylamine (0.104 ml) was added to stir the mixture at room temperature for 10 minutes. After acetic acid (0.059 ml) was added to the reaction mixture, a 35% aqueous formaldehyde solution (0.070 ml) and sodium triacetoxyborohydride (118 mg) were added, and the mixture was stirred at room temperature for 30 minutes. After a 1N aqueous solution (3 ml) of sodium hydroxide was added to the reaction mixture, water was added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was then distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 50:3) to obtain a colorless foamy substance. This substance was suspended in 1N hydrochloric

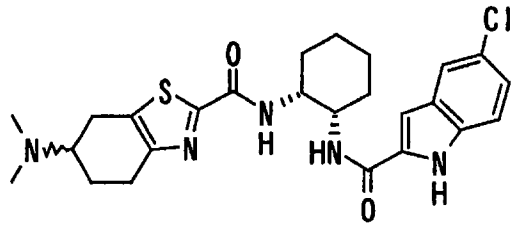
acid, and the suspension was concentrated under reduced pressure to obtain the title compound (85 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.40(2H,br.s), 1.50-1.71(4H,m), 1.97-2.05(2H,m), 2.87(3H,s), 2.98-3.20(1H,m), 3.30-3.38(2H,m), 3.54-3.70(1H,m), 4.05-4.42(4H,m), 7.14(1H,d,J=8.6Hz), 7.23(1H,s), 7.40(1H,d,J=8.6Hz), 7.63(1H,s), 7.77(1H,s), 8.17-8.27(2H,m), 10.83(1H,br.s), 11.92(1H,s).

MS (FAB) m/z: 471$(M+H)^+$.

[Example 19]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-6-(dimethylamino)-4,5,6,7-tetrahydrobenzothiazole-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 31 in a similar manner to Example 2.

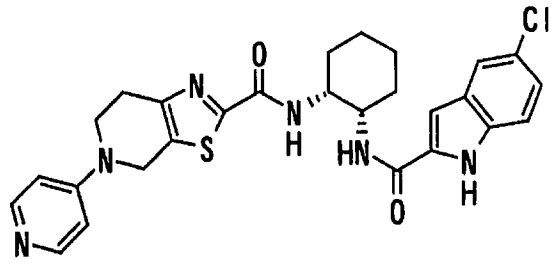
^{1}H-NMR (DMSO-d_6) δ: 1.44(2H,br.s), 1.52-1.68(4H,m), 1.87-2.08(3H,m), 2.30-2.40(1H,m), 2.65-2.75(1H,m), 2.77(6H,s), 2.95-3.17(2H,m), 3.30-3.70(2H,m), 4.15-4.30(2H,m), 7.10-7.20(2H,m), 7.41(1H,d,J=8.6Hz), 7.69(1H,s), 8.11(1H,d,J=5.1Hz), 8.34(1H,d,J=8.1Hz), 10.95(1H,br.s),

11.83(1H,s).

MS (FAB) m/z: 500$(M+H)^+$.

[Example 20]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-(pyridin-4-yl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



After n-butyllithium (1.60N hexane solution, 0.704 ml) was added dropwise to a solution of the compound (204 mg) obtained in Referential Example 24 in tetrahydrofuran (3 ml) at -78°C, the mixture was stirred at 0°C for 30 minutes. After the reaction mixture was cooled to -78°C again, it was warmed to room temperature in 20 minutes while blowing carbon dioxide, and the reaction mixture was concentrated under reduced pressure. The compound (400 mg) obtained in Referential Example 71, 1-hydroxy-benzotriazole monohydrate (254 mg), 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (360 mg) and isopropylamine (0.491 ml) were added to a solution of the resultant residue in N,N-dimethylformamide (6 ml) at room temperature. After stirring for 3 days, the reaction mixture was concentrated under reduced pressure, and methylene chloride (30 ml), a saturated aqueous solution

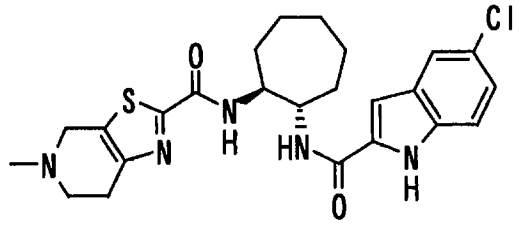
(100 ml) of sodium hydrogencarbonate and water (100 ml) were added to the residue to conduct liquid separation. The resultant water layer was extracted with methylene chloride (4 x 15 ml), the organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 → 10:1) and dissolved in 1N hydrochloric acid-methanol-methylene chloride. The resultant solution was then concentrated to obtain the title compound (245 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.42(2H,br.s), 1.60(4H,br.s), 1.84-1.94(1H,m), 1.94-2.08(1H,m), 2.97(2H,br.s), 3.97-4.13(2H,m), 4.19(1H,br.s), 4.27(1H,br.s), 5.03(2H,s), 7.13(1H,br.s), 7.16(1H,dd,J=8.8,2.0Hz), 7.32(2H,br.s), 7.40(1H,d,J=8.8Hz), 7.68(1H,d,J=2.0Hz), 8.15(1H,br,J=7.3Hz), 8.31(2H,d,J=5.9Hz), 8.39(1H,d,J=8.1Hz), 11.90(1H,s), 14.03(1H,br.s).

MS (ESI) m/z: 535$(M+H)^+$.

[Example 21]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cycloheptyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



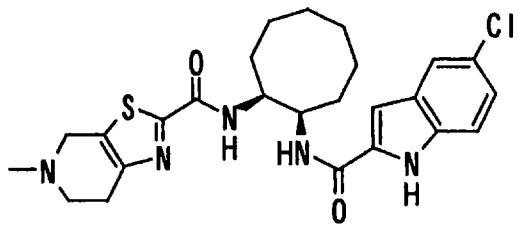
The title compound was obtained from the compound obtained in Referential Example 74 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.51-1.55(4H,m), 1.75-1.80(6H,m), 2.88(3H,s), 3.12(1H,br.s), 3.35-3.63(4H,m), 4.10-4.13(1H,m), 4.29-4.61(2H,m), 7.06(1H,s), 7.14(1H,dd,J=8.8,2.0Hz), 7.39(1H,d,J=8.8Hz), 7.67(1H,d,J=2.0Hz), 8.46(1H,d,J=8.3Hz), 8.77(1H,d,J=8.3Hz), 11.21-11.35(1H,m), 11.71(1H,s).

MS (ESI) m/z: 486$(M+H)^+$.

[Example 22]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cycloocty1)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 78 and the compound

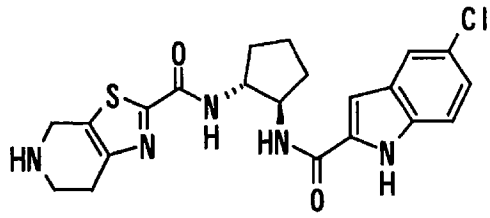
obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.61-2.06(12H,m), 2.90(3H,s), 3.08-3.17(2H,m), 3.43-3.45(1H,br.s), 3.67(1H,br.s), 4.43(3H,br.s), 4.67(1H,br.s), 7.16-7.18(2H,m), 7.42(1H,d,J=8.8Hz), 7.70(1H,s), 8.24(1H,br.s), 8.58(1H,d,J=8.3Hz), 11.43,11.63(1H,each br.s), 11.80(1H,s).

MS (ESI) m/z: 500$(M+H)^+$.

[Example 23]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



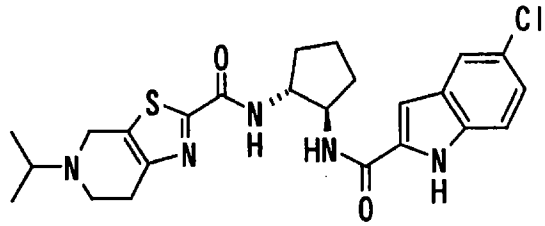
The title compound was obtained by treating a product obtained by the reaction of the compound obtained in Referential Example 63 with the compound obtained in Referential Example 34 with hydrochloric acid in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.60-1.82(4H,m), 1.91-2.15(2H,m), 3.08(2H,s), 3.37-3.49(2H,m), 4.28-4.56(4H,m), 7.13(1H,s), 7.15(1H,d,J=8.8Hz), 7.40(1H,d,J=8.8Hz), 7.69(1H,s), 8.61(1H,d,J=8.3Hz), 8.88(1H,d,J=8.3Hz), 10.05(2H,br.s), 11.82(1H,s).

MS (FAB) m/z: 444$(M+H)^+$.

[Example 24]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (30 mg) obtained in Example 23 was suspended in methylene chloride (20 ml), and triethylamine (260 µl) was added to stir the mixture at room temperature for 15 minutes. Acetic acid (179 µl) and acetone (920 µl) were added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 minutes. Sodium triacetoxyborohydride (796 mg) was added to the reaction mixture to stir them at room temperature for 5 hours. A 1N aqueous solution (10 ml) of sodium hydroxide was added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:3) to obtain a colorless foamy substance. This product was dissolved in methylene chloride, and a 1N ethanol solution (1 ml) of hydrochloric

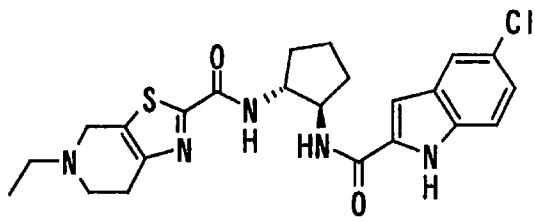
acid was added. The solution was concentrated under reduced pressure to obtain the title compound (205 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.27-1.39(6H,m), 1.58-1.80(4H,m), 1.95-2.10(2H,m), 3.00-3.12(1H,m), 3.25-3.45(2H,m), 3.59-3.77(2H,m), 4.25-4.39(1H,m), 4.40-4.55(2H,m), 4.57-4.65(1H,m), 7.10(1H,s), 7.14(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.68(1H,s), 8.56(1H,d,J=8.8Hz), 8.90(1H,d,J=8.8Hz), 11.39(1H,br.s), 11.76(0.5H,s), 11.80(0.5H,s).

MS (FAB) m/z: 486$(M+H)^+$.

[Example 25]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The compound (500 mg) obtained in Example 23 was dissolved in N,N-dimethylformamide (10 ml), and triethylamine (576 µl) and ethyl iodide (329 µl) were added to stir the mixture overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to collect insoluble matter by filtration. This product was purified by column chromatography on silica gel (methylene

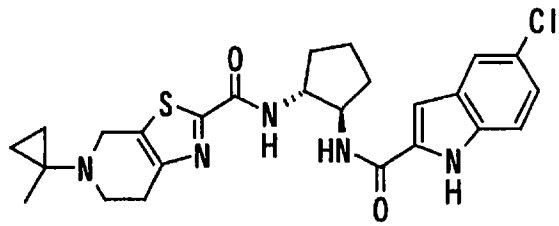
chloride:methanol = 100:3) to obtain a pale brown foamy substance. This substance was suspended in 1N hydrochloric acid, and the suspension was concentrated under reduced pressure to obtain the title compound (180 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.32(3H,t,J=7.1Hz), 1.60-1.80(4H,m), 1.96-2.10(2H,m), 3.20-3.39(5H,m), 3.70-3.80(1H,m), 4.26-4.58(3H,m), 4.68-4.79(1H,m), 7.11(1H,s), 7.15(1H,dd,J=8.8,2.0Hz), 7.39(1H,d,J=8.8Hz), 7.69(1H,d,J=1.5Hz), 8.55(1H,d,J=8.5Hz), 8.92(1H,d,J=8.5Hz), 11.38(1H,br.s), 11.70-11.80(1H,m).

MS (FAB) m/z: 472$(M+H)^+$.

[Example 26]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclopentyl)-5-(1-methylcyclopropyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 63 and the compound obtained in Referential Example 39 in a similar manner to Example 2.

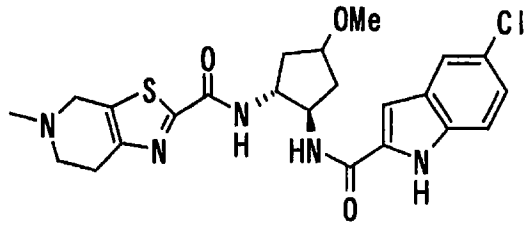
^{1}H-NMR (DMSO-d_6) δ: 0.81(2H,br.s), 1.20-1.55(5H,br), 1.55-1.80(4H,m), 1.95-2.12(2H,m), 3.05-3.40(2H,br), 3.60-

3.80(2H,br), 4.25-4.80(4H,m), 7.10(1H,s),
7.16(1H,d,J=8.8Hz), 7.39(1H,d,J=8.8Hz), 7.69(1H,s),
8.53(1H,d,J=8.6Hz), 8.85-8.95(1H,m), 10.60-10.90(1H,br),
11.73(1H,br.s).

MS (FAB) m/z: 498$(M+H)^+$.

[Example 27]

N-((1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-methoxycyclopentyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride (Stereoisomer A and Stereoisomer B):



A mixture of the title compounds, i.e., Stereoisomer A and Stereoisomer B was synthesized by condensing the compound (mixture of 4-position stereoisomers) (268 mg) obtained in Referential Example 82 with the compound obtained in Referential Example 10 in a similar manner to Example 2. The isomers were isolated by column chromatography on silica gel and then converted into hydrochlorides to obtain the title compounds [Stereoisomer A (75 mg) and Stereoisomer B (70 mg)].

Stereoisomer A:

^{1}H-NMR (DMSO-d_6) δ: 1.70-2.15(4H,m), 2.90(3H,s),
3.00-3.90(8H,m), 4.10-4.80(4H,m), 7.08(1H,s),

7.16(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.69(1H,s), 8.56(1H,d,J=8.8Hz), 8.88(1H,d,J=8.3Hz), 10.96(1H,br.s), 11.75(1H,br.s).

MS (FAB) m/z: 488$(M+H)^+$.

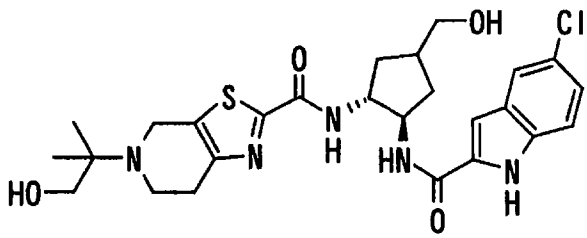
Stereoisomer B:

^{1}H-NMR (DMSO-d_6) δ: 1.60-2.10(4H,m), 2.89(3H,s), 3.00-3.70(7H,m), 3.70-3.90(1H,m), 4.20-4.80(4H,m), 7.05-7.20(2H,m), 7.38(1H,d,J=8.8Hz), 7.68(1H,s), 8.59(1H,d,J=8.3Hz), 8.90(1H,d,J=8.5Hz), 11.26(1H,br.s), 11.74(1H,br.s).

MS (FAB) m/z: 488$(M+H)^+$.

[Example 28]

N-[(1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-(hydroxymethyl)cyclopentyl]-5-(1,1-dimethyl-2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride (Stereoisomer A):



1) Stereoisomers A and B of N-((1R*,2R*)-4-[(benzyloxy)methyl]-2-{(5-chloroindol-2-yl)carbonyl}amino)cyclopentyl)-5-(2-{[tert-butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide were obtained from the compound obtained in Referential Example

85 and the compound obtained in Referential Example 42 in a similar manner to Example 2.

Stereoisomer A:

^{1}H-NMR ($CDCl_3$) δ: 1.05(9H,s), 1.168, 1.171(6H,each s), 1.53-1.61(1H,m), 1.76-1.88(1H,m), 2.30-2.37(2H,m), 2.78-2.79(2H,m), 2.87-2.90(1H,m), 2.96-3.00(1H,m), 3.37-3.47(2H,m), 3.58(2H,s), 3.96(1H,q,J=13.1Hz), 4.41-4.45(1H,m), 4.51-4.57(2H,m), 6.88(1H,d,J=1.5Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.23-7.43(12H,m), 7.52(1H,d,J=7.6Hz), 9.37(1H,br.s).

Stereoisomer B:

^{1}H-NMR ($CDCl_3$) δ: 1.05(9H,s), 1.17(6H,s), 1.43-1.47(1H,m), 1.85-1.88(1H,m), 2.09-2.14(1H,m), 2.58-2.63(1H,m), 2.78-2.79(2H,m), 2.86-2.90(1H,m), 2.96-3.00(1H,m), 3.38-3.46(2H,m), 3.59(2H,s), 3.95(1H,q,J=13.3Hz), 4.15-4.20(1H,m), 4.45-4.56(3H,m), 6.74(1H,d,J=2.0Hz), 7.16(1H,dd,J=8.8,2.0Hz), 7.27-7.43(12H,m), 7.57(1H,d,J=2.0Hz), 9.48(1H,br.s).

2) The above Stereoisomer A (288 mg) was suspended in methylene chloride (20 ml), and dimethyl sulfide (1.15 ml) and anhydrous aluminum chloride (350 mg) were added to stir the mixture at room temperature for 1 hour. A 1N aqueous solution (10 ml) of sodium hydroxide was added to the reaction mixture, and the mixture was extracted with methylene chloride. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified

by column chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain 5-(2-{[tert-butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-N-[(1R*,2R*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-(hydroxymethyl)cyclopentyl]-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A) (184 mg).

^{1}H-NMR ($CDCl_3$)δ: 1.04(9H,s), 1.15(6H,s), 1.54-1.62(1H,m), 1.73-1.81(1H,m), 1.99-2.25(2H,m), 2.34-2.38(2H,m), 2.67-2.85(3H,m), 2.92-2.97(1H,m), 3.48-3.62(4H,m), 3.93(1H,q,J=15.6Hz), 4.20-4.28(1H,m), 4.47-4.56(1H,m), 6.89(1H,s), 7.11-7.18(1H,m), 7.24-7.27(1H,m), 7.32-7.43(6H,m), 7.54(1H,d,J=1.7Hz), 7.63(4H,dd,J=7.8,1.5Hz), 7.90-7.92(2H,m), 10.13(1H,br.s).

MS (FAB) m/z: 784$(M+H)^+$.

3) Stereoisomer A (180 mg) obtained in the step 2) described above was dissolved in a 1N tetrahydrofuran solution (2 ml) of tetrabutylammonium fluoride, and the solution was stirred overnight at room temperature. Methylene chloride, a 1N aqueous solution of sodium hydroxide and sodium chloride were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 19:1). The thus-obtained powder was dissolved in methanol, and a 1N

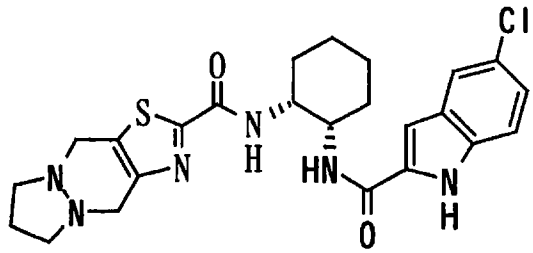
ethanol solution (229 μl) of hydrochloric acid was added, to which ethyl acetate was added. The solvent was concentrated under reduced pressure to obtain the title compound (63 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.33-1.50(8H,m), 1.70-1.91(2H,m), 2.07-2.14(1H,m), 2.23-2.24(1H,m), 3.04-3.10(1H,m), 3.27-3.44(4H,m), 3.57-3.70(2H,m), 3.92-3.95(1H,m), 4.29-4.72(4H,m), 5.81(1H,br.s), 7.11(1H,s), 7.15(1H,dd,J=8.6,2.0Hz), 7.39(1H,d,J=8.6Hz), 7.68(1H,d,J=2.0Hz), 8.53-8.56(1H,m), 8.83(1H,d,J=8.3Hz), 10.36(1H,br.s), 11.75,11.77(1H,each s).

MS (ESI) m/z: 546$(M+H)^+$.

[Example 29]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,7,8,10-tetrahydro-6H-pyrazolo[1,2-a]-thiazolo[4,5-d]pyridazine-2-carboxamide hydrochloride:



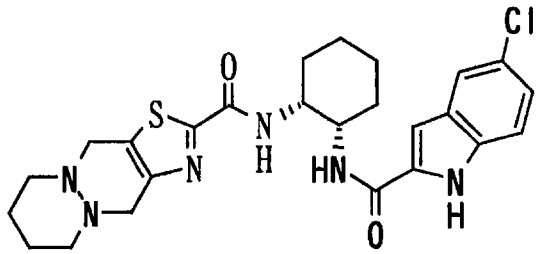
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 44 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(2H,m), 1.61(4H,br.s), 1.80-2.00(2H,m), 2.27(2H,br.s), 2.80-4.80(10H,m),

7.14(1H,d,J=1.5Hz), 7.17(1H,dd,J=8.5,2.0Hz),
7.41(1H,d,J=8.5Hz), 7.70(1H,d,J=2.0Hz), 8.09(1H,d,J=7.3Hz),
8.44(1H,br.s), 11.81(1H,br.s).
MS (FAB) m/z: 499$(M+H)^+$.

[Example 30]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,6,7,8,9,11-hexahydropyridazino[1,2-a]-thiazolo[4,5-d]pyridazine-2-carboxamide hydrochloride:

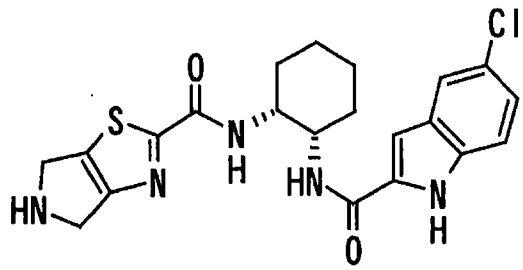


The title compound was obtained from the compound obtained in Referential Example 46 and the compound obtained in Referential Example 71 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.55(2H,m), 1.55-2.10(10H,m),
2.80-4.80(10H,m), 7.10-7.25(2H,m), 7.42(1H,d,J=8.8Hz),
7.72(1H,d,J=1.7Hz), 8.12(1H,br.s), 8.41(1H,br.s),
11.83(1H,br.s).
MS (FAB) m/z: 513$(M+H)^+$.

[Example 31]

5-Chloro-N-{(1R*,2S*)-2-[(5,6-dihydro-4H-pyrrolo[3,4-d]-thiazol-2-ylcarbonyl)amino]cyclohexyl}indole-2-carboxamide hydrochloride:



The compound (171 mg) obtained in Referential Example 33 was dissolved in diethyl ether (5 ml) in an argon atmosphere, and the solution was cooled to -78°C, to which n-butyllithium (1.60N hexane solution, 385 µl) was added dropwise. After the reaction mixture was stirred for 10 minutes at -78°C, and carbon dioxide was blown into the reaction mixture for 20 minutes, it was warmed to room temperature. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in N,N-dimethylformamide (10 ml). To the solution, were added the compound (184 mg) obtained in Referential Example 71 , 1-hydroxybenzotriazole monohydrate (76 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (215 mg). The resultant mixture was stirred for 3 days. The reaction mixture was concentrated, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3:97). After an ethanol solution (5 ml) of

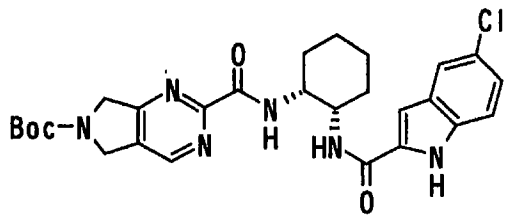
hydrochloric acid was added to the thus-obtained product, the mixture was stirred at room temperature for 1 hour, and the reaction mixture was concentrated. Ethyl acetate was added to the residue to solidify it. The resultant powder was collected by filtration to obtain the title compound (31 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.52(2H,m), 1.55-1.80(4H,m), 1.82-2.05(2H,m), 4.22(1H,br.s), 4.28(1H,br.s), 4.38(2H,s), 4.56(2H,s), 7.14-7.20(2H,m), 7.42(1H,d,J=8.6Hz), 7.71(1H,d,J=1.7Hz), 8.10(1H,d,J=7.1Hz), 8.45(1H,d,J=7.8Hz), 10.10-10.50(2H,br), 11.83(1H,br.s).

MS (FAB) m/z: 444$(M+H)^+$.

[Example 32]

tert-Butyl 2-{[((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)amino]carbonyl}-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate :



After the compound obtained in Referential Example 50 was hydrolyzed with lithium hydroxide, it was reacted with the compound obtained in Referential Example 71 in a similar manner to Example 2 to obtain the title compound.

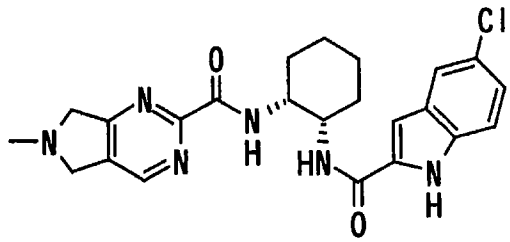
^{1}H-NMR ($CDCl_3$) δ: 1.54(9H,s), 1.55-2.30(8H,m), 4.23(1H,br.s), 4.53(1H,br.s), 4.74-4.83(4H,m),

6.99(1H,d,J=1.5Hz), 7.19(1H,dd,J=8.8,2.1Hz), 7.34(1H,d,J=8.8Hz), 7.62(1H,d,J=2.1Hz), 8.11(1H,br.s), 8.48-8.53(1H,br), 8.70-8.76(1H,br), 9.60-9.70(1H,br).

MS (ESI) m/z: 539$(M+H)^+$.

[Example 33]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-6-methyl-6,7-dihydro-5H-pyrrolo[3,4-d]-pyrimidine-2-carboxamide hydrochloride:



Trifluoroacetic acid (1 ml) was added to a solution of the compound (34.0 mg) obtained in Example 32 dissolved in methylene chloride (1 ml) at room temperature, and the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in methylene chloride (1 ml), to which triethylamine (17.6 µl), acetic acid (7.21 µl), 35% formalin (8.13 µl) and sodium triacetoxyborohydride (20.1 mg) were added at room temperature. The resultant mixture was stirred for 1 hour. Methylene chloride (10 ml) and saturated aqueous solution (10 ml) of sodium hydrogencarbonate were added to the reaction mixture to separate an organic layer. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled

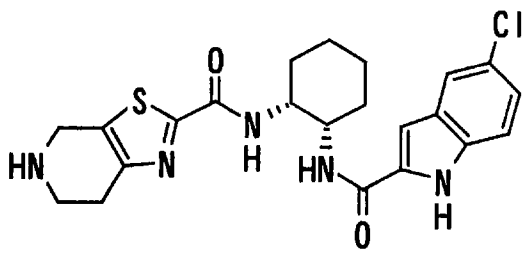
off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). A 1N ethanol solution of hydrochloric acid and ethyl acetate were added to the product thus obtained to solidify it, and the resultant solids were collected by filtration to obtain the title compound (8.0 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.40-1.55(2H,m), 1.55-1.75(4H,m), 1.80-2.05(2H,m), 2.98(3H,br.s), 4.28(2H,br.s), 4.65(4H,br.s), 7.14-7.20(2H,m), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 8.17(1H,d,J=6.9Hz),8.65(1H,d,J=8.3Hz), 8.93(1H,s), 11.73(1H,br.s), 11.82(1H,br.s).

MS (FAB) m/z: 453$(M+H)^+$.

[Example 34]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



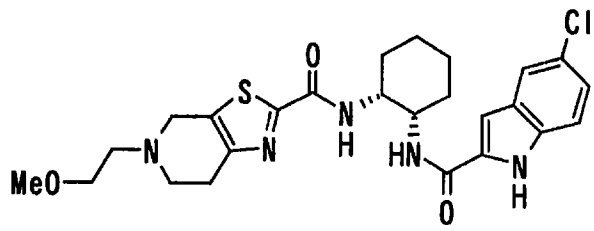
The title compound was obtained by treating a product obtained by the reaction of the compound obtained in Referential Example 71 with the compound obtained in Referential Example 34 with hydrochloric acid in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.39-1.52(2H,m), 1.62(4H,br.s), 1.86-2.09(2H,m), 3.03(2H,br.s), 3.40-3.47(2H,m), 4.17-4.32(2H,m), 4.44(2H,s), 7.15(1H,s), 7.17(1H,dd,J=8.6,2.0Hz), 7.41(1H,d,J=8.6Hz), 7.71(1H,s), 8.10-8.15(1H,m), 8.40-8.47(1H,m), 9.69(2H,br.s), 11.85(1H,s).

MS (FAB) m/z: 458$(M+H)^+$.

[Example 35]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-(2-methoxyethyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 34 and 2-methoxyethyl bromide in a similar manner to Example 25.

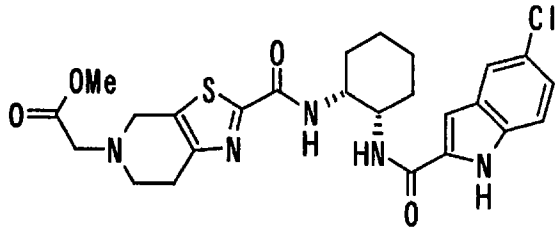
^{1}H-NMR (DMSO-d_6) δ: 1.44(2H,br.s), 1.62(4H,br.s), 1.85-2.10(2H,m), 2.76-3.21(6H,m), 3.28(3H,s), 3.64(2H,br.s), 4.00-4.52(4H,m), 7.14(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.70(1H,d,J=2.0Hz), 8.08-8.20(1H,m), 8.36-8.48(1H,m), 11.84(1H,s).

MS (FAB) m/z: 516$(M+H)^+$.

[Example 36]

Methyl 2-[2-{[((1R*,2S*)-2-{[(5-chloroindol-2-yl)-

carbonyl]amino}cyclohexyl)amino]carbonyl}-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]acetate hydrochloride:



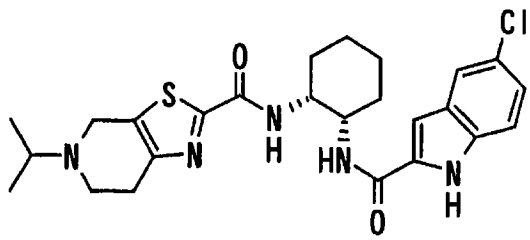
The title compound was obtained from the compound obtained in Example 34 and methyl bromoacetate in a similar manner to Example 25.

^{1}H-NMR ($CDCl_3$) δ: 1.52-1.98(7H,m), 2.17(1H,br.s), 2.87-3.10(4H,m), 3.49(2H,s), 3.76(3H,s), 3.93(1H,d,J=15.4Hz), 3.99(1H,d,J=15.4Hz), 4.22(1H,br.s), 4.45(1H,br.s), 6.86(1H,d,J=1.2Hz), 7.18(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.58-7.63(2H,m), 7.87(1H,br.s), 9.88(1H,br.s).

MS (FAB) m/z: 530$(M+H)^+$.

[Example 37]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound

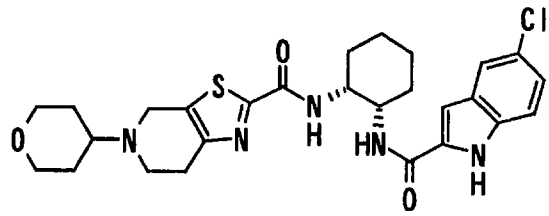
obtained in Example 34 and acetone in a similar manner to Example 24.

^{1}H-NMR (DMSO-d_6)δ: 1.18-1.73(8H,m), 1.81-2.10(2H,m), 2.97-3.16(1H,m), 3.20-3.41(2H,m), 3.52-3.80(2H,m), 4.19-4.31(2H,m), 4.34-4.77(2H,m), 7.17(1H,s), 7.18(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,d,J=2.0Hz), 8.15(1H,br.s), 8.28-8.51(1H,m), 11.31(1H,br.s), 11.86(1H,s).

MS (FAB) m/z: 500$(M+H)^+$.

[Example 38]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-(tetrahydro-2H-pyran-4-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



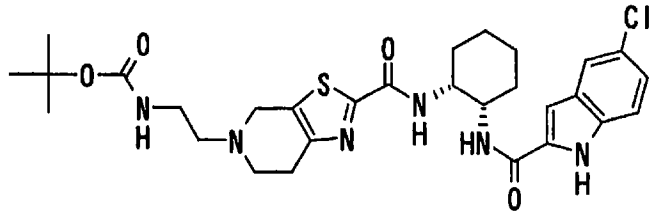
The title compound was obtained from the compound obtained in Example 34 and tetrahydro-4H-pyran-4-one in a similar manner to Example 24.

^{1}H-NMR (DMSO-d_6) δ: 1.30-3.56(19H,m), 3.70-4.01(3H,m), 4.17-4.30(2H,m), 4.32-4.80(1H,m), 7.15(1H,s), 7.17(1H,dd,J=8.6,2.0Hz), 7.41(1H,d,J=8.6Hz), 7.71(1H,d,J=2.0Hz), 8.14(1H,br.s), 8.39(1H,br.s), 11.84(1H,s).

MS (FAB) m/z: 542$(M+H)^+$.

[Example 39]

tert-Butyl 2-[2-{[((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)amino]carbonyl}-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]ethylcarbamate:



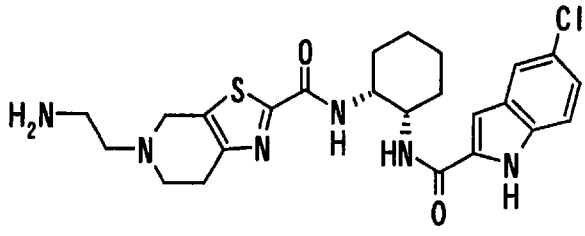
The title compound was obtained from the compound obtained in Example 34 and N-(tert-butoxycarbonyl)aminoacetoaldehyde (J. Org. Chem., 1988, Vol. 53, p.3457) in a similar manner to Example 24.

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.54-1.98(7H,m), 2.10-2.20(1H,m), 2.74(2H,br.s), 2.92(4H,br.s), 3.34(2H,br.s), 3.84(2H,br.s) ,4.21(1H,br.s), 4.45(1H,br.s), 6.86(1H,s), 7.19(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.57-7.63(2H,m), 7.81(1H,br.s), 9.66(1H,br.s).

MS (FAB) m/z: 601$(M+H)^+$.

[Example 40]

5-(2-Aminoethyl)-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)-carbonyl]amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (450 mg) obtained in Example 39 was

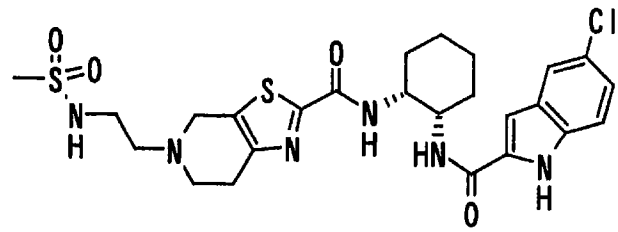
dissolved in methylene chloride (5 ml), and a saturated ethanol solution (30 ml) of hydrochloric acid was added to stir the mixture at room temperature for 1 minute. The reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the residue, and solids deposited were collected by filtration to obtain the title compound (367 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.38-1.50(2H,m), 1.61(4H,br.s), 1.85-2.08(2H,m), 3.00-4.62(12H,m), 7.14(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 8.12(1H,d,J=6.6Hz), 8.15-8.68(4H,m), 11.85(1H,s).

MS (FAB) m/z: 501$(M+H)^+$.

[Example 41]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-{2-[(methylsulfonyl)amino]ethyl}-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (110 mg) obtained in Example 40 was dissolved in pyridine (3 ml), methanesulfonyl chloride (30 µl) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and a 85:15 mixed solvent of

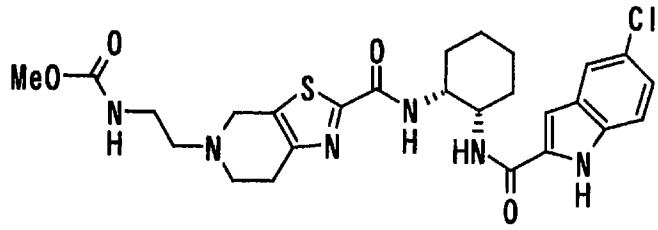
methylene chloride and methanol, and water were added to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain a pale yellow foamy substance. This product was suspended in 1N hydrochloric acid (0.3 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (63 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.38-1.50(2H,m), 1.55-1.70(4H,m), 1.86-2.05(2H,m), 2.97(3H,s), 3.02-3.25(2H,m), 3.30-3.60(5H,m), 3.78(1H,br.s), 4.18-4.30(2H,m), 4.45-4.86(2H,m), 7.14(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.40(1H,d,J=8.8Hz), 7.41(1H,br.s), 7.69(1H,d,J=2.0Hz), 8.09(1H,br.s), 8.43(1H,br.s), 11.18(1H,br.s), 11.82(1H,s).

MS (FAB) m/z: 579$(M+H)^+$.

[Example 42]

Methyl 2-[2-{[((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)amino]carbonyl}-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl]ethylcarbamate hydrochloride:



The compound (144 mg) obtained in Example 40 was

dissolved in pyridine (3 ml), triethylamine (138 μl) was added, and the mixture was stirred at room temperature for 5 minutes. A solution prepared by adding triphosgene (49 mg) to tetrahydrofuran (1 ml) containing methanol (20 μl) was added dropwise to this solution. After stirring for 1 hour, the reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a 9:1 mixed solvent of methylene chloride and methanol. Water was added to the solution to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain a colorless foamy substance. This product was suspended in 1N hydrochloric acid (0.2 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (60 mg).

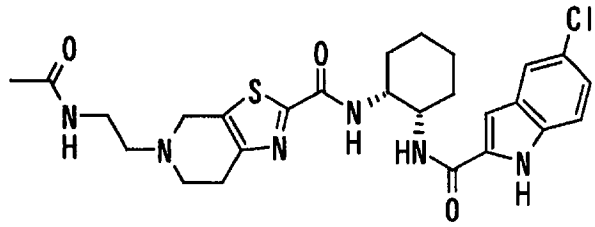
^{1}H-NMR (DMSO-d_6) δ: 1.38-1.50(2H,m), 1.61(4H,br.s), 1.85-2.04(2H,m), 2.80-3.49(8H,m), 3.52(3H,s), 3.62-4.91(4H,m), 7.14(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.37(1H,br.s), 7.40(1H,d,J=8.8Hz), 7.70(1H,s), 8.11(1H,d,J=6.8Hz), 8.40(1H,br.s), 11.05(1H,br.s), 11.82(1H,br.s).

MS (FAB) m/z: 559$(M+H)^+$.

[Example 43]

5-[2-(Acetylamino)ethyl]-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide

hydrochloride:



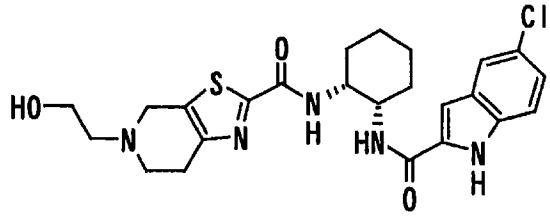
The compound (90 mg) obtained in Example 40 was dissolved in N,N-dimethylformamide (3 ml), triethylamine (65 µl) and acetic anhydride (22 µl) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and methylene chloride and a 0.3N aqueous solution of sodium hydroxide were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain a colorless foamy substance. This product was suspended in 1N hydrochloric acid (0.3 ml), and the suspension was concentrated under reduced pressure to obtain the title compound (73 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.39-1.52(2H,m), 1.54-1.70(4H,m), 1.83(3H,s), 1.84-2.06(2H,m), 3.02-3.87(8H,m), 4.16-4.32(2H,m), 4.40-4.52(1H,m), 4.78-4.88(1H,m), 7.14(1H,s), 7.16(1H,d,J=8.6Hz), 7.40(1H,d,J=8.6Hz), 7.70(1H,s), 8.07-8.17(1H,m), 8.22-8.30(1H,m), 8.38-8.52(1H,m), 11.14(1H,br.s), 11.83(1H,s).

MS (FAB) m/z: 543 $(M+H)^+$.

[Example 44]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-(2-hydroxyethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



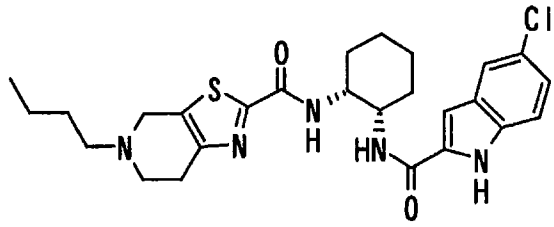
The title compound was obtained from the compound obtained in Example 34 and 2-bromoethanol in a similar manner to Example 25.

^{1}H-NMR (DMSO-d_6) δ: 1.37-1.69(6H,m), 1.86-2.03(2H,m), 2.54-2.61(2H,m), 2.75-2.86(4H,m), 3.52-3.59(2H,m), 3.75(2H,s), 4.47(1H,t,J=5.4Hz), 7.12(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.40(1H,d,J=8.8Hz), 7.70(1H,s), 8.05-8.13(1H,m), 8.28-8.35(1H,m), 11.78(1H,s).

MS (FAB) m/z: 502 $(M+H)^+$.

[Example 45]

5-Butyl-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



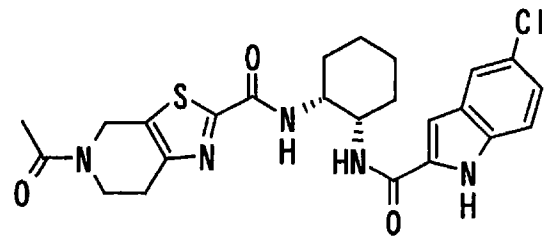
The title compound was obtained from the compound obtained in Example 34 and n-bromobutane in a similar manner to Example 25.

^{1}H-NMR (DMSO-d_6) δ: 0.88(3H,t,J=7.2Hz), 1.20-1.70(10H,m), 1.87-2.05(2H,m), 2.55-3.40(8H,m), 4.16-4.30(2H,m), 7.13(1H,s), 7.16(1H,d,J=8.8Hz), 7.40(1H,d,J=8.8Hz), 7.69(1H,s), 8.05-8.14(1H,m), 8.35(1H,br.s), 11.81(1H,s).

MS (FAB) m/z: 514$(M+H)^+$.

[Example 46]

5-Acetyl-N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:



The compound (100 mg) obtained in Example 34 was dissolved in N,N-dimethylformamide (3 ml), triethylamine (84 µl) and acetic anhydride (29 µl) were added, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure,

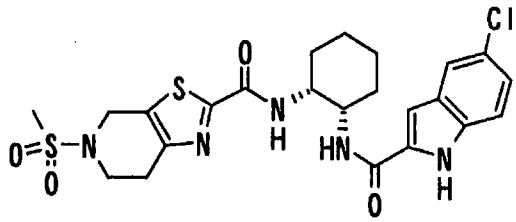
and methylene chloride and 1N hydrochloric acid were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 100:3) to obtain the title compound (86 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.52-1.85(5H,m), 1.91(2H,br.s), 2.10-2.28(4H,m), 2.77-3.00(2H,m), 3.70-4.00(2H,m), 4.19-4.38(1H,m), 4.45(1H,br.s), 4.68-4.99(2H,m), 6.85(1H,s), 7.17-7.22(1H,m), 7.30-7.39(1H,m), 7.50-7.84(3H,m), 9.72-10.05(1H,m).

MS (FAB) m/z: 500$(M+H)^+$.

[Example 47]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-cyclohexyl)-5-(methylsulfonyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide:



The compound (100 mg) obtained in Example 34 was dissolved in pyridine (3 ml), triethylamine (168 µl) and methanesulfonyl chloride (48 µl) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and methylene chloride and 1N hydrochloric acid were added

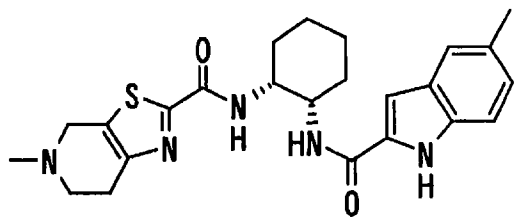
to the residue to separate an organic layer. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 100:1) to obtain the title compound (79 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.50-1.82(5H,m), 1.90(2H,br.s), 2.13(1H,br.s), 2.89(3H,s), 2.91-2.98(2H,m), 3.60-3.70(2H,m), 4.30(1H,br.s), 4.44(1H,br.s), 4.58(2H,s), 6.87(1H,s), 7.19(1H,d,J=8.8Hz), 7.34(1H,d,J=8.8Hz), 7.61(3H,br.s), 9.91(1H,br.s).

MS (FAB) m/z: 536$(M+H)^+$.

[Example 48]

5-Methyl-N-((1R*,2S*)-2-{[(5-methylindol-2-yl)carbonyl]-amino}cyclohexyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Referential Example 67 and 5-methylindole-2-carboxylic acid in a similar manner to Example 5.

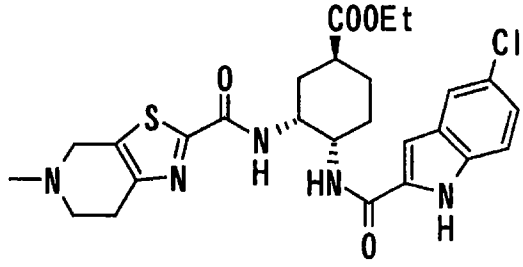
^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(2H,m), 1.50-1.80(4H,m), 1.85-2.07(2H,m), 2.36(3H,s),2.88(3H,s), 3.12(2H,br.s), 3.53(2H,br.s), 4.15-4.30(2H,m), 4.30-4.80(2H,br), 7.00(1H,dd,J=8.4,1.5Hz), 7.05(1H,d,J=1.5Hz),

7.30(1H,d,J=8.4Hz), 7.38(1H,s), 8.00(1H,d,J=7.3Hz), 8.43(1H,br.s), 11.45(1H,br.s), 11.49(1H,br.s).

MS (FAB) m/z: 452$(M+H)^+$.

[Example 49]

Ethyl (1R*,3S*,4R*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



The compound (1.40 g) obtained in Referential Example 91 was suspended in ethanol (8 ml), and a saturated ethanol solution (10 ml) of hydrochloric acid was added at room temperature to stir the mixture for 12 hours. The solvent was distilled off under reduced pressure to obtain ethyl (1R*,3S*,4R*)-3-amino-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexanecarboxylate hydrochloride (1.25 g).

The title compound was obtained from the above-described product and the compound obtained in Referential Example 10 in a similar manner to Example 2.

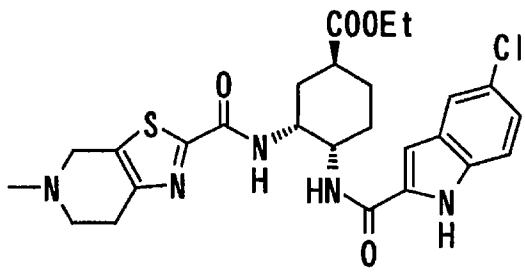
^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=7.1Hz), 1.52-1.80(2H,m), 2.03-2.37(4H,m), 2.53(3H,s), 2.57-2.71(1H,m), 3.73 and 3.78(total 1H,each d,J=14.4Hz), 4.08-4.17(1H,m), 4.18(2H,q,J=7.2Hz), 4.55-4.65(1H,m), 6.85(1H,br.s),

7.21(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz),
7.48(1H,d,J=7.6Hz), 7.63(1H,d,J=2.0Hz), 7.98(1H,d,J=7.6Hz),
9.30(1H,s).

MS (ESI) m/z: 544$(M+H)^+$.

[Example 50]

Ethyl (1S,3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



The compound (4.2 g) obtained in Referential Example 97 was suspended in ethanol (25 ml), and a saturated ethanol solution (55 ml) of hydrochloric acid was added at room temperature to stir the mixture for 11 hours. The solvent was distilled off under reduced pressure to obtain colorless solids (4.15 g).

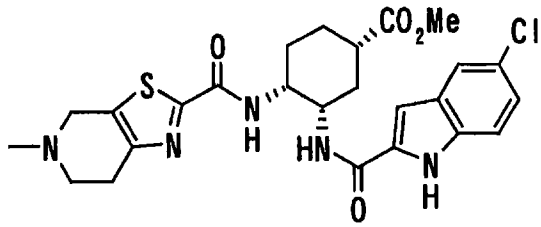
This product (4.15 g) was dissolved in N,N-dimethylformamide (40 ml), and the compound (2.86 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (1.72 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.15 g) were added to this solution at room temperature to stir the mixture for 39 hours. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to

conduct extraction with chloroform. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (chloroform:methanol = 100:1) to obtain the title compound (1.71 g).

$[\alpha]_D$ -94° (C=1.0, chloroform).

[Example 51]

Methyl (1R*,3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



The title compound was obtained by treating the compound obtained in Referential Example 107 with an ethanol solution of hydrochloric acid and then condensing this compound with the compound obtained in Referential Example 10 in a similar manner to Example 49.

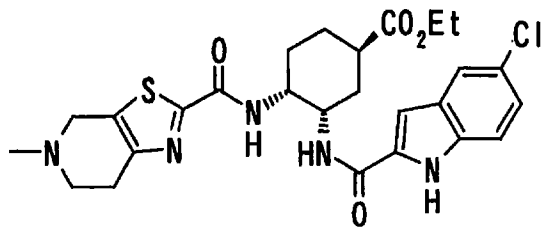
^{1}H-NMR (DMSO-d_6) δ: 1.55-1.80(3H,m), 1.80-2.20(3H,m), 2.60-2.75(1H,m), 2.92(3H,s), 3.15-3.30(1H,m), 3.30-3.50(4H,m), 3.57(3H,s), 3.55-3.70(1H,m), 4.20-4.30(1H,m), 4.30-4.40(1H,m), 7.02(1H,s), 7.17(1H,dd,J=8.5,2.0Hz), 7.41(1H,d,J=8.5Hz), 7.71(1H,s), 8.20-8.35(1H,m), 8.35-

8.45(1H,m), 11.82(1H,br).

MS (FAB) m/z: 530$(M+H)^+$.

[Example 52]

Ethyl (1R*,3S*,4R*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



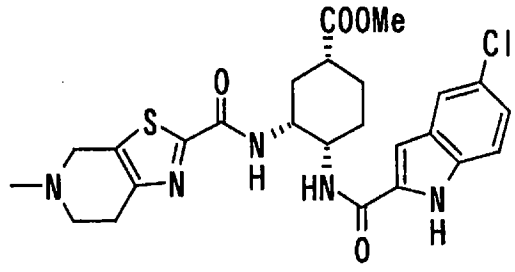
The title compound was obtained by treating the compound obtained in Referential Example 98 with a saturated ethanol solution of hydrochloric acid and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=7.1Hz), 1.82-2.30(6H,m), 2.49(3H,s), 2.62-2.73(1H,m), 3.74-3.85(2H,m), 3.85-3.93(2H,m), 3.71(2H,s), 4.12-4.29(3H,m), 4.49-4.59(1H,m), 6.89(1H,br.s), 7.21(1H,dd,J=8.8, 2.0Hz), 7.32(1H,d,J=8.8Hz), 7.33(1H,br.s), 7.41(1H,br.s), 7.62(1H,br.s), 9.37(1H,s).

MS (ESI) m/z: 544$(M+H)^+$.

[Example 53]

Methyl (1R*,3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



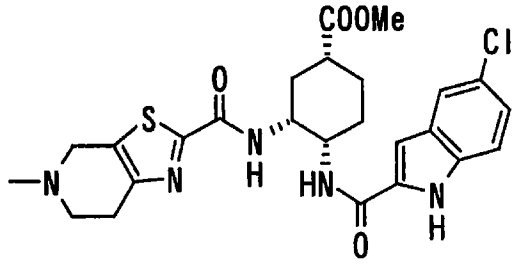
The title compound was obtained by treating the compound obtained in Referential Example 106 with a 4N dioxane solution of hydrochloric acid and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

^{1}H-NMR (DMSO-d_6) δ: 1.65-1.80(3H,m), 1.80-2.10(2H,m), 2.15-2.25(1H,m), 2.55-2.70(1H,m), 2.89(3H,s), 3.05-3.20(1H,m), 3.30-3.50(4H,m), 3.55-3.65(1H,m), 3.62(3H,s), 4.20-4.30(1H,m), 4.35-4.45(1H,m), 7.19(1H,dd,J=8.8,1.2Hz), 7.23(1H,s), 7.43(1H,d,J=8.8Hz), 7.73(1H,s), 8.03(1H,d,J=6.8Hz), 8.73(1H,d,J=8.5Hz), 11.15-11.38(1H,br), 11.85(1H,s).

MS (FAB) m/z: 530$(M+H)^+$.

[Example 54]

Methyl (1R,3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



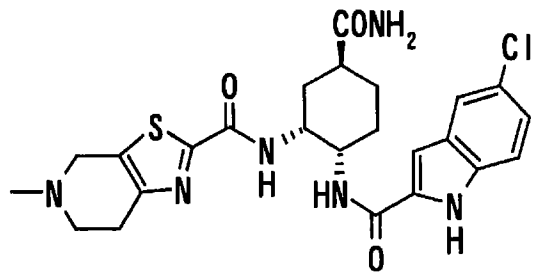
The title compound was obtained by treating the compound obtained in Referential Example 112 a 4N dioxane solution of hydrochloric acid and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Example 49.

^{1}H-NMR (DMSO-d_6) δ: 1.67-1.76(3H,m), 1.88-1.91(1H,m), 2.01(1H,br.s), 2.13-2.22(1H,m), 2.52-2.67(4H,m), 2.86(2H,br.s), 3.04(2H,br.s), 3.33-3.41(1H,m), 3.61(3H,s), 4.22-4.36(3H,m), 7.17-7.22(2H,m), 7.42(1H,d,J=8.8Hz), 7.72(1H,s), 8.00(1H,d,J=6.9Hz), 8.68(1H,d,J=8.6Hz), 11.80(1H,s).

MS (FAB) m/z: 530$(M+H)^+$.

[Example 55]

N-((1R*,2S*,5S*)-5-(Aminocarbonyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



The title compound was obtained by treating the compound obtained in Referential Example 113 with a 4N dioxane solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10.

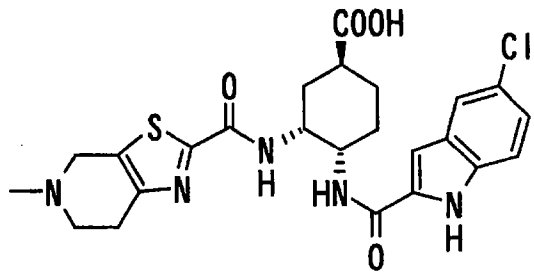
^{1}H-NMR ($CDCl_3$) δ: 0.78-2.40(7H,m), 2.53(3H,s), 2.80-2.89(1H,m), 2.91-3.00(1H,m), 3.68-3.76(2H,m), 4.08-

4.19(1H,m), 4.54-4.65(1H,m), 6.80(1H,br.s), 7.21(1H,dd,J=8.4, 1.6Hz), 7.33(1H,d,J=8.4Hz), 7.38-7.43(1H,m), 7.49-7.55(1H,m), 7.63(1H,br.s), 9.14(1H,br.s).

MS (ESI) m/z: 515$(M+H)^+$.

[Example 56]

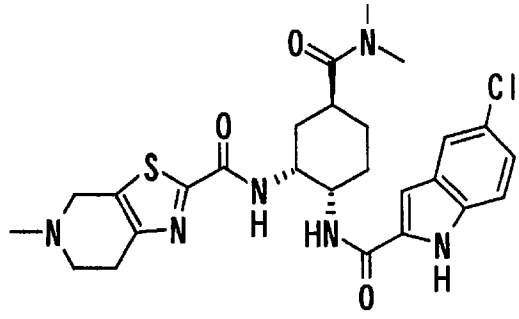
(1R*,3S*,4R*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylic acid:



The compound (916 mg) obtained in Example 49 was suspended in a mixed solvent of ethanol (10 ml) and tetrahydrofuran (8 ml), and a 1N aqueous solution (3.3 ml) of sodium hydroxide was added at room temperature to stir the mixture for 12 hours at the same temperature. After adding 1N hydrochloric acid (3.3 ml), the solvent was distilled off under reduced pressure, and the residue was washed with water and diethyl ether to obtain the title compound (712 mg).

[Example 57]

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



Triethylamine (0.25 ml), dimethylamine hydrochloride (133 mg), 1-hydroxybenzotriazole monohydrate (53 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg) were added to a chloroform suspension (10 ml) of the compound (168 mg) obtained in Example 56, and the mixture was stirred for 72 hours. The solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with chloroform. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 93:7). The thus-obtained colorless solids (135 mg) were suspended in ethanol (5 ml), to which 1N ethanol solution (0.5 ml) of hydrochloric acid was added. The mixture was stirred for 2 hours, and the solvent was distilled off to obtain the title compound (112 mg).

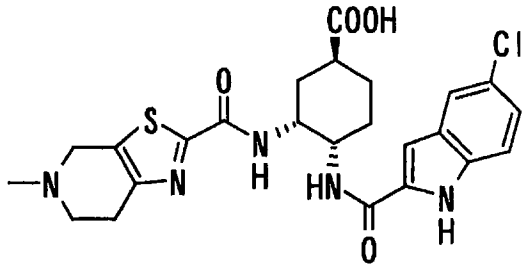
^{1}H-NMR (DMSO-d_6) δ: 1.42-2.07(6H,m), 2.73-3.70(10H,m), 2.88(3H,s), 2.97(3H,s), 4.03-4.20(1H,m), 4.51-4.67(1H,m), 7.04(1H,br.s), 7.16(1H,br,J=8.8Hz), 7.41(1H,d,J=8.8Hz),

7.68(1H,br.s), 8.32-8.47(2H,m), 10.76(1H,br.s).

MS (ESI) m/z: 543$(M+H)^+$.

[Example 58]

(1S,3R,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylic acid:



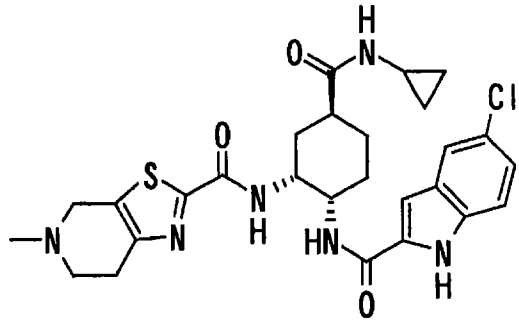
The compound (1.6 g) obtained in Example 50 was suspended in a mixed solvent of ethanol (20 ml) and tetrahydrofuran (15 ml), and a 1N aqueous solution (5.9 ml) of sodium hydroxide was added at room temperature to stir the mixture for 12 hours at the same temperature. After adding 1N hydrochloric acid (5.9 ml), the solvent was distilled off under reduced pressure, and the residue was washed with water and diethyl ether to obtain the title compound (1.19 g).

m.p. 234-236°C.

$[\alpha]_D$ -57° (C=1.0, methanol).

[Example 59]

N-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(cyclopropylamino)carboyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



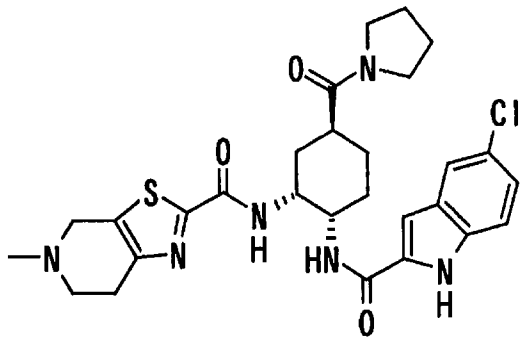
The title compound was obtained from the compound obtained in Example 58 and cyclopropylamine in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 0.32-0.40(2H,m), 0.53-0.63(2H,m), 1.50-2.10(6H,m), 2.25-2.40(1H,m), 2.45-2.70(2H,m), 2.91(3H,s), 3.05-3.80(3H,m), 4.05-4.17(1H,m), 4.30-4.55(2H,m), 4.55-4.80(1H,m), 7.03(1H,d,J=1.5Hz), 7.16(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.68(1H,d,J=2.0Hz), 7.86(1H,br,J=3.4Hz), 8.06(1H,br.s), 8.40(1H,br,J=7.6Hz), 11.20-11.60(1H,br), 11.79(1H,s).

MS (FAB) m/z: 555$(M+H)^+$.

[Example 60]

N-[(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(pyrrolidin-1-ylcarbonyl)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



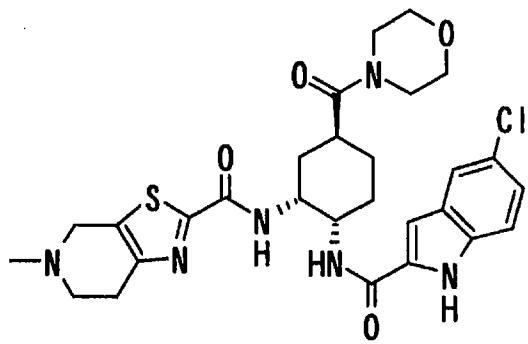
The title compound was obtained from the compound obtained in Example 58 and pyrrolidine in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.45-2.10(10H,m), 2.75-2.90(2H,m), 2.90(3H,s), 3.10-3.70(H,m), 4.05-4.20(1H,m), 4.25-4.80(3H,m), 7.05(1H,s), 7.17(1H,d,J=8.7Hz), 7.41(1H,d,J=8.7Hz), 7.69(1H,s), 8.32(1H,br,J=7.6Hz), 8.38(1H,br,J=7.1Hz), 11.22(1H,br.s), 11.78(1H,s).

MS (FAB) m/z: 569$(M+H)^+$.

[Example 61]

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



The title compound was obtained from the compound

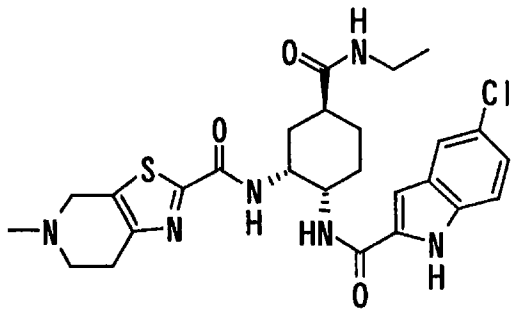
obtained in Example 56 and morpholine in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.40-2.05(6H,m), 2.75-3.70(18H,m), 4.02-4.17(1H,m), 4.55-4.69(1H,m), 7.05(1H,br.s), 7.17(1H,br,J=8.8Hz), 7.41(1H,d,J=8.8Hz), 7.67(1H,br.s), 8.35(1H,d,J=7.6Hz), 8.40(1H,d,J=7.6Hz), 10.79(1H,br.s).

MS (ESI) m/z: 585$(M+H)^+$.

[Example 62]

N-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(ethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (150 mg) obtained in Example 58 was dissolved in N,N-dimethylformamide (3 ml), to which N-ethylamine hydrochloride (119 mg), 1-hydroxybenzotriazole monohydrate (79 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (112 mg) and triethylamine (326 μl) were added, and the mixture was stirred at room temperature for 4 days. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to

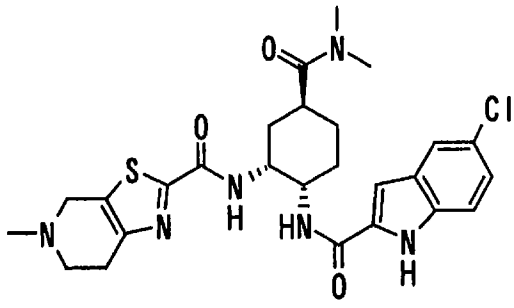
conduct extraction with methylene chloride. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 47:3). The thus-obtained solid was dissolved in methylene chloride, to which 1N ethanol solution (171 μl) of hydrochloric acid was added. The solvent was distilled off under reduced pressure, and methanol and diethyl ether were added to the residue to collect precipitate formed by filtration, thereby obtaining the title compound (74 mg).

^{1}H-NMR (DMSO-d_6) δ: 0.99(3H,t,J=7.2Hz), 1.57-2.02(6H,m), 2.33-2.38(1H,m), 2.92(3H,s), 3.01-3.08(2H,m), 3.17-3.20(2H,s), 3.45-3.70(2H,m), 4.10-4.17(1H,m), 4.40-4.69(3H,m), 7.04(1H,d,J=2.0Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 7.78-7.81(1H,m), 8.08-8.12(1H,m), 8.40(1H,d,J=8.1Hz), 11.23(1H,br.s), 11.79(1H,br.s).

MS (FAB) m/z: 543$(M+H)^+$.

[Example 63]

N-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (900 mg) obtained in Example 58 was dissolved in N,N-dimethylformamide (50 ml), to which dimethylamine hydrochloride (304 mg), 1-hydroxybenzotriazole monohydrate (262 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (369 mg) and diisopropylethylamine (1.83 ml) were added, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to conduct extraction with methylene chloride. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 47:3). The thus-obtained white solids were dissolved in methylene chloride, to which 1N ethanol solution (1.49 ml) of hydrochloric acid was added. The solvent was distilled off under reduced pressure, and methanol and diethyl ether were added to the residue to collect precipitate formed by filtration, thereby obtaining the title compound (777 mg).

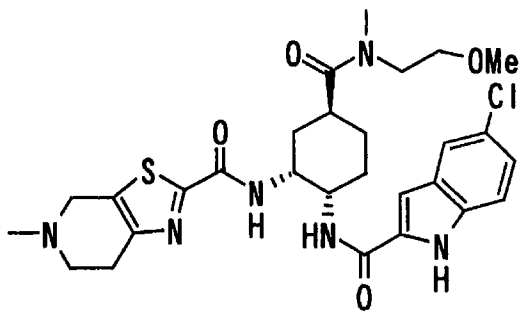
$[\alpha]_D$ = -53.9° (18°C, c = 0.505, methanol).

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.60(1H,m), 1.70-1.85(3H,m), 1.90-2.05(2H,m), 2.80(3H,s), 2.91(3H,s), 2.95-3.10(1H,m), 2.97(3H,s), 3.10-3.75(4H,m), 4.05-4.15(1H,m), 4.35-4.75(3H,m), 7.05(1H,s), 7.16(1H,dd,J=8.7,2.1Hz), 7.41(1H,d,J=8.6Hz), 7.67(1H,s), 8.30-8.45(2H,m), 11.63(1H,br), 11.78(1H,s).

MS (FAB) m/z: 543$(M+H)^+$.

[Example 64]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-{[(2-methoxyethyl)(methyl)amino]carbonyl}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



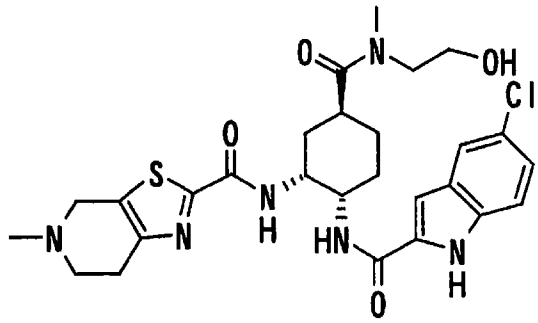
The title compound was obtained from the compound obtained in Example 58 in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.50-1.99(6H,m), 2.80,3.01(3H,each s), 2.91(3H,s), 3.03(1H,br.s), 3.16(2H,s), 3.23(3H,s), 3.35-3.67(6H,m), 4.09-4.16(1H,m), 4.43-4.67(3H,m), 7.04-7.06(1H,m), 7.16(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.69(1H,br.s), 8.29-8.41(2H,m), 11.59(1H,br.s), 11.80(1H,br.s).

MS (FAB) m/z: 587 $(M+H)^+$.

[Example 65]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-{[(2-hydroxyethyl)(methyl)amino]carbonyl}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



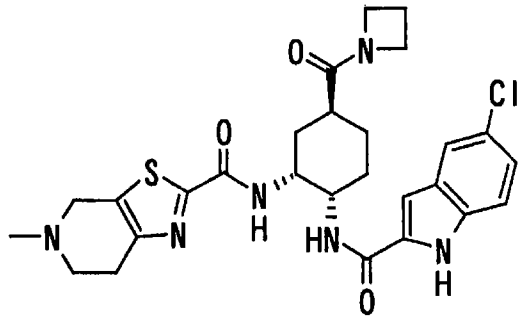
The title compound was obtained from the compound obtained in Example 58 in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.50-1.55(1H,m), 1.74-1.84(3H,m), 1.94-1.97(2H,m), 2.67,3.02(3H,each s), 2.91(3H,s), 3.10-3.68(9H,m), 4.11-4.13(1H,m), 4.43-4.66(4H,m), 7.05(1H,s), 7.16(1H,dd,J=8.7,2.0Hz), 7.41(1H,d,J=8.7Hz), 7.68(1H,s), 8.34-8.40(2H,m), 11.47(1H,br.s), 11.79(1H,s).

MS (FAB) m/z: 573 $(M+H)^+$.

[Example 66]

N-((1R,2S,5S)-5-(1-Azetidinylcarbonyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



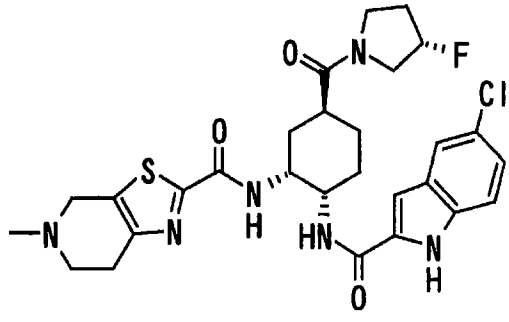
The title compound was obtained from the compound obtained in Example 58 and azetidine hydrochloride in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6)δ: 1.47-1.55(1H,m), 1.65-1.82(3H,m), 1.88-2.01(2H,m), 2.16(2H,quint.,J=7.6Hz), 3.17-3.67(5H,m), 3.82(2H,t,J=7.6Hz), 4.02-4.14(3H,m), 4.43-4.67(3H,m), 7.06(1H,s), 7.17(1H,dd,J=8.7,1.7Hz), 7.41(1H,d,J=8.7Hz), 7.69(1H,br.s), 8.31(1H,d,J=7.6Hz), 8.38(1H,d,J=7.6Hz), 11.41(1H,br.s), 11.80(1H,s).

MS (FAB) m/z: 555$(M+H)^+$.

[Example 67]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-{[(3S)-3-fluoropyrrolidinyl]carbonyl}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinecarboxamide hydrochloride:



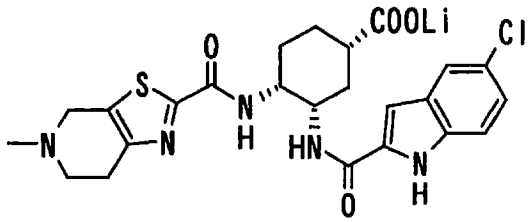
The title compound was obtained from the compound obtained in Example 58 and (S)-3-fluoropyrrolidine (Synlett., 1995, p. 55) in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.23-3.77(22H,m), 4.11-4.16(1H,m), 4.58-4.51(1H,m), 5.23-5.42(1H,m), 7.05(1H,s), 7.16(1H,d,J=8.3Hz), 7.42(1H,d,J=8.3Hz), 7.68(1H,s), 8.34-8.37(2H,m), 11.78(1H,s).

MS (FAB) m/z: 587$(M+H)^+$.

[Example 68]

Lithium (1R*,3R*,4S*)-3-{[(5-Chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexanecarboxylate:



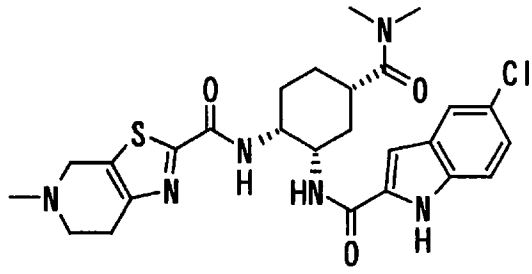
The compound (1.20 g) obtained in Example 51 was dissolved in tetrahydrofuran (32 ml), and lithium hydroxide (60.8 mg) and water (4 ml) were successively added under ice cooling to stir the mixture at room temperature for 14 hours. The solvent was distilled off under reduced pressure to obtain the title compound (1.12 g).

^{1}H-NMR (DMSO-d_6) δ: 1.55-1.70(2H,m), 1.70-2.05(4H,m), 2.10-2.20(1H,m), 2.25-2.40(4H,m), 2.50-2.80(4H,m), 3.45-3.65(3H,m), 4.10-4.30(2H,m), 7.00-7.20(2H,m), 7.50-

7.65(2H,m).

[Example 69]

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



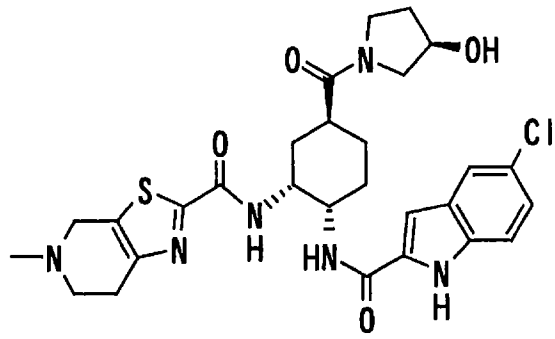
The title compound was obtained from the compound obtained in Example 68 and dimethylamine in a similar manner to Example 57.

^{1}H-NMR (DMSO-d_6) δ: 1.40-1.60(2H,m), 1.65-1.80(2H,m), 1.95-2.10(2H,m), 2.84(3H,s), 2.90-3.05(1H,m), 2.92(3H,s), 3.06(3H,s), 3.15-3.75(4H,m), 4.25-4.75(4H,m), 7.02(1H,d,J=1.5Hz), 7.15(1H,dd,J=8.8,2.1Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=2.1Hz), 8.05(1H,d,J=7.7Hz), 8.63(1H,d,J=7.7Hz), 11.20(1H,br), 11.79(1H,s).

MS (FAB) m/z: 543$(M+H)^+$.

[Example 70]

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



1) The compound (1.18 g) obtained in Referential Example 58 was dissolved in methanol (12 ml), 1N hydrochloric acid (240 µl) and palladium hydroxide (221 mg) were added, and hydrogen was introduced to conduct catalytic reduction under normal pressure at room temperature for 4.5 hours. The catalyst was removed by filtration, and the filtrate was concentrated to solid under reduced pressure to obtain crude (3R)-3-{[tert-butyl(diphenyl)silyl]oxy}pyrrolidine hydrochloride (984 mg).

The thus-obtained product (249 mg), the product (295 mg) obtained in Example 58, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (126 mg) and 1-hydroxybenzotriazole monohydrate (87 mg) were dissolved in N,N-dimethylformamide (10 ml). Diisopropylethylamine (450 µl) was added dropwise to the solution under ice cooling, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation. The resultant

organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was subjected to column chromatography on silica gel (methanol:methylene chloride = 3:97) to obtain N-((1R,2S,5S)-5-[((3R)-3-{[tert-butyl(diphenyl)silyl]oxy}-pyrrolidinyl)carbonyl]-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (248 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.06(9H,s), 1.50-1.60(1H,m), 1.75-2.10(5H,m), 2.20-2.50(2H,m), 2.54(3H,d,J=2.8Hz), 2.60-3.00(5H,m), 3.30-3.80(6H,m), 4.10-4.20(1H,m), 4.40-4.70(2H,m), 6.85(1H,s), 7.15-7.25(1H,m), 7.30-7.50(8H,m), 7.60-7.70(5H,m), 7.90-8.00(1H,m), 9.38(1H,s).

MS (FAB) m/z: 823$(M+H)^+$.

2) The above product (240 mg) was dissolved in pyridine (10 ml), and hydrogen fluoride-pyridine complex (3.0 ml) was added dropwise under ice cooling to stir the mixture at 0°C for 4.5 hours. Ethyl acetate (80 ml) was added to the reaction mixture under ice cooling to dilute it. The diluted reaction mixture was poured into ice. After sodium hydrogencarbonate was added to this solution to alkalify it, liquid separation was conducted. The resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride =1:19 → 1:9). The resultant crude purified product was dissolved in

methylene chloride and methanol, to which 1N ethanol solution (225 μl) of hydrochloric acid was added to dry it once. Methanol and diethyl ether were added to the residue to solidify it, thereby obtaining the title compound (114 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.50-1.60(1H,m), 1.70-2.10(6H,m), 2.75-2.85(1H,m), 2.92(3H,s), 3.10-3.80(8H,m), 4.10-5.10(6H,m), 7.05(1H,d,J=1.7Hz), 7.16(1H,dd,J=8.8,1.7Hz), 7.42(1H,d,J=8.8Hz), 7.68(1H,s), 8.30-8.45(2H,m), 11.10-11.40(1H,m), 11.78(1H,s).

MS (FAB) m/z: 585$(M+H)^+$.

[Example 71]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5,5-dimethoxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide or N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4,4-dimethoxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The title compound was obtained from the compound obtained in Referential Example 118 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR ($CDCl_3$) δ: 2.11-2.15(1H,m), 2.21-2.25(1H,m), 2.41-2.43(1H,m), 2.46(3H,s), 2.70-2.75(1H,m), 2.81-2.88(1H,m), 3.21(3H,s), 3.24(3H,s), 3.49(1H,s), 3.58(1H,d,J=15.6Hz), 3.71(1H,d,J=15.6Hz), 3.87-3.93(1H,m), 4.26-4.29(1H,m), 6.85(1H,d,J=2.0Hz), 7.19(1H,dd,J=8.5,2.0Hz),

7.30(1H,d,J=8.5Hz), 7.62(1H,s), 9.21(1H,s).

[Example 72]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-oxocyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide or N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-oxocyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The compound (100 mg) obtained in Example 71 was dissolved in chloroform (2 ml), and trifluoroacetic acid (0.5 ml) and water (0.5 ml) were added to stir the mixture at room temperature for 3.5 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 19:1). The thus-obtained white solids were dissolved in methanol (4 ml), to which a 1N ethanol solution (0.38 ml) of hydrochloric acid was added. The solvent was distilled off under reduced pressure to obtain the title compound (35 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.83-1.90(1H,m), 2.08-2.10(1H,m), 2.28-2.32(1H,m), 2.50-2.59(1H,m), 2.87(3H,s), 2.96(1H,t,J=13.0Hz), 3.06-3.10(2H,m), 3.33-3.36(3H,m), 4.02-4.04(2H,m), 4.55-4.57(2H,m), 7.03(1H,s),

7.15(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.69(1H,s), 8.43(1H,d,J=8.8Hz), 8.91(1H,d,J=8.8Hz), 11.75(1H,s).

[Example 73]

N-[(1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(hydroxyimino)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-[(1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-(hydroxyimino)-cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The compound (133 mg) obtained in Example 72 was dissolved in a mixed solvent of pyridine (8 ml) and methanol (8 ml), and hydroxylamine hydrochloride (30 mg) was added to stir the mixture at room temperature for 3 days. The reaction mixture was concentrated, and water was added to the residue to conduct extraction with ethyl acetate. The resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3 → 17:3) to obtain the title compound (131 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.43-1.86(3H,m), 1.98-2.03(1H,m), 2.26-2.30(1H,m), 2.45(3H,s), 2.47-2.51(1H,m), 2.67-2.71(1H,m), 2.78-2.86(3H,m), 3.86-3.43(2H,m), 4.16-4.24(2H,m), 6.85(1H,s), 7.13-7.16(1H,m), 7.20-7.24(1H,m), 7.46,7.50(total 1H,s), 7.56-7.64(2H,m), 9.59,9.62(total

1H,s).

[Example 74]

N-((7R*,8S*)-8-{[(5-Chloroindol-2-yl)carbonyl]amino}-1,4-dioxaspiro[4.5]dec-7-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-((7R*,8S*)-7-{[(5-chloroindol-2-yl)carbonyl]amino}-1,4-dioxaspiro[4.5]dec-8-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

The title compound was obtained from the compound obtained in Referential Example 120 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR ($CDCl_3$) δ: 1.69-1.87(6H,m), 2.14-2.17(1H,m) 2.30-2.32(1H,m), 2.47(3H,s), 2.70-2.75(1H,m), 2.81-2.89(2H,m), 3.58(1H,d,J=15.4Hz), 3.72(1H,d,J=15.4Hz), 3.89-3.91(1H,m), 3.99(4H,s), 4.37-4.40(1H,m), 6.86(1H,d,J=2.0Hz), 7.19(1H,dd,J=8.8,2.0Hz), 7.30(1H,d,J=8.8Hz), 7.38(1H,d,J=7.3Hz), 7.62(1H,d,J=2.0Hz), 9.15(1H,s).

[Example 75]

N-[(1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(methoxyimino)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-[(1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-(methoxyimino)-cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide:

1) The compound (2.21 g) obtained in Referential Example 124 was dissolved in methylene chloride (30 ml),

and trifluoroacetic acid (6 ml) was added to stir the mixture at room temperature for 1.5 hours. The reaction mixture was concentrated, dried with a vacuum pump and then dissolved in N,N-dimethylformamide (20 ml), to which 5-chloroindole-2-carboxylic acid (500 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (593 mg), 1-hydroxybenzotriazole monohydrate (473 mg) and N-methylmorpholine (2.8 ml) were added. The mixture was stirred at room temperature for 10 hours. Additionally, 5-chloroindole-2-carboxylic acid (242 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (237 mg) and 1-hydroxybenzotriazole monohydrate (189 mg) were added to stir the mixture for 4 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with ethyl acetate and with a mixed solvent of ethyl acetate and tetrahydrofuran. The resultant organic layers were washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 97:3 → 4:1) to obtain N-[(1R*,2S*)-2-amino-5-(methoxyimino)cyclohexyl]-5-chloroindole-2-carboxamide (368 mg) and N-[(1R*,2S*)-2-amino-4-(methoxyimino)-cyclohexyl]-5-chloroindole-2-carboxamide (300 mg).

2) The title compound (mixture of syn and anti

isomers at the methoxyimino group) from one of the above-obtained N-[(1R*,2S*)-2-amino-5-(methoxyimino)-cyclohexyl]-5-chloroindole-2-carboxamide or N-[(1R*,2S*)-2-amino-4-(methoxyimino)cyclohexyl]-5-chloroindole-2-carboxamide and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR ($CDCl_3$) δ: 1.84-2.00(3H,m), 2.26-2.56(3H,m), 2.46(3H,s), 2.80-2.83(4H,m), 3.57(1H,q,J=15.4Hz), 3.70(1H,q,J=15.4Hz), 3.84,3.85(total 3H,s), 4.08-4.14(1H,m), 4.26-4.30(1H,m), 6.84(1H,s), 7.17(1H,d,J=8.8Hz), 7.27(1H,d,J=8.8Hz), 7.46-7.48(2H,m), 7.56(1H,m), 9.42,9.55(total 1H,s).

[Example 76]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-hydroxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (Stereoisomer A) or N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxycyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (Stereoisomer A):

1) N-((1R*,2S*)-2-amino-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)-5-chloroindole-2-carboxamide (Stereoisomer A) and N-((1R*,2S*)-2-amino-5-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)-5-chloroindole-2-carboxamide (Stereoisomer A) were obtained by subjecting the ((1R*,2S*)-form obtained in Referential Example 125 to de(tert-butoxycarbonylation) in the same manner as in the step 1) of Example 75 and reacting the

formed product with 5-chloroindole-2-carboxylic acid.

2) N-((1R*,2S*)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A) or N-((1R*,2S*)-4-{[tert-butyl(diphenyl)silyl]oxy}-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl-5)-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A) was obtained from the product obtained by the above reaction and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR ($CDCl_3$) δ: 1.06(9H,s), 1.55-1.61(1H,m), 1.85-1.90(1H,m), 2.18-2.25(1H,m), 2.46(3H,s), 2.51(2H,d,J=7.6Hz), 2.72(1H,m), 3.56(1H,s), 3.57(1H,d,J=15.3Hz), 3.72(1H,d,J=15.3Hz), 3.71-3.81(1H,m), 3.88-3.95(1H,m), 6.78(1H,s), 7.17(1H,dd,J=2.0,8.8Hz), 7.37-7.44(7H,m), 7.59(1H,s), 7.65-7.68(6H,m), 9.30(1H,s).

3) The title compound was obtained from the compound obtained by the above-described reaction in the same manner as in the step 3) of Example 28.

^{1}H-NMR (DMSO-d_6) δ: 1.25-1.30(2H,m), 1.45-1.64(2H,m), 1.86(1H,d,J=9.0Hz), 1.98-2.03(1H,m), 2.33(3H,s), 2.66-2.73(2H,m), 2.75-2.79(2H,m), 3.54(1H,d,J=15.6Hz), 3.62(1H,d,J=15.6Hz), 3.96-4.02(2H,m), 4.78(1H,d,J=4.2Hz), 7.00(1H,s), 7.14(1H,dd,J=2.0,8.8Hz), 7.38(1H,d,J=8.8Hz), 7.66(1H,s), 8.20(1H,d,J=7.8Hz), 8.54(1H,d,J=7.8Hz), 11.69(1H,s).

[Example 77]

N-((1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-hydroxy-5-methylcyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A1) or N-((1R*,2S*)-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxy-4-methylcyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer A2):

The title compounds were obtained by reacting the compound obtained in Referential Example 128 with the compound obtained in Referential Example 10 in a similar manner to Example 2.

Stereoisomer A1:

^{1}H-NMR (DMSO-d_6) δ: 1.24(3H,s), 1.33-1.82(4H,m), 2.34(3H,s), 2.67-3.64(8H,m), 4.02-4.10(2H,m), 4.67(1H,br.s), 7.02(1H,s), 7.13(1H,d,J=8.6Hz), 7.38(1H,d,J=8.6Hz), 7.66(1H,d,J=2.0Hz), 8.21-8.26(1H,br), 8.59(1H,d,J=8.1Hz), 11.73(1H,br.s)

MS (FAB) m/z: 502$(M+H)^+$.

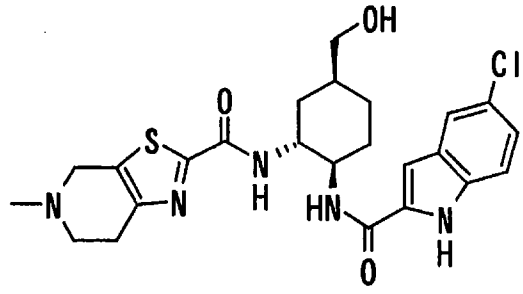
Stereoisomer A2:

^{1}H-NMR (DMSO-d_6) δ: 1.25(3H,s), 1.33-1.79(4H,m), 2.33(3H,s), 2.65-3.63(8H,m), 3.88-3.94(1H,m), 4.20-4.25(1H,m), 4.59(1H,br), 7.01(1H,s), 7.13(1H,d,J=7.8Hz), 7.38(1H,d,J=8.6Hz), 7.67(1H,s), 8.29(1H,br), 8.43(1H,d,J=9.3Hz), 11.67(1H,br)

MS (FAB) m/z: 502$(M+H)^+$.

[Example 78]

N-[(1R*,2R*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(hydroxymethyl)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



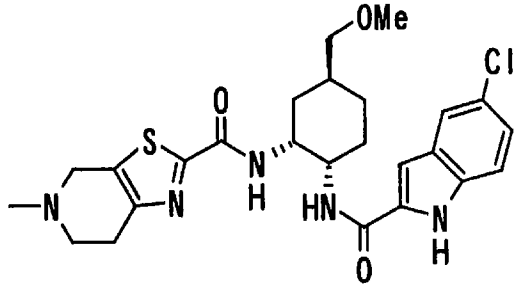
The title compound was obtained by treating the compound obtained in Referential Example 129 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in a similar manner to Example 49.

^{1}H-NMR (DMSO-d_6) δ: 1.42-1.90(5H,m), 2.07-2.26(3H,m), 2.46(3H,s), 2.67-2.95(4H,m), 3.55-3.80(4H,m), 3.80-3.95(1H,m), 4.13-4.25(1H,m), 6.84(1H,br.s), 7.17(1H,dd,J=8.8,2.0Hz), 7.23-7.35(2H,m), 7.43(1H,d,J=7.2Hz), 7.58(1H,br.s), 9.29(1H,s).

MS (ESI) m/z: 502$(M+H)^+$.

[Example 79]

N-[(1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-(methoxymethyl)cyclohexyl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:

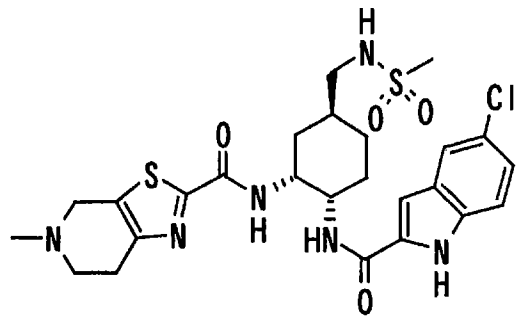


The title compound was obtained by treating the compound obtained in Referential Example 135 with an ethanol solution of hydrochloric acid and then condensing it with the compound obtained in Referential Example 10 in a similar manner to Example 49.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.38(1H,m), 1.50-1.67(2H,m), 1.88-2.03(2H,m), 2.03-2.14(1H,m), 2.21-2.32(1H,m), 2.53(3H,s), 2.75-2.95(2H,m), 3.20-3.35(2H,m), 3.37(3H,s), 3.73(1H, d,J=16.0 Hz), 3.76(1H,d,J=16.0Hz), 4.04-4.13(1H,m), 4.53-4.62(1H,m), 6.85(1H,d,J=2.0Hz), 7.19(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.54(1H,d,J=7.2Hz), 7.63(1H,d,J=2.0Hz), 8.07(1H,d,J=5.6Hz), 9.49(1H,br.s).

[Example 80]

N-((1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-{[(methylsulfonyl)amino]methyl}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



1) The compound (437 mg) obtained in Referential Example 137 was dissolved in ethanol (5 ml), and a 4N dioxane solution (5 ml) of hydrochloric acid was added at room temperature to stir the mixture for 13 hours. The solvent was distilled off, and the residue was dissolved in N,N-dimethylformamide (10 ml) , to which triethylamine (0.7 ml), the compound (300 mg) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (162 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (230 mg) were added. The mixture was stirred for 13 hours, and water was added to the reaction mixture to conduct extraction with chloroform. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 97:3) to obtain N- ((1R*,2S*,5S*)-5-(azidomethyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide

(330 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.15-2.08(7H,m), 2.33(3H,s), 2.34-2.95(6H,m), 3.64(2H,s), 4.05-4.17(1H,m), 4.36-4.47(1H,m), 7.02(1H,s), 7.15(1H,dd,J=8.8,2.0Hz), 7.40(1H,d,J=8.8Hz), 7.67(1H,d,J=2.0Hz), 8.02(1H,d,J=7.6Hz), 8.44(1H,d,J=7.6Hz), 11.8(1H,s).

2) The compound (300 mg) obtained by the above reaction was dissolved in ethanol (8 ml), and a catalytic amount of 10% palladium on carbon was added to stir the mixture at room temperature for 168 hours in a hydrogen atmosphere. Insoluble matter was filtered, and the solvent was distilled off. The thus-obtained crude N-((1R*,2S*,5S*)-5-(aminomethyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (150 mg) was dissolved in chloroform (6 ml), and triethylamine (0.2 ml) and methanesulfonyl chloride (0.035 ml) were added to stir the mixture for 13 hours. The solvent was distilled off under reduced pressure, and water was added to the residue to conduct extraction with chloroform. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (methylene chloride: methanol = 24:1) to obtain the title compound

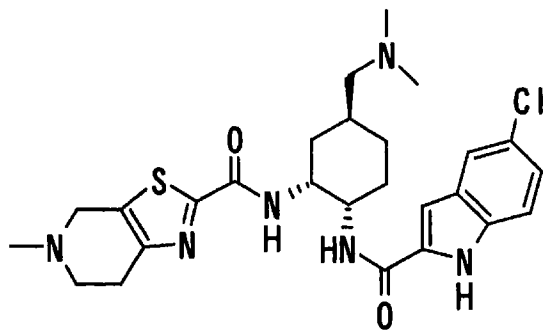
(56 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.34(2H,m), 1.50-1.75(4H,m), 1.90-2.30(4H,m), 2.53(3H,s), 2.78-2.90(2H,m), 2.90-3.05(6H,m), 3.20-3.30(1H,m), 3.68-3.81(2H,m), 3.98-4.08(1H,m), 4.54-4.62(1H,m), 6.10-6.19(1H,m), 6.86(1H,s), 7.19(1H,dd,J=8.8,2.0Hz), 7.35(1H,d,J=8.8Hz), 7.52(1H,d,J=7.6Hz), 7.62(1H,d,J=2.0Hz), 8.21(1H,d,J=5.6Hz), 9.89(1H,s).

MS (ESI) m/z: 579$(M+H)^+$.

[Example 81]

N-{(1R*,2S*,5S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(dimethylamino)methyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide trifluoroacetate:



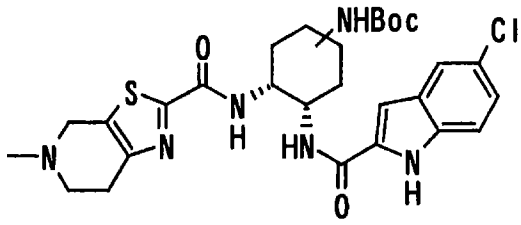
The title compound was obtained from the amine obtained in the step 2) of Example 80 in a similar manner to Example 24.

^{1}H-NMR (DMSO-d_6) δ: 1.15-2.22(7H,m), 2.40-2.65(2H,m), 2.68-2.85(6H,m), 2.92-3.08(5H,m), 3.10-3.18(2H,m), 4.08-4.20(1H,m), 4.35-4.51(2H,m), 7.04(1H,s), 7.14-7.20(1H,m),

7.41(1H,d,J=8.8Hz), 7.67(1H,s), 8.25-8.42(2H,m),
9.11(1H,br.s), 9.89(1H,s).
MS (ESI) m/z: 529$(M+H)^+$.

[Example 82]

tert-Butyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexylcarbamate (Isomer B) and tert-butyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}cyclohexylcarbamate (Isomer B):



The compound (Stereoisomer B) (1.79 g) obtained in Referential Example 140 was dissolved in tetrahydrofuran (36 ml), and 10% palladium on carbon (0.40 g) was added to stir the mixture at room temperature for 20 hours in a hydrogen atmosphere. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (36 ml), to which p-nitrophenyl 5-chloroindole-2-carboxylate (2.02 g) was added to stir the mixture for 16 hours. The reaction mixture was concentrated under reduced pressure, and ethyl acetate and

water were added to the residue to collect insoluble matter by filtration. The product was washed with ethyl acetate to obtain crude tert-butyl ($3R^*,4S^*$)-3-amino-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexylcarbamate (or ($3R^*,4S^*$)-4-amino-3-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexylcarbamate) (Isomer B1) (1.49 g). The organic layer of the filtrate was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride: methanol = 30:1 → 10:1) to obtain tert-butyl ($3R^*,4S^*$)-4-amino-3-{[(5-chloroindol-2-yl)carbonyl]amino}-cyclohexylcarbamate (or tert-butyl ($3R^*,4S^*$)-3-amino-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexylcarbamate) (Isomer B2) (0.37 g).

One of the title compounds was obtained from the Isomer B1 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{1}H-NMR (DMSO-d_6) δ: 1.25-1.50(1H,m), 1.37(9H,s), 1.50-1.65(1H,m), 1.75-2.20(4H,m), 2.37(3H,s), 2.70-3.00(4H,m), 3.60-3.80(3H,m), 4.13(1H,br.s), 4.43(1H,br.s), 6.92(1H,d,J=7.1Hz), 7.05(1H,s), 7.17(1H,dd,J=8.8,2.2Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.15(1H,d,J=7.8Hz), 8.37(1H,d,J=7.1Hz), 11.78(1H,s).

MS (FAB) m/z: 587$(M+H)^+$.

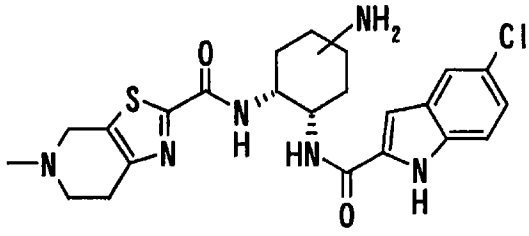
The other title compound was obtained from the Isomer B2 in the same manner.

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.30(1H,m), 1.35(9H,s), 1.45-1.60(1H,m), 1.65-1.75(1H,m), 1.85-1.95(1H,m), 2.05-2.20(2H,m), 2.34(3H,s), 2.65-2.85(4H,m), 3.55-3.70(3H,m), 4.05-4.14(1H,m), 4.40(1H,br.s), 6.80(1H,d,J=7.3Hz), 7.15-7.25(2H,m), 7.43(1H,d,J=8.8Hz), 7.73(1H,d,J=2.0Hz), 8.05(1H,d,J=6.6Hz), 8.51(1H,d,J=8.8Hz), 11.82(1H,s).

MS (FAB) m/z: 587$(M+H)^+$.

[Example 83]

N-((1R*,2S*)-5-Amino-2-{[(5-chloroindol-2-yl)carbonyl]-amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide (or N-((1R*,2S*)-4-amino-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide) hydrochloride (Stereoisomer B):



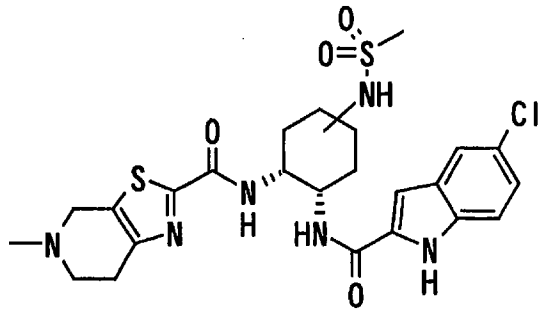
The compound (Stereoisomer B) (1.11 g) synthesized from Isomer B1 in Example 82 was suspended in methylene chloride (20 ml), and an ethanol solution (20 ml) of hydrochloric acid was added to stir the mixture at room temperature for 2 hours. The solvent was distilled off under reduced pressure, and the residue was purified by gel filtration (Sephadex LH-20, methanol) to obtain the title compound (1.05 g).

^{1}H-NMR (DMSO-d_6) δ: 1.55-1.65(1H,m), 1.75-1.90(2H,m), 1.95-2.20(2H,m), 2.20-2.40(1H,m), 2.90(3H,s), 3.10-3.20(1H,m), 3.20-3.50(3H,m), 3.65-3.75(1H,m), 4.10-4.20(1H,m), 4.35-4.50(1H,m), 4.55-4.65(1H,m), 4.65-4.75(1H,m), 7.07(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.69(1H,s), 8.05-8.30(3H,br), 8.40-8.50(2H,m), 11.70-11.90(2H,m).

MS (FAB) m/z: 487$(M+H)^+$.

[Example 84]

N-{(1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(methylsulfonyl)amino]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-{(1R*,2S*)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-[(methylsulfonyl)amino]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer B):



The compound (0.20 g) obtained in Example 83 was suspended in methylene chloride (7 ml), and triethylamine (0.16 ml) and methanesulfonyl chloride (28 µl) were added to stir the mixture at room temperature for 20 hours. After the reaction mixture was diluted with methylene chloride, it was washed with an aqueous solution of sodium

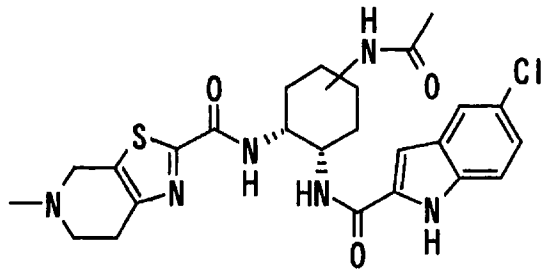
hydroxide and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1 → 15:1) to obtain the title compound (67.9 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.40-1.55(1H,m), 1.65-1.85(2H,m), 1.90-2.05(2H,m), 2.15-2.25(1H,m), 2.41(3H,s), 2.75-2.95(4H,m), 2.92(3H,s), 3.55-3.80(3H,m), 4.10-4.20(1H,m), 4.45-4.55(1H,m), 7.08(1H,s), 7.15-7.20(2H,m), 7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.27(1H,d,J=7.3Hz), 8.33(1H,d,J=8.1Hz), 11.77(1H,s).

MS (FAB) m/z: 565$(M+H)^+$.

[Example 85]

N-((1R*,2S*)-5-(Acetylamino)-2-{[(5-chloroindol-2-yl)-carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide or N-((1R*,2S*)-4-(acetylamino)-2-{[(5-chloroindol-2-yl)-carbonyl]amino}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide (Stereoisomer B):



The compound (Stereoisomer B) (0.20 g) obtained in Example 83 was suspended in methylene chloride (7 ml), and

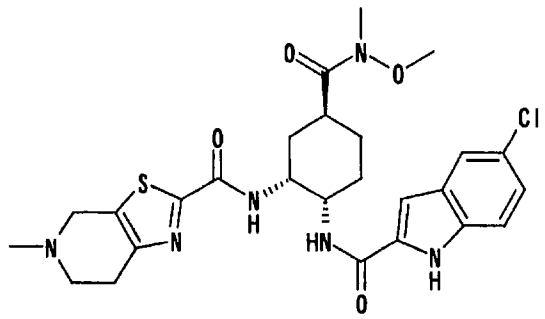
triethylamine (0.16 ml) and acetic anhydride (34 µl) were added to stir the mixture at room temperature for 20 hours. Methylene chloride and an aqueous solution of sodium hydroxide were added to the reaction mixture to separate insoluble matter by filtration. The organic layer of the filtrate was separated and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 15:1 → 10:1) to obtain the title compound (0.12 g).

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.50(1H,m), 1.55-1.70(1H,m), 1.80(3H,s), 1.80-2.05(3H,m), 2.05-2.20(1H,m), 2.47(3H,s), 2.80-3.00(4H,m), 3.75-4.00(3H,m), 4.15-4.30(1H,m), 4.45-4.55(1H,m), 7.07(1H,s), 7.17(1H,dd,J=8.8,1.0Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,s), 7.89(1H,d,J=7.3Hz), 8.24(1H,d,J=8.1Hz), 8.31(1H,d,J=7.3Hz), 11.77(1H,s).

MS (FAB) m/z: 528$(M+H)^+$.

[Example 86]

N-((1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-{[methoxy(methyl)amino]carbonyl}cyclohexyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (250 mg) obtained in Example 58 was dissolved in N,N-dimethylformamide (5 ml), and N,O-dimethylhydroxylamine hydrochloride (142 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (111 mg), 1-hydroxybenzotriazole monohydrate (89 mg) and N-methylmorpholine (213 ml) were added to stir the mixture at room temperature for 19 hours. After the reaction mixture was concentrated, an aqueous solution of sodium hydrogencarbonate was added to the residue to conduct extraction with ethyl acetate. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (methylene chloride:methanol = 47:3 → 23:2) to obtain a colorless amorphous solid (179 mg). This prodcut was dissolved in methanol-tetrahydrofuran, and 1N ethanol solution (960 ml) of hydrochloric acid was added to obtain the title compound.

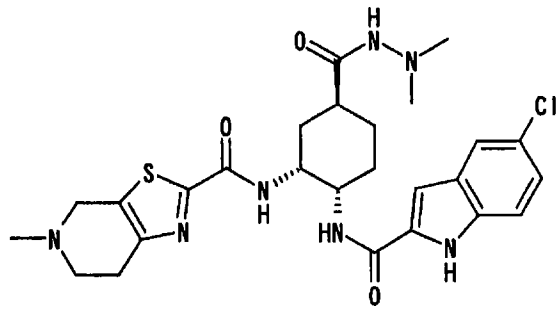
^{1}H-NMR (DMSO-d_6) δ: 1.57-1.91(4H,m), 1.96-2.00(1H,m), 2.10-2.21(1H,m), 2.92(3H,s), 2.93-3.03(2H,m), 3.08(3H,s), 3.10-

3.28(2H,m), 4.16-4.19(1H,m), 4.50-4.52(1H,m), 4.69(1H,br.s), 7.06(1H,s), 7.17(1H,dd,J=8.8,1.5Hz), 7.42(1H,d,J=8.8Hz), 7.70(1H,s), 8.33(1H,br.s), 8.41(1H,d,J=7.8Hz), 11.81(1H,br.s).

MS (ESI) m/z: 559$(M+H)^+$.

[Example 87]

N-{(1R,2S,5S)-2-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-[(2,2-dimethylhydrazino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 58 and N,N-dimethylhydrazine in a similar manner to Example 57.

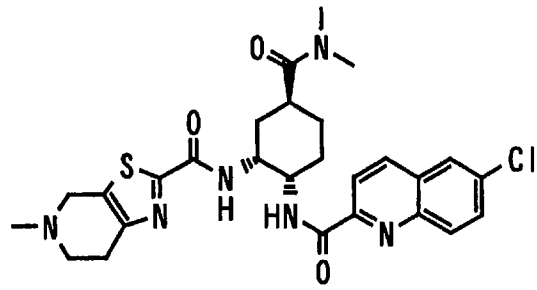
^{1}H-NMR (DMSO-d_6) δ: 1.49-1.54(1H,m), 1.76-1.81(2H,m), 1.89-1.93(2H,m), 2.07-2.17(1H,m), 2.33-3.60(14H,m), 4.15-4.19(1H,m), 4.40-4.47(2H,m), 4.70-4.72(1H,m), 7.04(1H,s), 7.17(1H,dd,J=8.5,2.0Hz), 7.42(1H,d,J=8.5Hz), 7.70(1H,s), 8.17-8.22(1H,m), 8.41-8.43(1H,m), 11.80(1H,br.s).

MS (ESI) m/z: 558$(M+H)^+$.

[Example 88]

6-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-

methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)-2-quinolinecarboxamide hydrochloride:



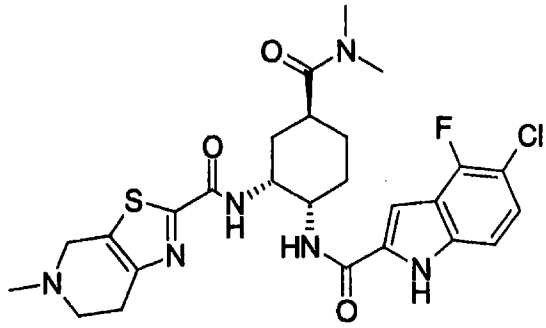
The title compound was obtained by treating the compound obtained in Referential Example 145 with an ethanol solution of hydrochloric acid in a similar manner to Example 49 and then condensing it with the compound obtained in Referential Example 10.

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.60(1H,m), 1.75-1.90(3H,m), 1.90-2.00(1H,m), 2.00-2.20(1H,m), 2.80(3H,s), 2.90(3H,s), 2.99(3H,s), 3.10-3.30(5H,m), 3.56(1H,br), 4.10-4.20(1H,m), 4.40-4.70(2H,m), 7.88(2H,s), 8.15(1H,d,J=8.6Hz), 8.22(1H,s), 8.52(1H,d,J=8.6Hz), 8.72(1H,d,J=8.3Hz), 8.89(1H,d,J=8.3Hz).

MS (FAB) m/z: 555$(M+H)^+$.

[Example 89]

N-{(1R,2S,5S)-2-{[(5-Chloro-4-fluoroindol-2-yl)carbonyl]-amino}-5-[(dimethylamino)carbonyl]cyclohexyl}-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



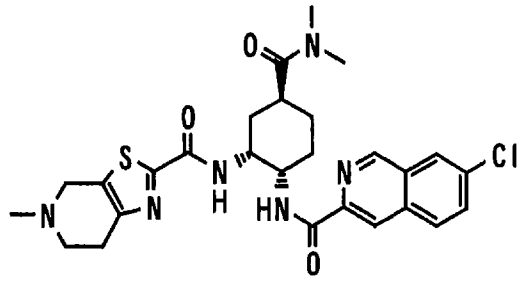
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 274 in a similar manner to Referential Example 91 and treating the resultant compound with a 4N dioxane solution of hydrochloric acid and then with the compound obtained in Referential Example 10.

^{1}H-NMR (DMSO-d_6) δ:1.24-1.98(6H,m), 2.33-3.33(6H,m), 2.81(3H,s), 2.90(3H,s), 2.99(3H,s), 4.12(1H,br.s), 4.30-4.70(1H,m), 4.60(1H,br.s), 7.21(1H,s), 7.27(2H,br.s), 8.37(1H,d,J=8.1Hz), 8.43(1H,d,J=7.6Hz), 12.11(1H,s).

MS (FAB) m/z: 561$(M+H)^+$.

[Example 90]

7-Chloro-N-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino}cyclohexyl)isoquinoline-3-carboxamide hydrochloride:



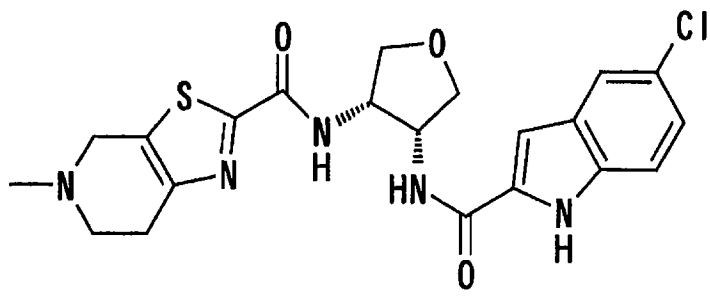
The title compound was obtained by treating the compound obtained in Referential Example 146 with an ethanol solution of hydrochloric acid in a similar manner to Example 49 and then condensing it with the compound obtained in Referential Example 10.

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.65(1H,m), 1.70-1.85(3H,m), 1.95-2.10(1H,m), 2.10-2.20(1H,m), 2.80(3H,s), 2.92(3H,s), 2.96(3H,s), 2.95-3.10(1H,m), 3.10-3.40(3H,m), 3.70-3.80(1H,m), 4.20-4.30(1H,m), 4.40-4.60(2H,m), 4.65-4.80(1H,m), 7.83-7.93(1H,m), 8.26(1H,d,J=8.8Hz), 8.38(1H,s), 8.60(1H,s), 8.85-9.00(2H,m), 9.30-9.40(1H,m).

MS (FAB) *m/z*: 555(M+H)$^+$.

[Example 91]

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



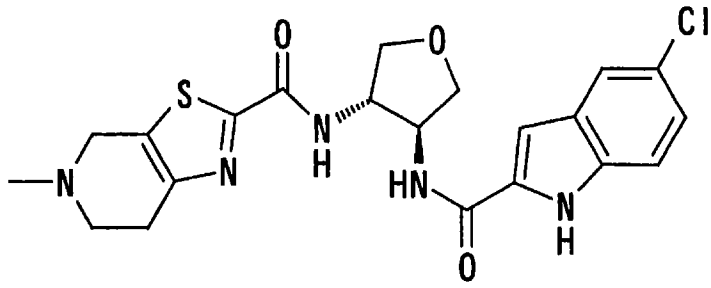
The compound (0.1 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (78 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2 g) were successively added to a solution of the compound (0.12 g) obtained in Referential Example 172 in N,N-dimethylformamide (20 ml), and the mixture was stirred at room temperature for 1 day. After the reaction mixture was concentrated, and the resultant residue was diluted with chloroform-methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, the resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform:methanol = 95:5) to obtain a free base of the title compound. This product was treated with an ethanol solution of hydrochloric acid to obtain the title compound (0.1 g).

^{1}H-NMR ($CDCl_3$) δ: 2.50(3H,s), 2.70-2.90(4H,m), 3.67(1H,s), 3.70(1H,s), 3.86(1H,dd,J=9.2,6.3Hz), 3.97(1H,dd,J=9.7,4.1Hz), 4.15(1H,dd,J=9.7,5.8Hz), 4.24(1H,dd,J=9.2,7.0Hz), 4.75-4.89(1H,m), 4.92-5.03(1H,m), 6.88(1H,s), 7.20(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.35-7.43(1H,m), 7.58(1H,d,J=2.0Hz), 7.64(1H,d,J=7.1Hz), 9.38(1H,s).

MS (FAB) m/z: 460($M+H^+$).

[Example 92]

N-((3S,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-tetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide:



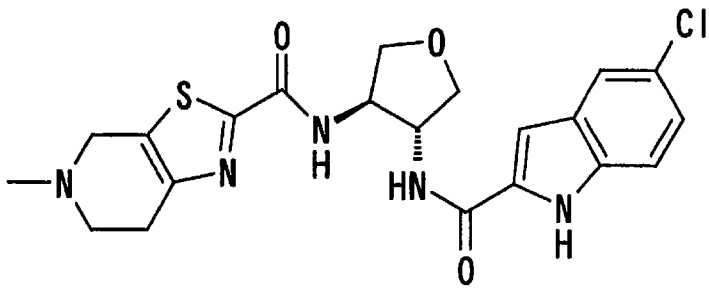
The title compound was obtained from the compound obtained in Referential Example 183 in accordance with the processes of Referential Example 172 and Example 91.

^{1}H-NMR ($CDCl_3$) δ: 2.51(3H,s), 2.83(2H,t,J=5.3Hz), 2.93(2H,t,J=5.3Hz), 3.72(2H,s), 3.78-3.89(2H,m), 4.31(1H,dd,J=9.2,7.3Hz), 4.41-4.56(2H,m), 4.63-4.75(1H,m), 6.88(1H,s), 7.22(1H,dd,J=8.8,2.0Hz), 7.32(1H,d,J=8.8Hz), 7.35-7.46(1H,m), 7.55(1H,d,J=7.1Hz), 7.60(1H,d,J=2.0Hz), 9.38(1H,s).

MS (FAB) m/z: 460($M+H^+$).

[Example 93]

N-((3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-tetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:

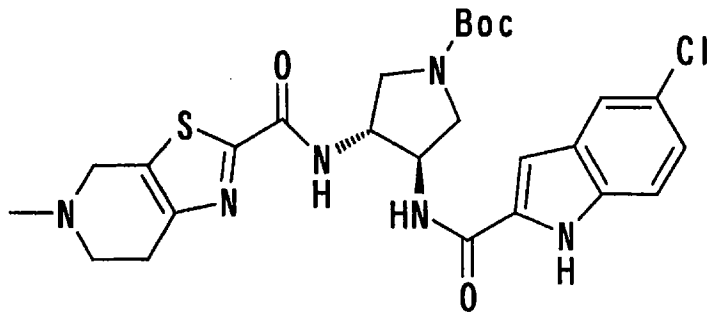


The title compound was obtained from the compound obtained in Referential Example 187 in accordance with the processes of Referential Example 172 and Example 91.

^{1}H-NMR and MS (FAB): The same as those of the enantiomer in Example 92.

[Example 94]

tert-Butyl (3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate:



The title compound was obtained from the compound obtained in Referential Example 193 and the compound obtained in Referential Example 10 in accordance with the process of Example 91.

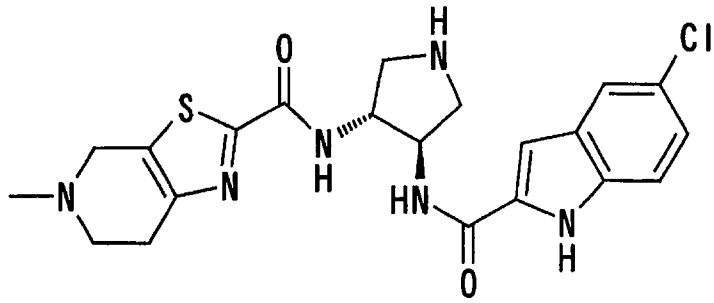
Melting point: 190-192°C.

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.46(3H,s), 2.74-2.81(4H,m), 3.24-3.37(2H,m), 3.54-3.70(2H,m), 3.96-4.00(1H,m), 4.15-4.23(1H,m), 4.50-4.65(1H,m), 4.77-4.82(1H,m), 6.79,6.87(total 1H,each s), 7.12-7.95(5H,m), 9.91,9.97(total 1H,each s).

MS (FAB) m/z: 559($M+H^+$).

[Example 95]

N-((3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-pyrrolidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (170 mg) obtained in Example 94 was dissolved in methylene chloride (3 ml), and trifluoroacetic acid (2 ml) was added at room temperature to stir the mixture for 1 hour. After concentrating the reaction mixture, chloroform and a saturated aqueous solution of sodium hydrogencarbonate were added. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (chloroform:methanol:water = 7:3:1 under layer). A methanol solution of hydrochloric acid was added to the resultant intended product to obtain the title compound (90 mg) as a hydrochloride (NMR was measured in the form of a free base).

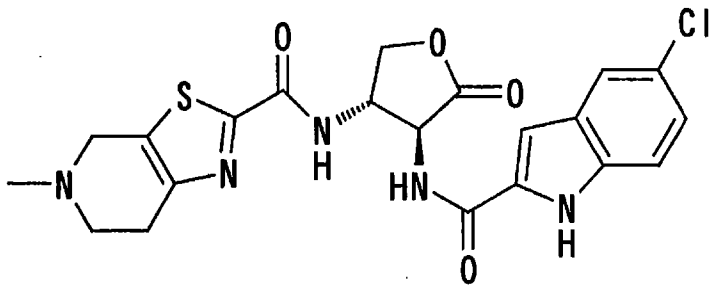
Melting point: 248-250°C (decomposed).

^{1}H-NMR ($CDCl_3$) δ: 2.44(3H,s), 2.70-2.80(4H,m), 2.97-3.05(2H,m), 3.46-3.68(4H,m), 4.49-4.52(1H,m), 4.60-

4.65(1H,m), 6.86(1H,s), 7.05-7.08(1H,m),
7.20(1H,d,J=8.5Hz), 7.44(1H,s), 7.89(2H,br), 10.51(1H,br).
MS (FAB) m/z: 459($M+H^+$).

[Example 96]

N-((3S,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-5-oxotetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:

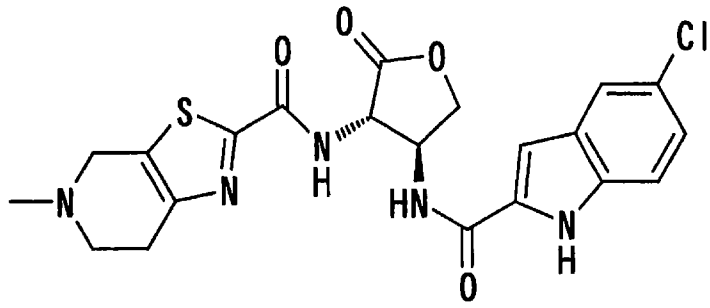


The title compound was obtained by removing the tert-butoxycarbonyl group of the compound obtained in Referential Example 196 in a similar manner to Referential Example 69 and reacting the resultant product with the compound obtained in Referential Example 10 in a similar manner to Example 91.

^{1}H-NMR (DMSO-d_6) δ: 2.90(3H,s), 3.02-3.17(2H,m), 3.23-3.34(4H,m), 4.20(1H,t,J=8.6Hz), 4.61(1H,t,J=8.6Hz), 4.92-5.01(1H,m), 5.14-5.26(1H,m), 7.09(1H,s),
7.19(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz),
7.73(1H,d,J=2.0Hz), 9.27(1H,d,J=6.8Hz), 9.35(1H,d,J=6.8Hz),
11.22-11.33(1H,m), 11.89(1H,s).
MS (FAB) m/z: 474($M+H^+$).

[Example 97]

N-((3S,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-2-oxotetrahydrofuran-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained by removing the tert-butoxycarbonyl group of the compound obtained in Referential Example 197 in a similar manner to Referential Example 69 and reacting the resultant product with 5-chloroindole-2-carboxylic acid in a similar manner to Example 91.

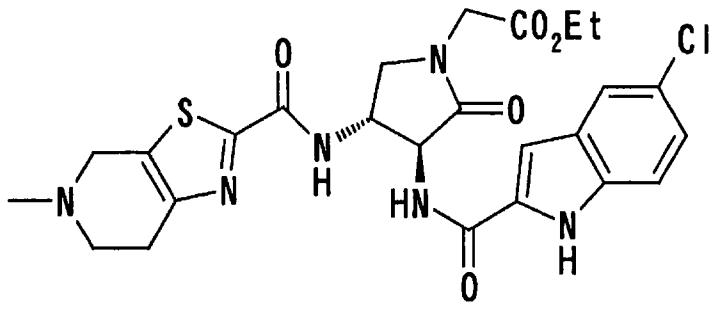
^{1}H-NMR (DMSO-d_6) δ: 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.91-3.00(2H,m), 3.73(2H,s), 4.23(1H,t,J=8.6Hz), 4.40-4.53(1H,m), 4.96(1H,dd,J=10.8,5.2Hz), 5.16(1H,dd,J=9.2,7.3Hz), 7.01(1H,s), 7.25(1H,dd,J=8.8,2.0Hz), 7.34(1H,d,J=8.8Hz), 7.52(1H,d,J=2.0Hz), 8.01(1H,d,J=5.4Hz), 8.51-8.63(1H,m),9.22(1H,s).

MS (FAB) m/z: 474($M+H^+$).

[Example 98]

Ethyl (3S,4R)-2-(3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}-2-oxopyrrolidin-1-yl)acetate

hydrochloride:



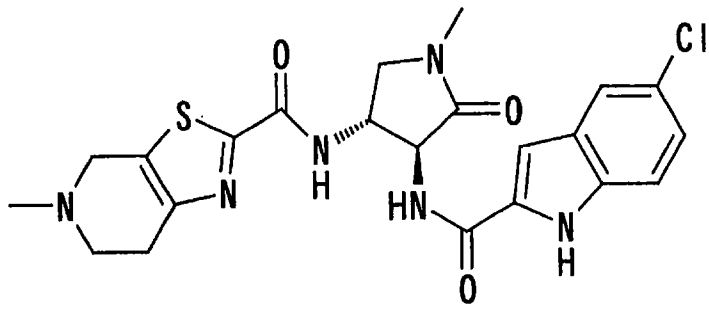
The title compound was obtained from the compound obtained in Referential Example 199 and the compound obtained in Referential Example 10 in a similar manner to Example 91. NMR was measured in the form of a free base.

^{1}H-NMR (DMSO-d_6) δ: 1.19(3H,t,J=7.1Hz), 2.35(3H,s), 2.71-2.84(2H,m), 2.80-2.90(2H,m), 3.40(1H,d,J=10.3Hz), 3.61(2H,d,J=10.8Hz), 3.84(1H,dd,J=10.3,5.6Hz), 4.01-4.23(4H,m), 4.80-4.94(1H,m), 5.04(1H,t,J=8.6Hz), 7.01(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.40(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 8.73(1H,d,J=8.6Hz), 8.90(1H,d,J=8.8Hz), 11.86(1H,s).

MS (FAB) m/z: 559($M+H^+$).

[Example 99]

N-((3R,4S)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-methyl-5-oxopyrrolidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide:



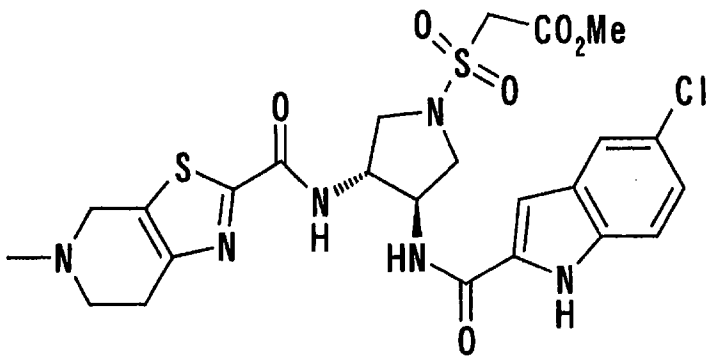
The title compound was obtained from the compound obtained in Referential Example 201 and the compound obtained in Referential Example 10 in a similar manner to Example 91.

^{1}H-NMR ($CDCl_3$) δ: 2.49(3H,s), 2.77-2.82(2H,m), 2.86-2.91(5H,m), 3.69(2H,d,J=1.2Hz), 4.39-4.54(3H,m), 4.93-4.98(1H,m), 6.98(1H,d,J=1.2Hz), 7.05-7.34(3H,m), 7.63(1H,d,J=2.0Hz), 8.11(1H,d,J=7.8Hz), 9.00(1H,s)

MS (FAB) m/z: 487($M+H^+$).

[Example 100]

Methyl 2-[((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)-sulfonyl]acetate:



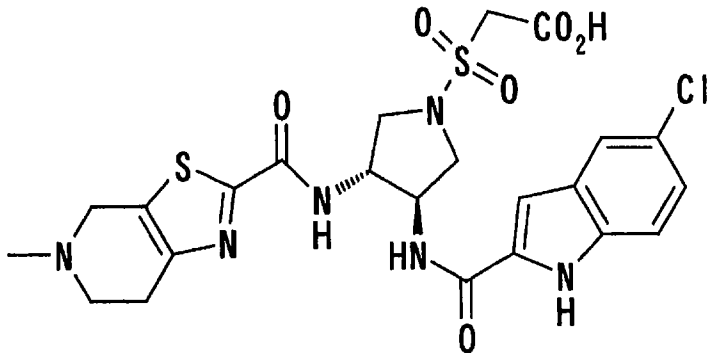
The compound (230 mg) obtained in Example 95 and triethylamine (0.10 ml) were dissolved in methylene chloride (6.9 ml), and the mixture was cooled with ice. Methoxycarbonylmethanesulfonyl chloride (Synthesis, p. 321, 1975) (105 mg) was added, and the resultant mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with chloroform, washed with water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (chloroform:methanol = 20:1) and powdered with methanol-water to obtain the title compound (150 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.48(3H,s), 2.76-2.86(4H,m), 3.49-3.73(4H,m), 3.87(3H,s), 3.94-3.98(1H,m), 4.08-4.11(1H,m), 4.13(2H,s), 4.69-4.72(1H,m), 4.88-4.91(1H,m), 6.89(1H,s), 7.12-7.15(1H,m), 7.27-7.28(1H,m), 7.50(1H,s), 7.81-7.86(2H,m), 9.92(1H,s).

MS (FAB) m/z: 595($M+H^+$).

[Example 101]

2-[((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)sulfonyl]acetic acid:

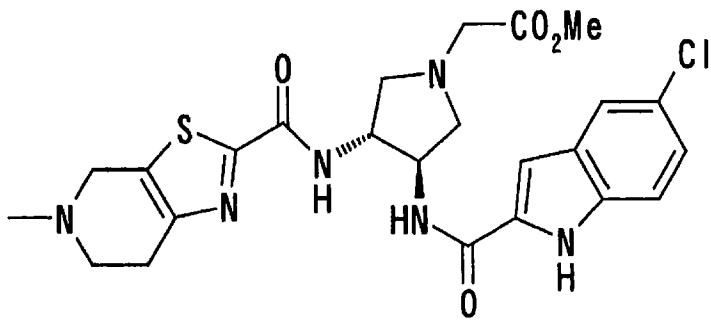


The compound (100 mg) obtained in Example 100 was dissolved in tetrahydrofuran (4 ml)-water (1 ml), and the mixture was cooled with ice. Lithium hydroxide monohydrate (7.8 mg) was added, and the resultant mixture was heated to room temperature and stirred for 4 hours. After the reaction mixture was neutralized with 1N hydrochloric acid, it was concentrated. Deposits were collected by filtration, washed with water and 50% ethanol and dried overnight at 50°C under reduced pressure to obtain the title compound (87 mg).

^{1}H-NMR (DMSO-d_6) δ: 2.50(3H,s), 2.92(4H,s), 3.34-3.43(4H,m), 3.76-3.85(2H,m), 4.27(each 1H,AB type d,J=14.5Hz), 4.65-4.71(1H,m), 4.78-4.84(1H,m), 7.14(1H,s), 7.18(1H,d,J=8.8Hz), 7.40(1H,d,J=8.8Hz), 7.72(1H,s), 8.87(1H,d,J=7.8Hz), 9.12(1H,d,J=8.2Hz), 11.83(1H,s).

[Example 102]

Methyl 2-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)acetate:



The compound (230 mg) obtained in Example 95 and potassium carbonate (90 mg) were dissolved in N,N-dimethylformamide (4.6 ml), and the mixture was cooled with ice. Methyl bromoacetate (0.062 ml) was added, and the resultant mixture was stirred for 45 minutes. The reaction mixture was diluted with ethyl acetate, washed with water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (chloroform:methanol = 10:1) and solidifier with methanol-water to obtain the title compound (190 mg).

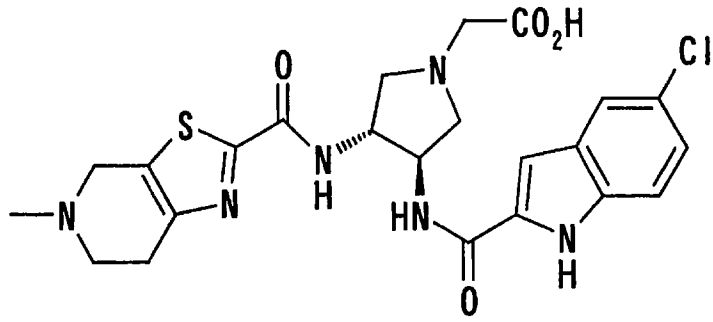
^{1}H-NMR ($CDCl_3$) δ: 2.35(2H,s), 2.48(3H,s), 2.73-2.95(4H,m), 3.34-3.42(2H,m), 3.46(2H,q,J=6.5Hz), 3.67(2H,q,J=6.5Hz), 3.75(3H,s), 4.57-4.71(2H,m), 6.91(1H,s), 7.10-7.13(1H,m), 7.31(1H,d,J=9.0Hz), 7.53(1H,s), 7.77(1H,d,J=8.0Hz), 7.87(1H,d,J=6.8Hz), 10.22(1H,s).

MS (FAB) m/z: 531($M+H^+$).

[Example 103]

2-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-

methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)acetic acid:

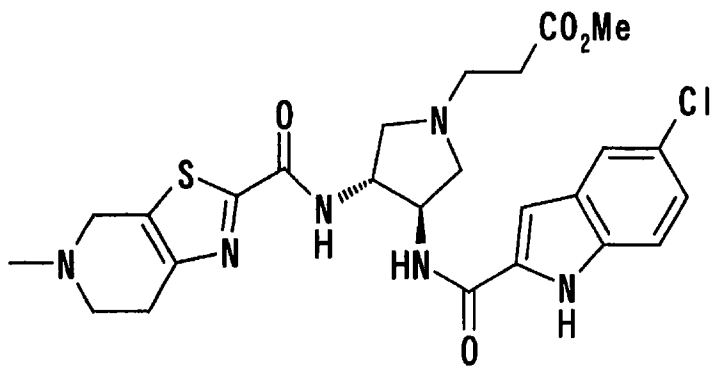


The title compound was obtained from the compound obtained in Example 102 in a similar manner to Example 101.

^{1}H-NMR (DMSO-d_6) δ: 2.42(3H,s), 2.69-2.87(6H,m), 3.13(1H,t,J=9.0Hz), 3.22(1H,t,J=9.0Hz), 3.33(each 1H,AB type d,J=6.8Hz), 3.72(2H,s), 4.53-4.60(1H,m), 4.65-4.72(1H,m), 7.16-7.20(2H,m), 7.42(1H,d,J=8.8Hz), 7.70(1H,s), 8.85(1H,d,J=7.5Hz), 9.00(1H,d,J=8.3Hz), 11.79(1H,s).

[Example 104]

Methyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionate:



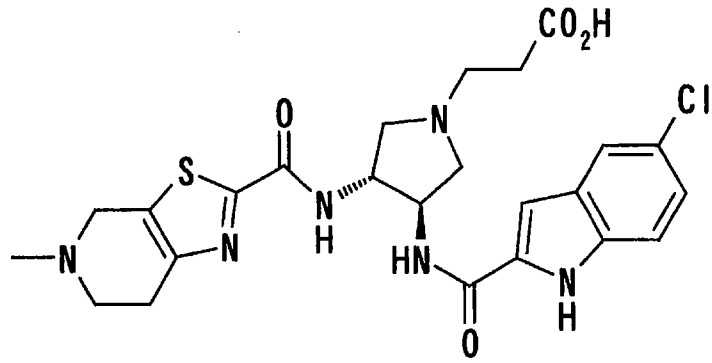
The title compound was obtained from the compound obtained in Example 95 and methyl 3-bromopropionate in a similar manner to Example 102.

^{1}H-NMR ($CDCl_3$) δ: 1.96-2.20(2H,m), 2.49(3H,s), 2.61-2.96(8H,m), 3.17-3.21(2H,m), 3.62-3.72(2H,m), 3.69(3H,s), 4.46-4.49(1H,m), 4.56-4.61(1H,m), 6.87(1H,s), 7.05-7.14(1H,m), 7.32(1H,d,J=9.2Hz), 7.53(1H,s), 7.65-7.71(2H,m), 10.02(1H,s).

MS (FAB) m/z: 545($M+H^+$).

[Example 105]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionic acid:

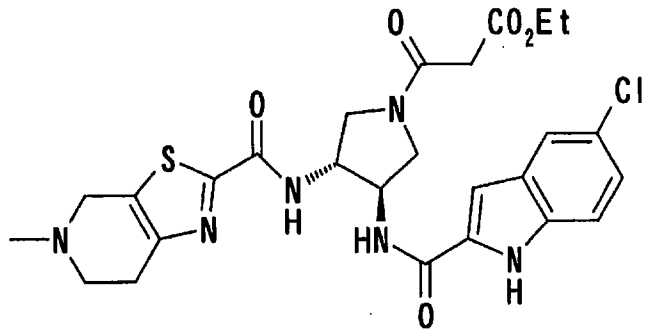


The title compound was obtained from the compound obtained in Example 104 in a similar manner to Example 101.

^{1}H-NMR (DMSO-d_6) δ: 2.38(3H,s), 2.39-2.84(10H,m), 2.93(1H,t,J=8.8Hz), 3.05(1H,t,J=8.8Hz), 3.65(2H,s), 4.51-4.56(1H,m), 4.63-4.68(1H,m), 7.16-7.19(2H,m), 7.41(1H,d,J=8.8Hz), 7.69(1H,s), 8.81(1H,d,J=7.8Hz), 8.97(1H,d,J=8.3Hz), 11.75(1H,s).

[Example 106]

Ethyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)-3-oxopropionate:

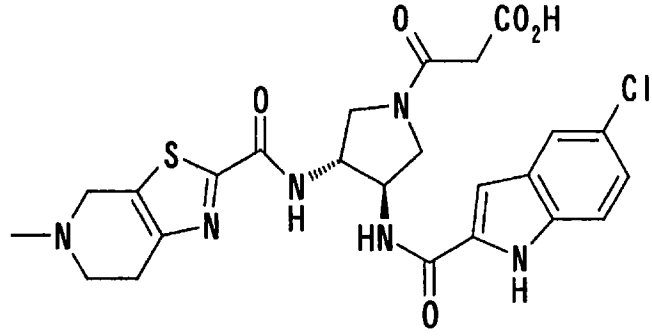


The title compound was obtained from the compound obtained in Example 95 and ethylmalonyl chloride in a similar manner to Example 100.

^{1}H-NMR (DMSO-d_6) δ: 1.20(3H,t,J=7.0Hz), 2.37(3H,s), 2.73-2.75(2H,m), 2.82-2.84(2H,m), 3.35-3.38(2H,m), 3.64(2H,s), 3.68-3.83(2H,m), 3.91-4.00(2H,m), 4.10(2H,q,J=7.0Hz), 4.61-4.84(2H,m), 7.13(1H,s), 7.18(1H,dd,J=8.5,2.0Hz), 7.41(1H,d,J=8.5Hz), 7.72(1H,s), 8.73(1H,t,J=9.0Hz), 9.10(1H,d,J=9.0Hz), 11.79(1H,s).

[Example 107]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)-3-oxopropionic acid:

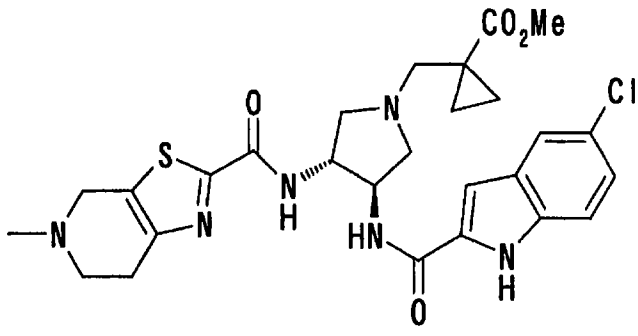


The title compound was obtained from the compound obtained in Example 106 in a similar manner to Example 101.

^{1}H-NMR (DMSO-d_6) δ: 2.39(3H,s), 2.77(2H,s), 2.85(2H,s), 3.29-3.55(4H,m), 3.68(2H,s), 3.82-4.01(2H,m), 4.62-4.68(1H,m), 4.77-4.86(1H,m), 7.14(1H,s), 7.18(1H,d,J=8.8Hz), 7.41(1H,d,J=8.8Hz), 7.72(1H,s), 8.75(1H,t,J=8.8Hz), 9.12(1H,d,J=7.8Hz), 11.81(1H,s).

[Example 108]

Methyl 1-[((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)methyl]-cyclopropanecarboxylate:



The title compound was obtained from the compound

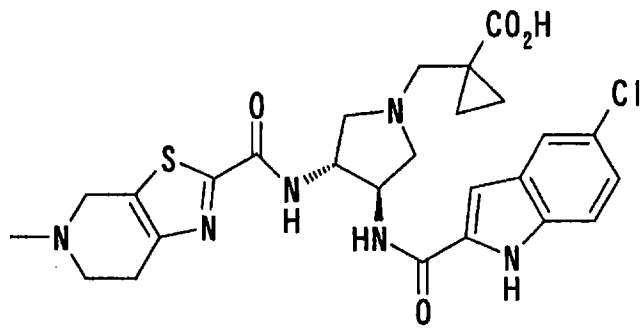
obtained in Example 95 and methyl 1-(bromomethyl)-cyclopropanecarboxylate in a similar manner to Example 102.

^{1}H-NMR ($CDCl_3$) δ: 0.78-0.79(2H,m), 1.24-1.26(2H,m), 2.49(3H,s), 2.62-2.88(6H,m), 3.20-3.28(2H,m), 3.66(3H,s), 3.61-3.75(4H,m), 4.45-4.62(2H,m), 6.86(1H,s), 7.12-7.15(1H,m), 7.24-7.28(1H,m), 7.52(1H,d,J=8.5Hz), 7.54(1H,s), 7.69(1H,d,J=8.0Hz), 10.00(1H,s).

MS (ESI) m/z: 571($M+H^+$).

[Example 109]

1-[((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)methyl]-cyclopropanecarboxylic acid:

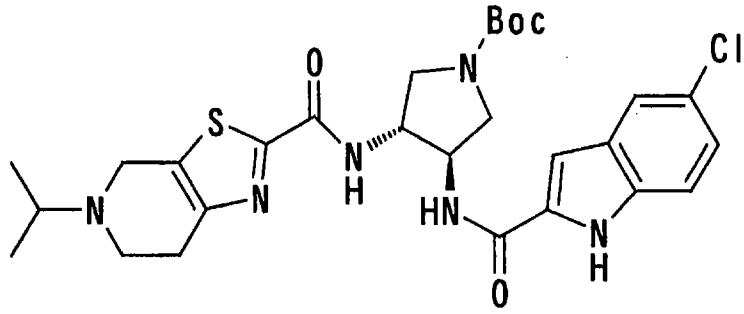


The title compound was obtained from the compound obtained in Example 108 in a similar manner to Example 101.

^{1}H-NMR (DMSO-d_6) δ: 0.73-0.78(2H,m), 1.04-1.07(2H,m), 2.37(3H,s), 2.65-2.84(6H,m), 3.11-3.20(4H,m), 3.64(2H,s), 4.59-4.74(2H,m), 7.16(1H,s), 7.17(1H,d,J=8.5Hz), 7.40(1H,d,J=8.5Hz), 7.70(1H,s), 8.84(1H,d,J=7.5Hz), 9.12(1H,d,J=7.5Hz), 11.77(1H,s).

[Example 110]

tert-Butyl (3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate:

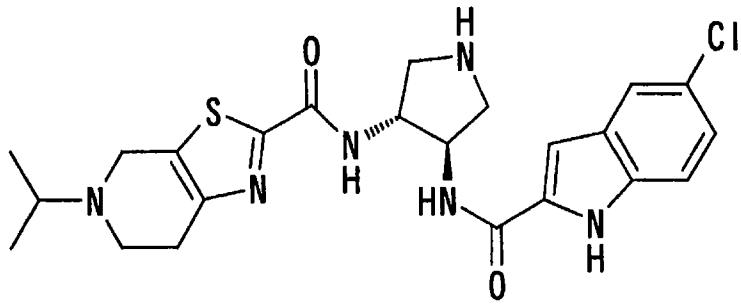


The title compound was obtained from the compound obtained in Referential Example 193 and Referential Example 148 in a similar manner to Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.12(6H,d,J=6.6Hz), 1.47(9H,s), 2.83-2.88(4H,m), 2.94-2.99(1H,m), 3.20-3.29(1H,m), 3.31-3.42(1H,m), 3.75-3.81(2H,m), 3.98(1H,t,J=8.5Hz), 4.15-4.35(2H,m), 4.50-4.65(1H,m), 6.85,6.91(total 1H,each s), 7.15-7.90(5H,m), 9.41,9.50(total 1H,each s).

[Example 111]

N-((3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}pyrrolidin-3-yl)-5-isopropyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide:

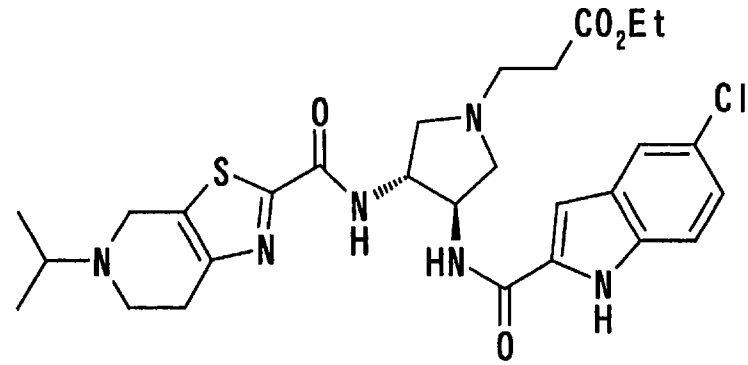


The title compound was obtained from the compound obtained in Example 110 in a similar manner to Example 95.

^{1}H-NMR ($CDCl_3$) δ: 1.13(6H,d,J=6.3Hz), 2.85(4H,br.s), 2.96-3.05(3H,m), 4.51-4.52(1H,m), 4.76-4.80(2H,m), 5.36-5.39(2H,m), 5.53-5.58(1H,m), 7.17-7.19(1H,m), 7.27-7.31(2H,m), 7.57(1H,s), 7.64(2H,br), 9.82(1H,br).

[Example 112]

Ethyl 3-((3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionate:



The title compound was obtained from the compound obtained in Example 111 and ethyl 3-bromopropionate in a similar manner to Example 102.

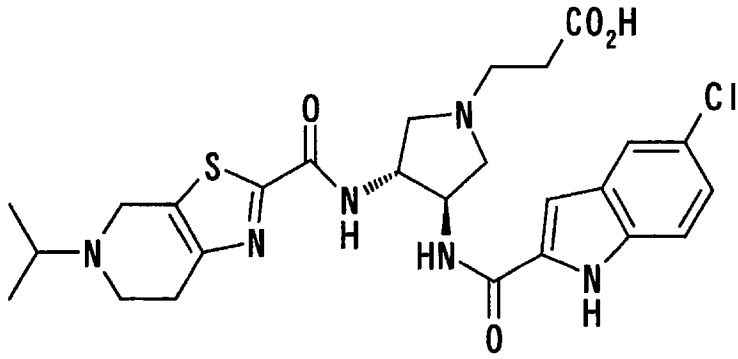
^{1}H-NMR ($CDCl_3$) δ: 1.14(6H,d,J=6.5Hz), 1.26(3H,t,J=7.0Hz),

2.51(3H,t,J=7.0Hz), 2.63(1H,dd,J=9.5,6.5Hz), 2.73-2.91(6H,m), 2.95-3.02(1H,m), 3.22(2H,q,J=7.0Hz), 3.81(each 1H,AB type d,J=14.5Hz), 4.16(2H,q,J=7.0Hz), 4.40-4.45(1H,m), 4.52-4.59(1H,m), 6.88(1H,d,J=2.0Hz), 7.17-7.19(1H,m), 7.30-7.32(2H,m), 7.59(1H,s), 7.62(1H,s), 9.56(1H,s).

MS (FAB) m/z: 587($M+H^+$).

[Example 113]

3-((3R,4R)-3-{[(5-Chloroindol-2-yl)carbonyl]amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidin-1-yl)propionic acid:

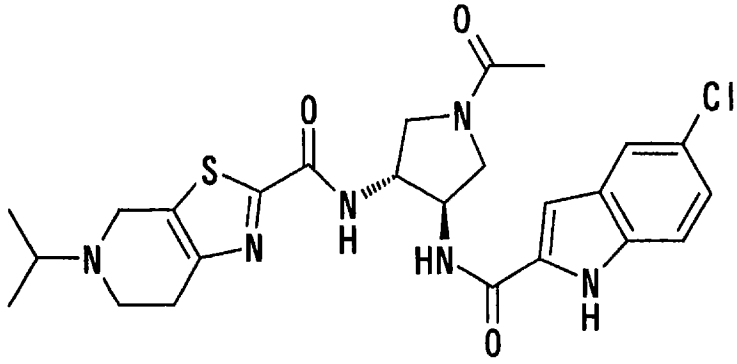


The title compound was obtained from the compound obtained in Example 112 in a similar manner to Example 101.

^{1}H-NMR (DMSO-d_6) δ: 1.04(6H,d,J=6.6Hz), 2.40(2H,q,J=7.0Hz), 2.50(4H,s), 2.60-2.74(4H,m), 2.90-2.94(2H,m), 3.02-3.06(1H,m), 3.20-3.35(2H,m), 4.50-4.53(1H,m), 4.61-4.65(1H,m), 7.15-7.18(2H,m), 7.41(1H,d,J=8.8Hz), 7.68(1H,s), 8.78(1H,d,J=7.5Hz), 8.90(1H,d,J=8.0Hz), 11.73(1H,s).

[Example 114]

N-((3R,4R)-1-Acetyl-4-{[(5-chloroindol-2-yl)carbonyl]-amino}pyrrolidin-3-yl)-5-isopropyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 111 and acetic anhydride in a similar manner to Example 100.

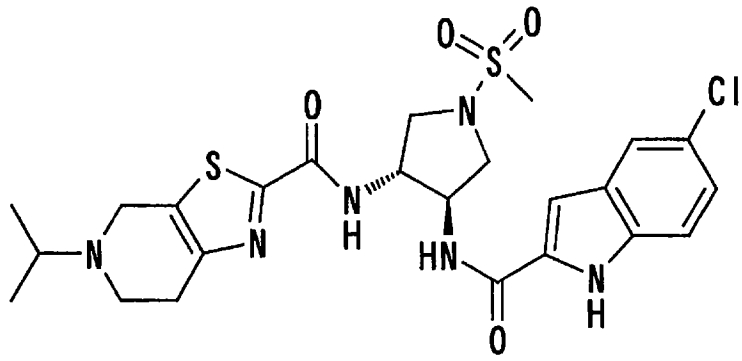
Melting point: 254-258°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.34-1.37(6H,m), 1.96(3H,s), 3.30-3.55(5H,m), 3.66-3.82(3H,m), 3.95(1H,q,J=8.3Hz), 4.45-4.82(4H,m), 7.15(1H,s), 7.18(1H,d,J=9.0Hz), 7.41(1H,d,J=9.0Hz), 7.71(1H,s), 8.75-8.81(1H,m), 9.21(1H,d,J=8.0Hz), 11.32(1H,br), 11.83(1H,d,J=7.3Hz).

MS (FAB) m/z: 529($M+H^+$).

[Example 115]

N-[(3R,4R)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(methylsulfonyl)pyrrolidin-3-yl]-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 111 and methanesulfonyl chloride in a similar manner to Example 100.

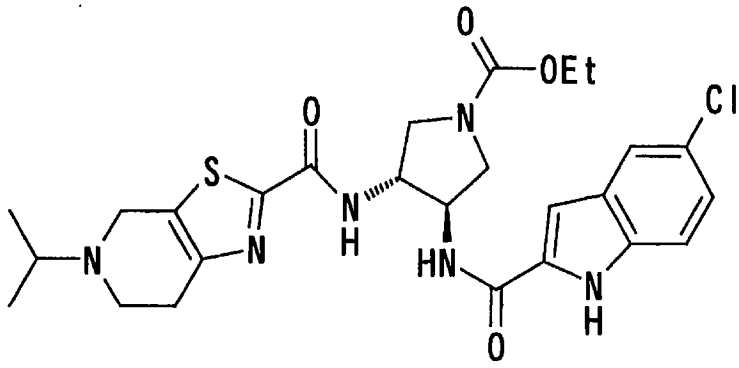
Melting point: 230-235°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.32-1.36(6H,m), 3.32(3H,s), 3.43-3.46(5H,m), 3.68-3.75(4H,m), 4.48(1H,m), 4.62-4.72(2H,m), 4.83(1H,t,J=5.5Hz), 7.14(1H,s), 7.18(1H,d,J=8.6Hz), 7.40(1H,d,J=8.6Hz), 7.72(1H,s), 8.82(1H,br), 9.20(1H,d,J=8.3Hz), 11.30(1H,br), 11.86(1H,d,J=7.5Hz).

MS (FAB) m/z: 565($M+H^+$).

[Example 116]

Ethyl (3R,4R)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 111 and ethyl chloroformate in a similar manner to Example 100.

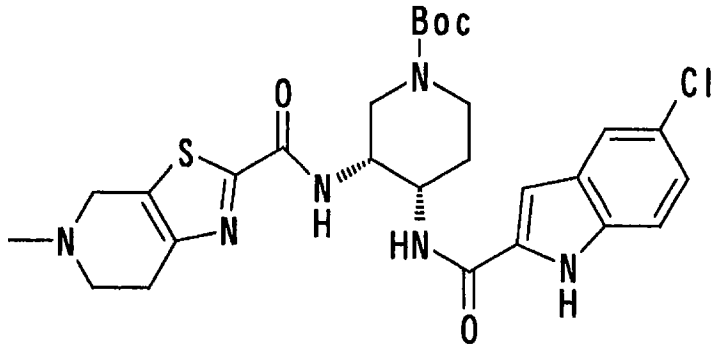
Melting point: 225-228°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.20(3H,t,J=7.0Hz), 1.31-1.37(6H,m), 3.33-3.45(5H,m), 3.66-3.75(4H,m), 4.05(2H,q,J=7.0Hz), 4.45-4.77(4H,m), 7.15(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,d,J=2.0Hz), 8.77(1H,d,J=7.0Hz), 9.20(1H,d,J=8.0Hz), 11.30(1H,br), 11.83(1H,d,J=7.5Hz).

MS (FAB) m/z: 559($M+H^+$).

[Example 117]

tert-Butyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



The title compound was obtained from the compound obtained in Referential Example 207 and Referential Example 10 in a similar manner to Example 91.

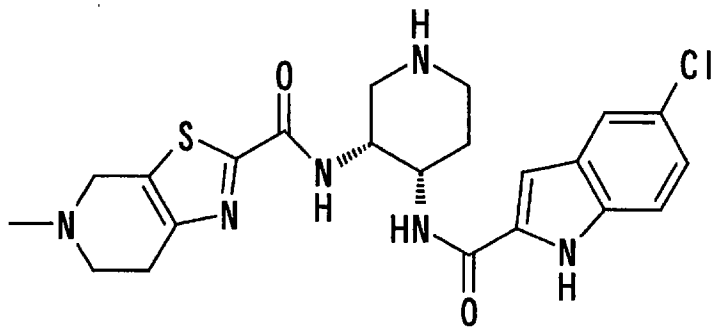
Melting point: 152-154°C (decomposed).

^{1}H-NMR ($CDCl_3$) δ: 1.53(9H,s), 1.62-1.80(1H,m), 2.23-2.30(1H,m), 2.52(3H,s), 2.75-3.05(5H,m), 3.10-3.25(1H,m), 3.68-3.82(2H,m), 4.15-4.45(4H,m), 6.89(1H,s), 7.19(1H,dd,J=8.8,1.8Hz), 7.32(1H,d,J=8.8Hz), 7.92(1H,d,J=1.8Hz), 7.75(1H,br.s), 8.21(1H,br.s), 9.39(1H,s).

MS (ESI) m/z: 573$(M+H)^+$.

[Example 118]

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



The title compound was obtained from the compound obtained in Example 117 in a similar manner to Example 95.

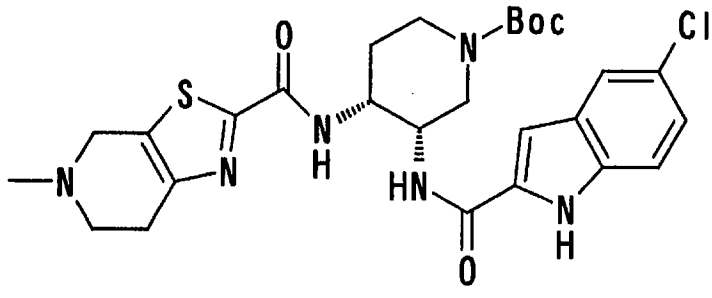
Melting point: 240-258°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.85-2.00(1H,m), 2.05-2.20(2H,m), 2.93(3H,s), 3.05-3.60(7H,m), 3.65-3.75(1H,m), 4.10-4.52(2H,m), 4.60-4.75(2H,m), 7.10-7.21(2H,m), 7.43(1H,d,J=8.6Hz), 7.70(1H,s), 8.50(1H,br.d,J=7.8Hz), 8.90-9.05(2H,m), 9.27(1H,br.s), 11.9(1H,br.d,J=13.4Hz).

MS (ESI) m/z: 473$(M+H)^+$.

[Example 119]

tert-Butyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



The title compound was obtained from the compound obtained in Referential Example 208 and 5-chloroindole-2-carboxylic acid in a similar manner to Example 91.

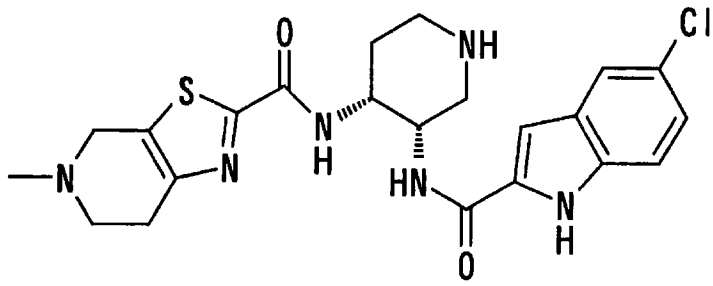
Melting point: 187-189°C (decomposed).

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 1.72-1.90(1H,m), 2.00(1H,br.s), 2.00-2.10(1H,m), 2.45(3H,s), 2.60-2.70(2H,m), 2.70-2.80(2H,m), 3.23(1H,t,J=10.8Hz), 3.35-3.50(1H,m), 3.50-3.72(2H,m), 3.90-4.20(2H,m), 4.30-4.40(1H,m), 4.45-4.55(1H,m), 6.85(1H,d,J=1.5Hz), 7.17(1H,dd,J=8.8,1.9Hz), 7.20-7.30(1H,m), 7.33(1H,d,J=8.8Hz), 7.58(1H,d,J=1.9Hz), 10.17(1H,s).

MS (ESI) m/z: 573($M+H^+$).

[Example 120]

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



The title compound was obtained from the compound obtained in Example 119 in a similar manner to Example 95.

Melting point: 276-278°C (decomposed).

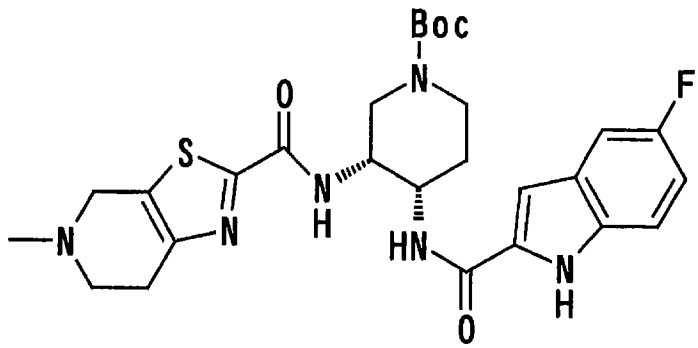
^{1}H-NMR (DMSO-d_6) δ: 1.77-1.88(1H,m), 2.40-2.50(2H,m), 2.89(3H,s), 2.90-3.20(4H,m), 3.30-3.50(2H,m),

3.63(1H,br.s), 4.33-4.47(2H,m), 4.62-4.75(2H,m), 7.18(1H,dd,J=8.8,1.9Hz), 7.42(1H,d,J=8.8Hz), 7.48(1H,br.s), 7.71(1H,d,J=1.9Hz), 8.66(1H,br.s), 8.95(1H,d,J=8.1Hz), 9.20-9.30(1H,m), 9.45-9.70(1H,m), 11.61(1H,s), 11.90(1H,s).

MS (ESI) m/z: 473$(M+H)^+$.

[Example 121]

tert-Butyl (3R*,4S*)-4-{[(5-fluoroindol-2-yl)carbonyl]-amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate:



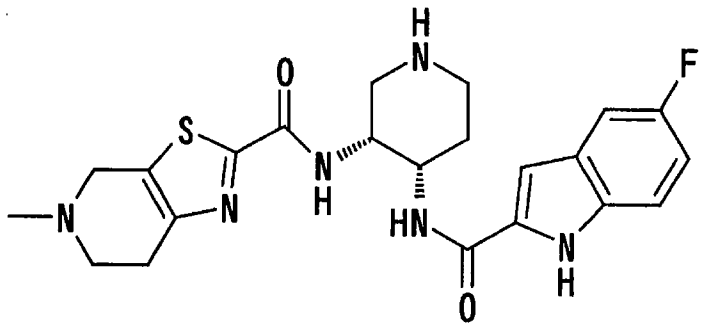
The title compound was obtained from the compound obtained in Referential Example 209 and Referential Example 10 in a similar manner to Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.53(9H,s), 1.65-1.78(1H,m), 2.23-2.32(1H,br), 2.52(3H,s), 2.78-3.03(5H,m), 3.15-3.24(1H,br), 3.68-3.82(2H,br), 4.16-4.45(4H,br), 6.91(1H,s), 7.02(1H,td,J=9.0,2.7Hz), 7.30(1H,dd,J=9.0,2.7Hz), 7.34(1H,dd,J=9.0,4.4Hz), 7.65-7.90(1H,br), 8.10-8.40(1H,br), 9.31-9.41(1H,br).

MS (ESI) m/z: 557$(M+H^+)$.

[Example 122]

N-((3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



The title compound was obtained from the compound obtained in Example 121 in a similar manner to Example 95.

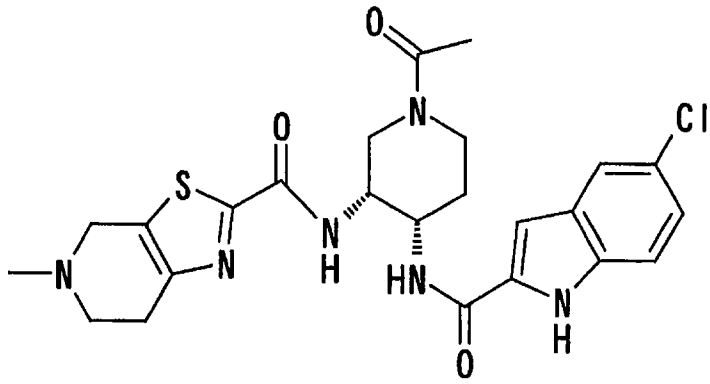
Melting point: 236-245°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.85-1.98(1H,br), 2.06-2.18(1H,br), 2.89(3H,s), 3.05-3.75(8H,s), 4.34-4.54(2H,br), 4.60-4.75(2H,br), 7.04(1H,td,J=9.3,2.4Hz), 7.15(1H,br.s), 7.37-7.44(2H,m), 8.46(1H,d,J=7.8Hz), 8.88-9.00(1H,br), 9.09-9.27(2H,br), 11.55-11.75(1H,br), 11.76-11.84(1H,br).

MS (FAB) m/z: 457($M+H^+$).

[Example 123]

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



The title compound was obtained from the compound obtained in Example 118 and acetic anhydride in a similar manner to Example 100.

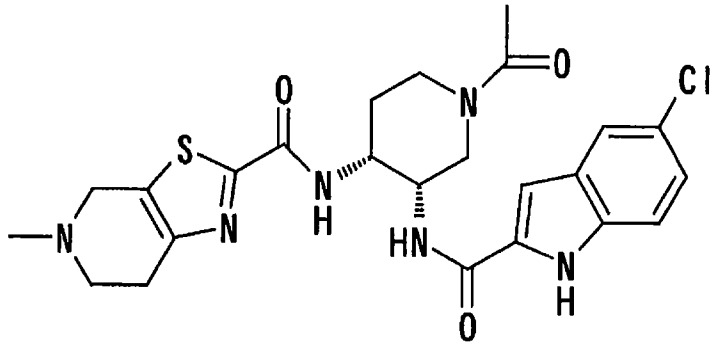
Melting point: 215-225°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.65-1.85(1H,m), 1.88,2.06(total 3H,each s), 1.90-2.10(1H,m), 2.91(3H,s), 3.00-3.30(2H,m), 3.30-3.55(2H,m), 3.60-3.90(3H,m), 3.98-4.50(4H,m), 4.65-4.75(1H,m), 7.09(1H,d,J=15.6Hz), 7.17(1H,d,J=8.8Hz), 7.41(1H,d,J=8.8Hz),7.71(1H,s), 8.23-8.53(2H,m), 11.20-11.55(1H,m), 11.85(1H,br.d,J=5.4Hz).

MS (ESI) m/z: 515($M+H^+$).

[Example 124]

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



The title compound was obtained from the compound obtained in Example 120 and acetic anhydride in a similar manner to Example 100.

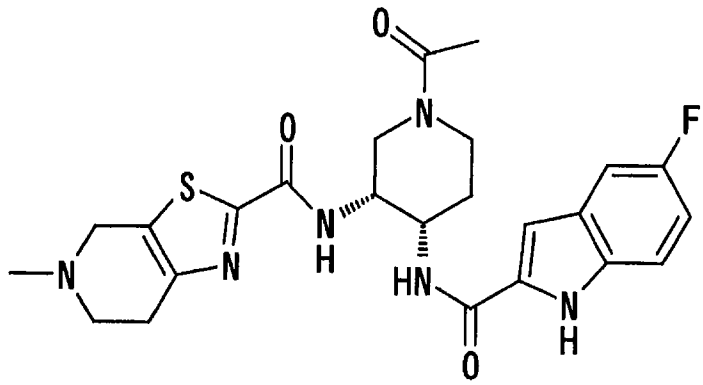
Melting point: 225-250°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.65-1.80(1H,m), 1.81,2.05(total 3H,each s), 2.00-2.20(1H,m), 2.70-2.85(1H,m), 2.89(3H,s),3.00-3.20(2H,m), 3.20-3.50(2H,m), 3.64(1H,br.s), 3.78-4.30(2H,m), 4.30-4.50(3H,m), 4.55-4.75(1H,m), 7.05-7.23(2H,m), 7.38-7.48(1H,m), 7.70-7.80(1H,m), 7.79,8.12(total 1H,each d,J=6.8Hz), 8.73,8.83(total 1H,each d,J=8.3Hz), 11.20-11.50(1H,m), 11.89,11.92(total 1H,each s).

MS (FAB) m/z: 515($M+H^+$).

[Example 125]

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



The title compound was obtained from the compound obtained in Example 122 and acetic anhydride in a similar manner to Example 100.

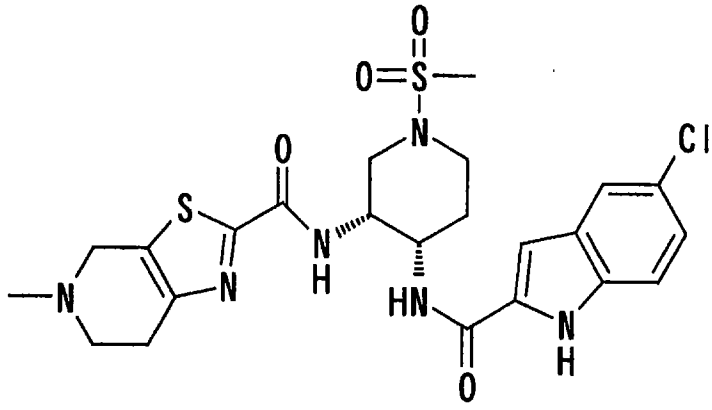
Melting point: 202°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.67-1.85(1H,m), 1.87(1.5H,s), 1.87-2.10(1H,m), 2.06(1.5H,s), 2.88-2.96(3H,br.s), 3.05-3.30(2H,m), 3.32-3.83(5H,br), 3.97-4.33(2H,m), 4.35-4.50(2H,br), 4.67-4.78(1H,br), 7.01-7.14(2H,m), 7.38-7.44(2H,m), 8.25-8.50(2H,m), 10.85-11.15(1H,br), 11.72-11.80(1H,br).

MS (FAB) m/z: 499($M+H^+$).

[Example 126]

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



The title compound was obtained from the compound obtained in Example 118 and methanesulfonyl chloride in a similar manner to Example 100.

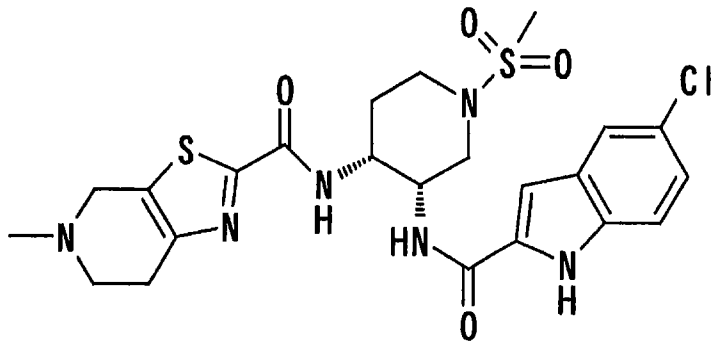
Melting point: 225-230°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.80-1.90(1H,m), 2.05-2.15(1H,m), 2.30-2.80(5H,m), 2.85-3.80(9H,m), 4.20-4.90(4H,m), 7.08(1H,d,J=1.7Hz), 7.18(1H,dd,J=8.7,1.7Hz), 7.42(1H,d,J=8.7Hz), 7.77(1H,s), 8.02-8.20(1H,m), 8.40-8.50(1H,m), 11.00-11.60(1H,m), 11.87(1H,s).

MS (ESI) m/z: 551($M+H^+$).

[Example 127]

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



The title compound was obtained from the compound obtained in Example 120 and methanesulfonyl chloride in a similar manner to Example 100.

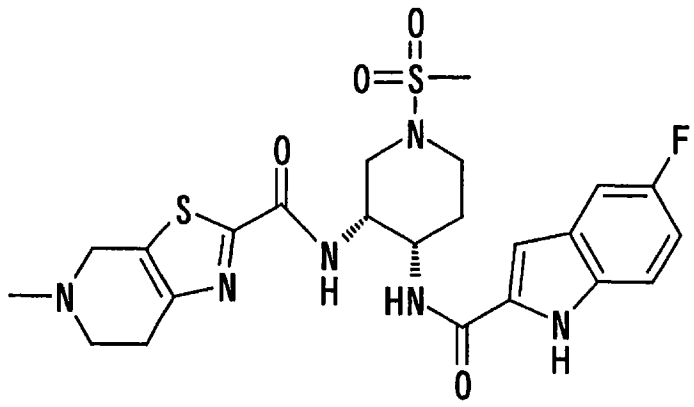
Melting point: 228-245°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.75-1.85(1H,m), 2.25-2.40(1H,m), 2.40-2.60(2H,m), 2.76(3H,br.s), 2.90(3H,s), 2.93-3.05(3H,m), 3.12(1H,d,J=10.6Hz), 3.55-3.80(2H,m), 4.25-4.40(4H,m), 7.17(1H,d,J=1.7Hz), 7.19(1H,dd,J=8.7,2.0Hz), 7.43(1H,d,J=8.7Hz), 7.74(1H,d,J=2.0Hz), 8.03(1H,d,J=6.6Hz), 8.78(1H,d,J=7.4Hz), 10.90-11.20(1H,br.s), 11.89(1H,s).

MS (ESI) m/z: 551($M+H^+$).

[Example 128]

N-[(3R*,4S*)-4-{[(5-Fluoroindol-2-yl)carbonyl]amino}-1-(methylsulfonyl)piperazin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 122 and methanesulfonyl chloride in a similar manner to Example 100.

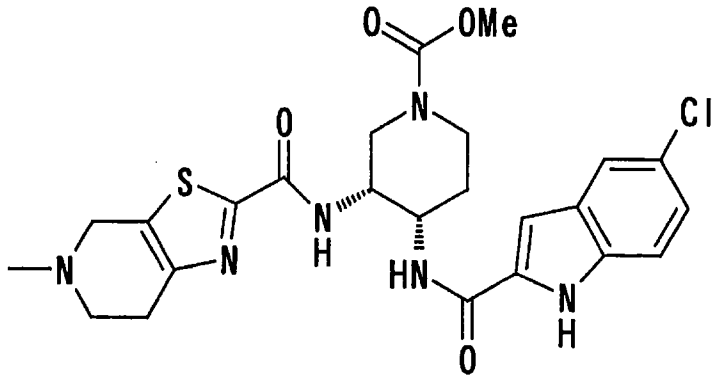
Melting point: 216-250°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.80-1.90(1H,m), 2.01-2.12(1H,m), 2.92(3H,s), 2.94(3H,s), 3.00-3.80(8H,m), 4.28-4.53(3H,m), 4.60-4.80(1H,br), 7.01-7.12(2H,m), 7.37-7.44(2H,m), 8.00-8.18(1H,br), 8.39-8.50(1H,br), 11.00-11.60(1H,br), 11.72-11.80(1H,br).

MS (FAB) m/z: 535($M+H^+$).

[Example 129]

Methyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and methyl chloroformate in a similar manner to Example 100.

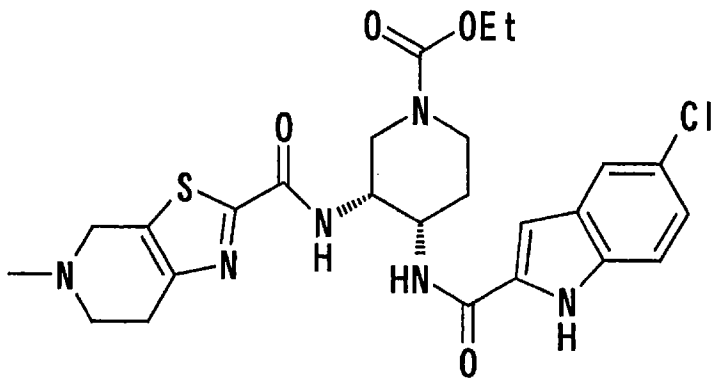
Melting point: 248-253°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.65-1.78(1H,m), 1.88-2.03(1H,m), 2.90(3H,s), 3.00-3.80(9H,m), 3.80-3.90(1H,m), 3.95-4.08(1H,m), 4.20-4.70(4H,m), 7.10(1H,s), 7.17(1H,dd,J=8.8,1.8Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,d,J=1.8Hz), 8.29(1H,br.s), 8.41(1H,d,J=8.1Hz), 11.29(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 531($M+H^+$).

[Example 130]

Ethyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and ethyl chloroformate in a similar manner to Example 100.

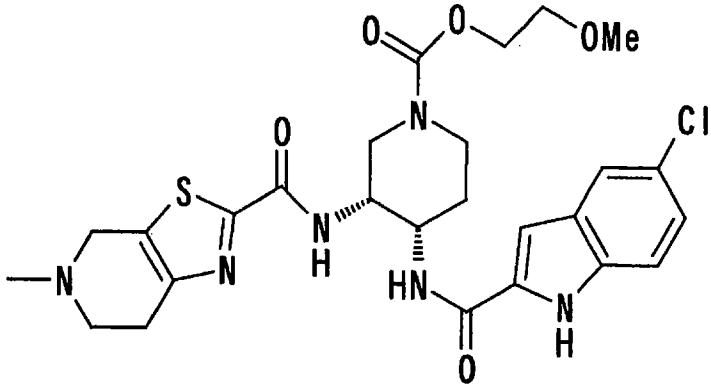
Melting point: 215-225°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.85-1.30(3H,m), 1.65-1.78(1H,m), 1.90-2.03(1H,m), 2.90(3H,s), 3.10-3.40(4H,m), 3.48(1H,br.s), 3.65(1H,br.s), 3.75-4.15(4H,m), 4.25(1H,br.s), 4.32-4.50(2H,m), 4.66(1H,br.s), 7.09(1H,s), 7.18(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,d,J=2.0Hz), 8.23(1H,br.s), 8.45(1H,br.d,J=8.1Hz), 11.50(1H,br.s), 11.86(1H,s).

MS (ESI) m/z: 545($M+H^+$).

[Example 131]

2-Methoxyethyl (3R*,4S*)-4-{[(5-chloroindol-2-yl)-carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and 2-methoxyethyl chloroformate in a similar manner to Example 100.

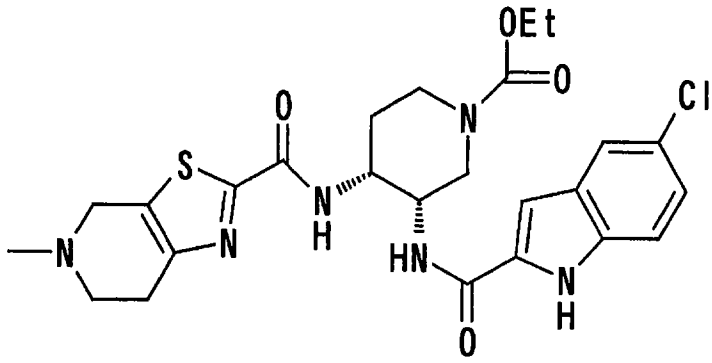
Melting point: 224-226°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.68-1.78(1H,m), 1.90-2.03(1H,m), 2.89(3H,s), 3.00-3.75(11H,m), 3.80-3.90(1H,m), 3.95-4.18(3H,m), 4.20-4.70(4H,m), 7.10(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,d,J=2.0Hz), 8.26(1H,br.s), 8.42(1H,d,J=7.8Hz), 11.30(1H,br.s), 11.86(1H,s).

MS (ESI) m/z: 575($M+H^+$).

[Example 132]

Ethyl (3R*,4S*)-3-{[(5-chloroindol-2-yl)carbonyl]amino}-4-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidine-1-carboxylate hydrochloride:



The title compound was obtained from the compound obtained in Example 120 and ethyl chloroformate in a similar manner to Example 100.

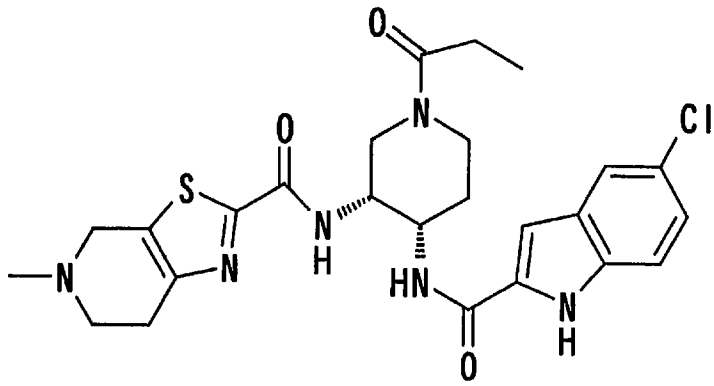
Melting point: 213-225°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.75-1.30(3H,m), 1.60-1.72(1H,m), 2.12-2.25(1H,m), 2.89(3H,s), 2.95-3.20(4H,m), 3.40-3.88(4H,m), 3.90-4.10(2H,m), 4.10-4.30(2H,m), 4.30-4.40(1H,m), 4.40-4.80(1H,m), 7.10(1H,s), 7.18(1H,dd,J=8.8,2.0Hz), 7.43(1H,d,J=8.8Hz), 7.74(1H,s), 8.03(1H,d,J=5.6Hz), 8.79(1H,s), 11.37(1H,s), 11.88(1H,s).

MS (ESI) m/z: 545($M+H^+$).

[Example 133]

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



The title compound was obtained from the compound obtained in Example 118 and propionyl chloride in a similar manner to Example 100.

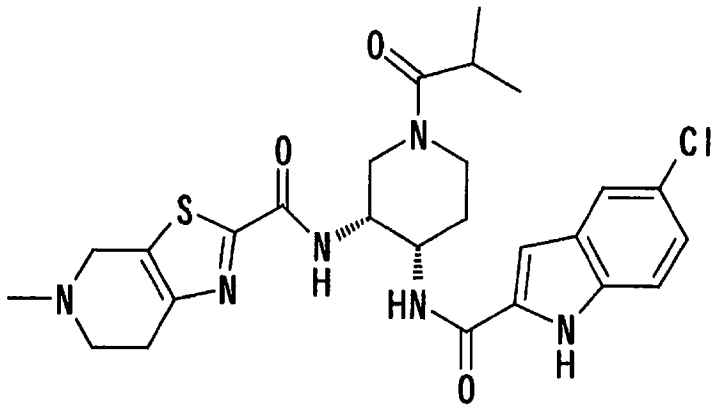
Melting point: 214-228°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.88-1.10(3H,m), 1.70-2.05(2H,m), 2.06-2.60(2H,m), 2.91(3H,s), 3.14(2H,br.s), 3.20-3.90(5H,m), 3.95-4.80(5H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,1.2Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,s), 8.20-8.50(2H,m), 11.00-11.40(1H,m), 11.86(1H,s).

MS (ESI) m/z: 529($M+H^+$).

[Example 134]

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



The title compound was obtained from the compound obtained in Example 118 and isobutyryl chloride in a similar manner to Example 100.

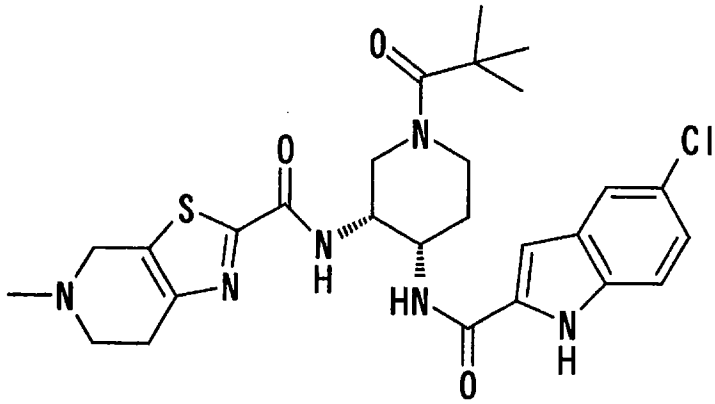
Melting point: 266-272°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.80-1.15(6H,m), 1.70-2.05(2H,m), 2.65-2.80(1H,m), 2.90(3H,s), 2.90-4.80(12H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.41(1H,d,J=8.8Hz), 7.71(1H,s), 8.00-8.30(1H,m), 8.30-8.50(1H,m), 10.95-11.50(1H,m), 11.86(1H,s).

MS (ESI) m/z: 543($M+H^+$).

[Example 135]

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



The title compound was obtained from the compound obtained in Example 118 and pivaloyl chloride in a similar manner to Example 100.

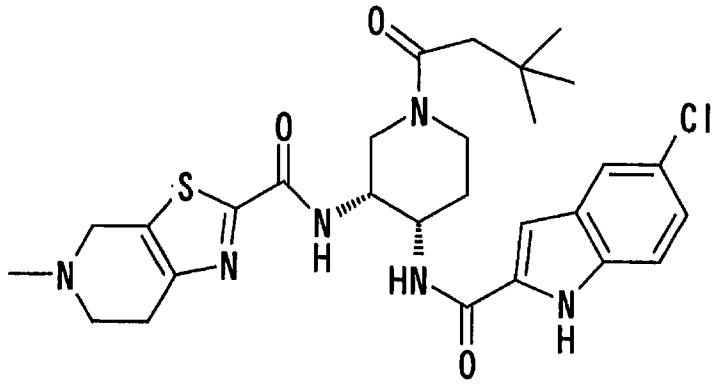
Melting point: 250-255°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.20(9H,s), 1.70-1.81(1H,m), 1.90-2.00(1H,m), 2.88(3H,s), 3.10(2H,br.s), 3.20-3.70(4H,m), 3.95-4.08(1H,m), 4.10-4.20(1H,m), 4.25-4.35(1H,m), 4.35-4.80(3H,m), 7.10(1H,s), 7.16(1H,dd,J=8.8,1.9Hz), 7.41(1H,d,J=8.8Hz), 7.69(1H,d,J=1.9Hz), 8.06(1H,br.s), 8.38(1H,d,J=7.8Hz), 11.31(1H,br.s), 11.84(1H,s).

MS (ESI) m/z: 557($M+H^+$).

[Example 136]

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



The title compound was obtained from the compound obtained in Example 118 and tert-butylacetyl chloride in a similar manner to Example 100.

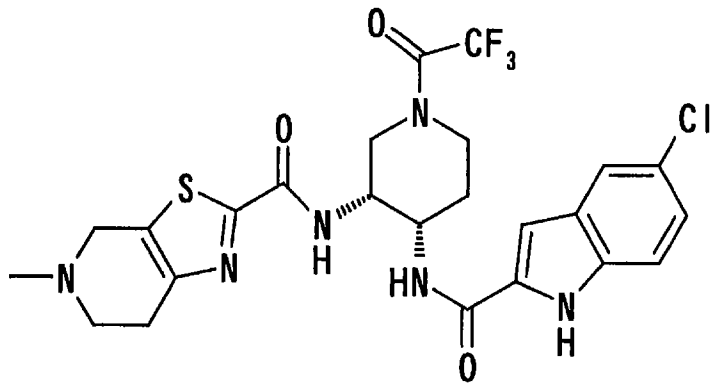
Melting point: 260-265°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.91,1.04(total 9H,each s), 1.68-1.82(1H,m), 1.93-2.40(3H,m), 2.91(3H,s), 3.00-3.20(2H,m), 3.20-4.80(10H,m), 7.08(1H,s), 7.17(1H,dd,J=8.7,1.2Hz), 7.41(1H,d,J=8.7Hz), 7.69(1H,d,J=7.6Hz), 7.93-8.18(1H,m), 8.38-8.45(1H,m), 10.95-11.30(1H,m), 11.80-11.90(1H,m).

MS (ESI) m/z: 571($M+H^+$).

[Example 137]

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



The title compound was obtained from the compound obtained in Example 118 and trifluoroacetic anhydride in a similar manner to Example 100.

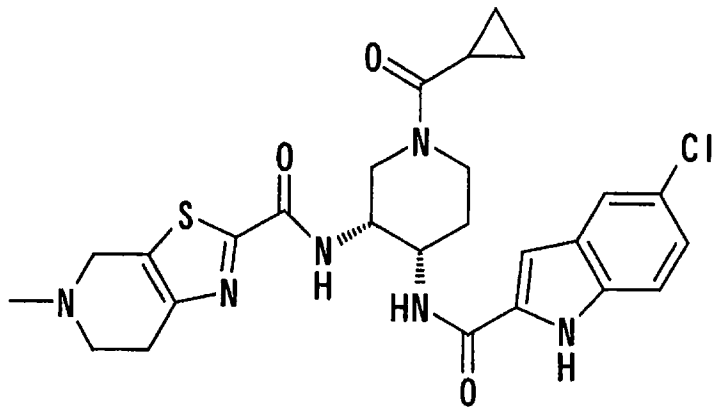
Melting point: 262-267°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.82-1.98(1H,m), 2.05-2.21(1H,m), 2.89(3H,s), 3.05-3.20(2H,m), 3.40-3.75(4H,m), 3.85-3.95(1H,m), 4.00-4.07(1H,m), 4.20-4.70(4H,m), 7.10(1H,s), 7.18(1H,dd,J=8.6,1.9Hz), 7.41(1H,d,J=8.6Hz), 7.72(1H,s), 8.47(1H,dd,J=22.4,7.9Hz), 8.60(1H,br), 11.08(1H,br.s), 11.87(1H,s).

MS (ESI) m/z: 569($M+H^+$).

[Example 138]

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



The title compound was obtained from the compound obtained in Example 118 and cyclopropanecarbonyl chloride in a similar manner to Example 100.

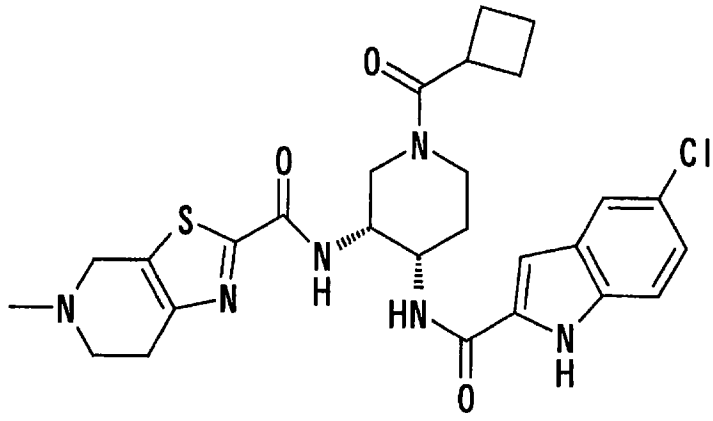
Melting point: 280-286°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 0.25-0.80(4H,m), 1.65-2.15(4H,m), 2.91(3H,s), 2.90-3.20(3H,m), 3.35-3.70(2H,m), 4.00-4.80(6H,m), 7.06(1H,s), 7.18(1H,d,J=8.8Hz), 7.42(1H,d,J=8.7Hz), 7.71(1H,s), 8.18(1H,br.s), 8.40,8.48(total 1H,each br.s), 11.11(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 542($M+H^+$).

[Example 139]

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



The title compound was obtained from the compound obtained in Example 118 and cyclobutanecarbonyl chloride in a similar manner to Example 100.

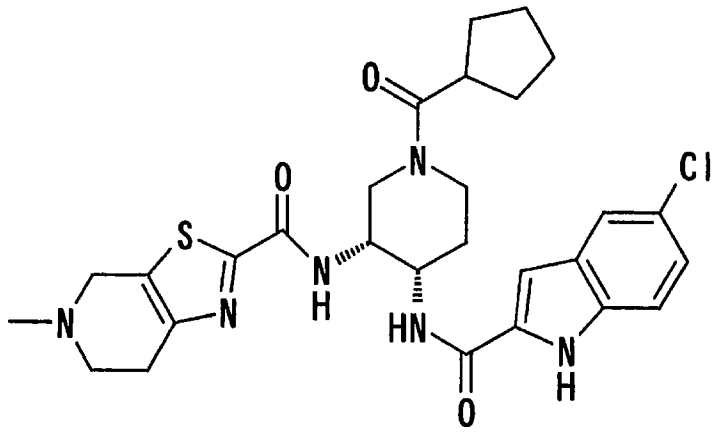
Melting point: 271-275°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.60-2.30(8H,m), 2.89(3H,s), 3.12(2H,br.s), 3.20-3.75(6H,m), 3.75-3.90(1H,m), 4.05-4.80(4H,m), 7.08(1H,s), 7.15(1H,dd,J=9.0,2.0Hz), 7.39(1H,d,J=9.0Hz), 7.68(1H,d,J=2.0Hz), 8.15(1H,br.s), 8.39(1H,br), 11.19(1H,br.s), 11.84(1H,s).

MS (ESI) m/z: 555($M+H^+$).

[Example 140]

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



The title compound was obtained from the compound obtained in Example 118 and cyclopentanecarbonyl chloride in a similar manner to Example 100.

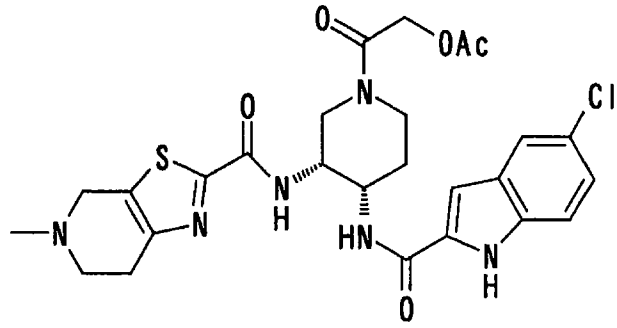
Melting point: 254-260°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.30-2.10(10H,m), 2.90(3H,s), 3.00-3.20(2H,m), 3.20-3.75(5H,m), 3.80-4.80(6H,m), 7.09(1H,s), 7.17(1H,dd,J=8.7,2.0Hz), 7.42(1H,d,J=8.7Hz), 7.71(1H,s), 7.95-8.30(1H,m), 8.35-8.50(1H,m), 11.23(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 569($M+H^+$).

[Example 141]

2-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidin-1-yl)-2-oxoethyl acetate:



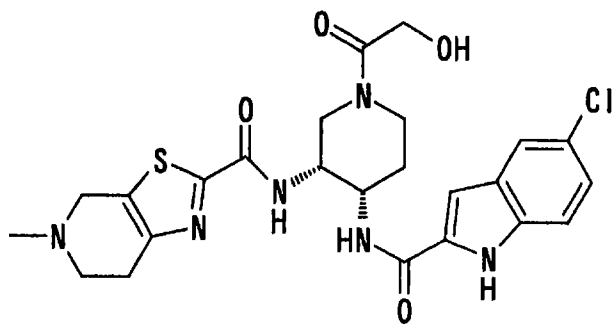
The title compound was obtained from the compound obtained in Example 118 and acetoxyacetyl chloride in a similar manner to Example 100.

^{1}H-NMR ($CDCl_3$) δ: 1.70-2.00(1H,m), 2.05-2.48(3H,m), 2.51(3H,s), 2.70-3.05(4H,m), 3.05-4.10(5H,m), 4.20-4.48(1H,m), 4.50-5.10(4H,m), 6.87(1H,br.s), 7.10-7.82(4H,m), 7.32(1H,d,J=8.8Hz), 8.35(1H,br.s), 9.34,9.45(total 1H,each br.s).

MS (ESI) m/z: 573($M+H^+$).

[Example 142]

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



The compound (301.8 mg) obtained in Example 141 was dissolved in tetrahydrofuran (10 ml), and a 1N aqueous solution (0.53 ml) of sodium hydroxide was added to stir the mixture at room temperature for 18 hours. Water was added to the reaction mixture to conduct extraction with methylene chloride. The resultant organic layer was successively washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1 - 10:1), and the solvent was distilled off under reduced pressure. The thus-obtained purified product was dissolved in ethanol (3 ml) and methylene chloride (2 ml), and a 1N ethanol solution of hydrochloric acid to stir the mixture for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was solidified with diethyl ether to obtain the title compound (195 mg).

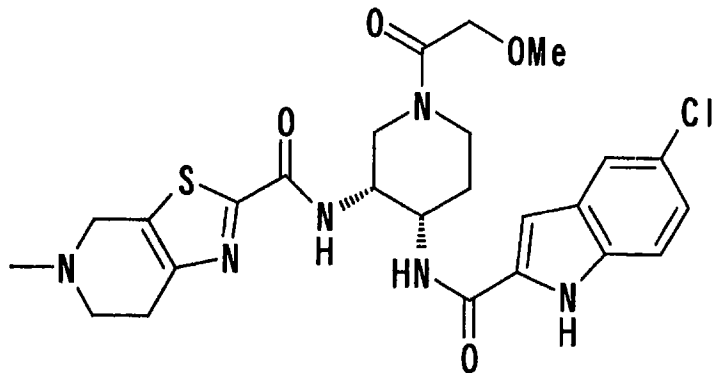
Melting point: 216-230°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.70-1.80(1H,m), 1.88-2.10(2H,m), 2.68(3H,s), 3.18(2H,s), 3.08-3.70(5H,m), 3.80-3.95(1H,m), 4.00-4.25(3H,m), 4.25-4.50(2H,m), 4.50-4.65(1H,m), 7.09(1H,d,J=11.0Hz), 7.17(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,s), 8.33(1H,br.s), 8.35-8.50(1H,m), 10.80-11.30(1H,br.s), 11.84(1H,br.s).

[Example 143]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-(2-

methoxyacetyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 in a similar manner to Example 100.

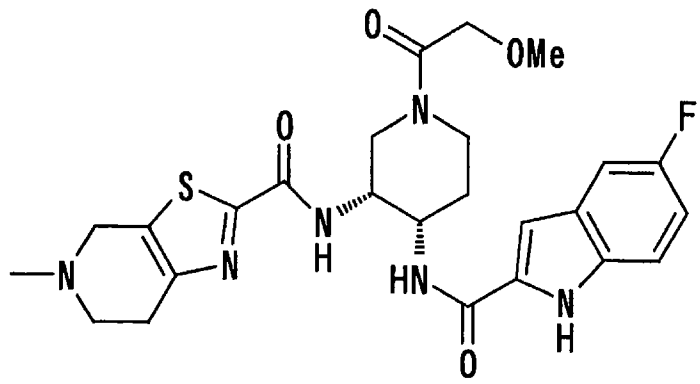
Melting point: 214-228°C (decomposed).

^{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=9.0Hz), 7.17(1H,dd,J=8.8,1.9Hz), 7.42(1H,d,J=8.8Hz), 7.70(1H,d,J=1.9Hz), 8.29(1H,br.s),8.40-8.50(1H,m), 11.34(1H,br.s), 11.86(1H,s).

MS (ESI) m/z: 545$(M+H)^+$.

[Example 144]

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



The title compound was obtained from the compound obtained in Example 122 and methoxyacetyl chloride in a similar manner to Example 100.

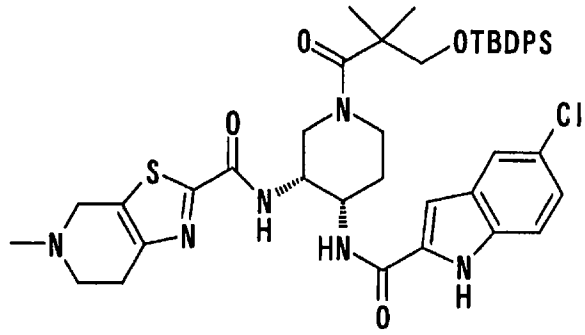
Melting point: 190-208°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.70-1.83(1H,br), 1.85-2.10(1H,m), 2.91(3H,s), 3.00-3.55(10H,m), 3.62-3.85(1H,m), 3.90-4.50(6H,m), 4.63-4.78(1H,br), 7.04(1H,td,J=9.4,2.4Hz), 7.07-7.13(1H,br), 7.37-7.44(1H,m), 8.16-8.49(2H,m), 11.30-11.70(1H,br), 11.72-11.80(1H,br).

MS (FAB) m/z: 529($M+H^+$).

[Example 145]

N-((3R*,4S*)-1-(3-{tert-butyl(diphenyl)silyl}oxy)-2,2-dimethylpropanoyl)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}piperidin-3-yl)-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-carboxamide:



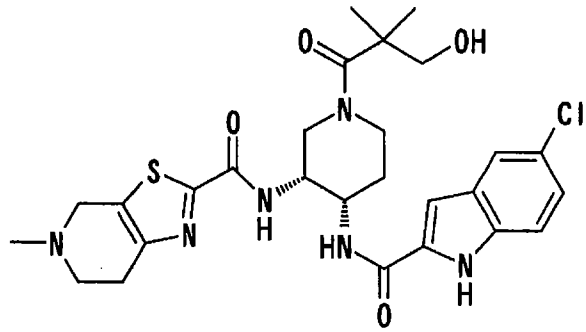
Thionyl chloride (3.0 ml) and a catalytic amount of dimethylformamide were added to a solution of the compound (261 mg) obtained in Referential Example 158 in chloroform (10 ml), and the mixture was stirred overnight at 60°C. The reaction mixture was concentrated under reduced pressure, giving a pale yellow oil. The title compound was obtained from this product and the compound (200 mg) obtained in Example 118 in a similar manner to Example 100.

Melting point: 153°C.

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.39(6H,d,J=3.9Hz), 1.57(1H,br.s), 2.26(1H,d,J=10.7Hz), 2.57(3H,s), 2.86(4H,s), 2.97-3.01(2H,m), 3.78(4H,s), 4.20(1H,br.s), 4.33(1H,d,J=13Hz), 4.42(1H,br.s), 4.67(1H,d,J=13Hz), 6.88(1H,s), 7.20-7.23(1H,m), 7.32-7.46(7H,m), 7.64-7.65(6H,m), 7.86(1H,d,J=6.8Hz), 8.23(1H,s), 9.10(1H,s).

[Example 146]

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



Tetrabutylammonium fluoride (1 M tetrahydrofuran solution, 0.594 ml) was added to a solution of the compound (241 mg) obtained in Example 145 in tetrahydrofuran (30 ml) under ice cooling, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in methylene chloride. The solution was washed with water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain the title compound (116 mg).

Melting point: 220°C (decomposed).

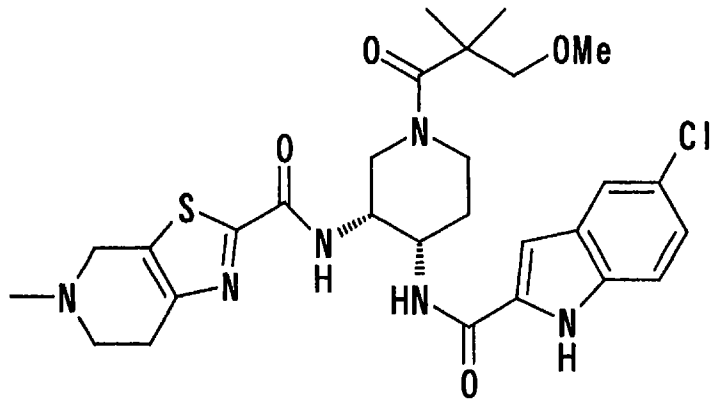
^{1}H-NMR (DMSO-d_6) δ: 1.17(6H,d,J=8.3Hz), 1.79(1H,br.s), 1.91-1.97(1H,m), 2.49(3H,s), 2.87(4H,s), 3.35-3.50(4H,m), 3.81(1H,br.s), 3.97(1H,m), 4.10-4.15(1H,m), 4.32(1H,br.s), 4.42(1H,br.s), 4.52(1H,t,J=5.7Hz), 7.10(1H,s), 7.16-7.19(1H,m), 7.42(1H,d,J=8.8Hz), 7.69(1H,s),

8.11(1H,d,J=8.8Hz), 8.37(1H,d,J=7.3Hz), 11.8(1H,s).

MS (FAB) m/z: 573($M+H^+$).

[Example 147]

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



The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 160 in a similar manner to Example 145.

Melting point: 240°C (decomposed).

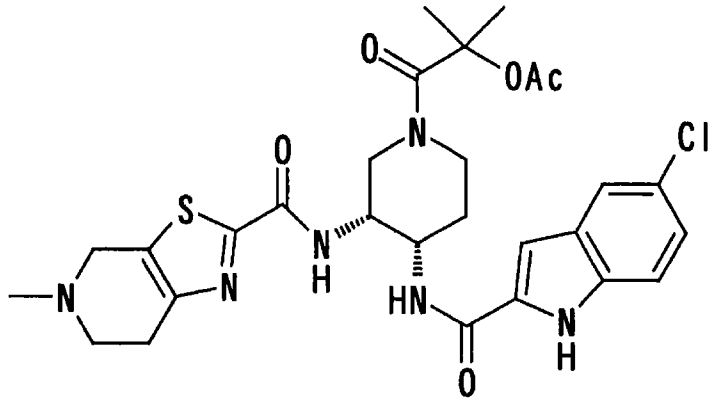
^{1}H-NMR ($CDCl_3$) δ: 1.34(3H,s), 1.37(3H,s), 1.65-1.77(1H,m), 2.33-2.37(1H,m), 2.53(3H,s), 2.82-3.29(6H,m), 3.34(3H,s), 3.41(1H,d,J=9.3Hz), 3.56(1H,d,J=9.3Hz), 3.76(2H,d,J=5.9Hz), 4.26(1H,m),4.44-4.53(2H,m), 4.82(1H,d,J=13.7Hz), 6.88(1H,d,J=1.5Hz), 7.20-7.23(1H,m), 7.33(1H,d,J=8.8Hz), 7.64(1H,d,J=1.5Hz), 7.90(1H,d,J=7.1Hz), 8.22(1H,d,J=5.1Hz), 9.18(1H,s).

MS (FAB) m/z: 587($M+H^+$).

[Example 148]

2-((3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-3-

{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}piperidin-1-yl)-1,1-dimethyl-2-oxoethyl acetate:



The title compound was obtained from the compound obtained in Example 118 and 2-acetoxyisobutyryl chloride in a similar manner to Example 100.

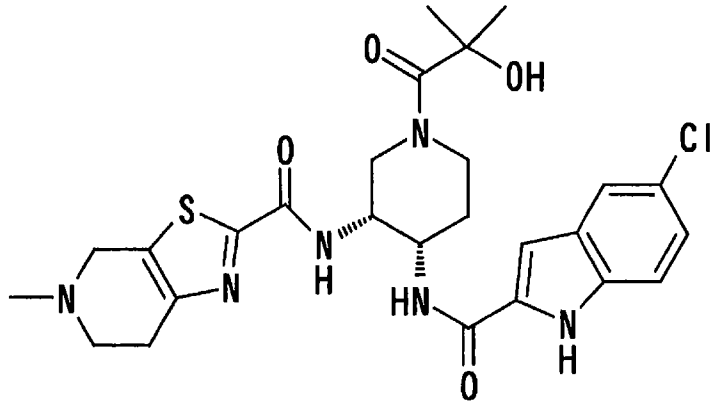
Melting point: 190°C (decomposed).

^{1}H-NMR ($CDCl_3$) δ: 1.56-1.67(8H,m), 2.08(3H,s), 2.35(1H,d,J=10.5Hz), 2.52(3H,s), 2.82-2.84(2H,m), 2.90-2.96(2H,m), 3.14(1H,br.s), 3.75(2H,s), 4.25(1H,br.s), 4.40-4.47(1H,m), 4.54(1H,br.s), 4.80(1H,br.s), 6.86(1H,s), 7.20-7.33(3H,m), 7.64(1H,d,J=1.7Hz), 7.76(1H,d,J=7.3Hz), 9.11(1H,s).

MS (FAB) m/z: 601($M+H^+$).

[Example 149]

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



Sodium methoxide (76.8 mg) was added to a solution of the compound (190 mg) obtained in Example 148 in methanol (50 ml), and the mixture was stirred overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, the resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:methanol = 9:1) to obtain the title compound (130 mg).

Melting point: 190°C (decomposed).

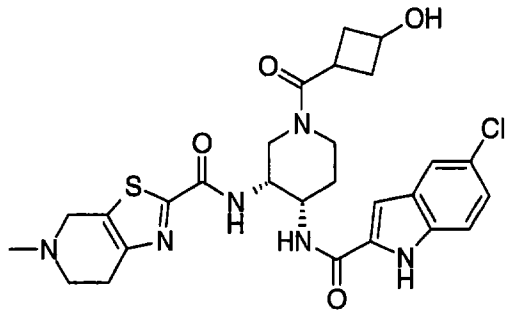
^{1}H-NMR ($CDCl_3$) δ: 1.53(3H,s), 1.56-1.78(5H,m), 2.34(1H,d,J=10.5Hz), 2.53(3H,s), 2.83-2.86(2H,m), 2.91-2.93(2H,m), 3.30(1H,d,J=12.5Hz), 3.75(2H,s), 4.28(1H,d,J=5.6Hz), 4.43(1H,s), 4.65(1H,d,J=13.5Hz), 4.95(1H,d,J=13.5Hz), 6.92(1H,d,J=1.5Hz), 7.20-7.23(1H,m), 7.33(1H,d,J=8.6Hz), 7.65(1H,d,J=2.0Hz), 8.43(1H,d,J=5.6Hz), 9.14(1H,s).

MS (FAB) m/z: 559($M+H^+$).

[Example 150]

N-{(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-1-[(3-hydroxycyclobutyl)carbonyl]piperidin-3-yl}-5-methyl-

4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The compound (306 mg) obtained in Example 118, n-methylmorpholine (200 µl), 1-hydroxybenzotriazole monohydrate (87 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (197 mg) were added to a solution of the compound (117 mg) obtained Referential Example 152 in a mixed solvent of tetrahydrofuran (20 ml), methylene chloride (3.0 ml) and N,N-dimethylformamide (2.0 ml), and the mixture was stirred at room temperature for 3 days. The reaction mixture was diluted with methylene chloride, and a saturated aqueous solution of sodium hydrogencarbonate was added to separate the mixture into two layers. The resultant organic layer was washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 10:1) to obtain a free base (207 mg) of the title compound. The free base was treated with a 1N ethanol solution of hydrochloric acid to obtain the title compound.

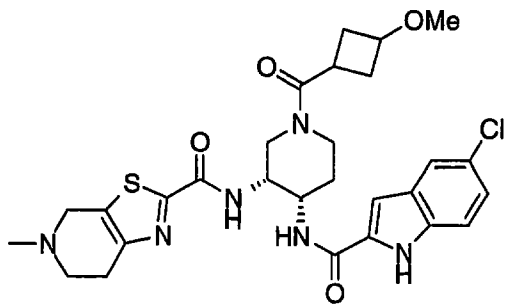
Melting point: 200°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.78-2.10(4H,m), 2.24-2.68(3H,m), 2.75-5.20(14H,m), 2.91(3H,s), 7.08(0.5H,s), 7.09(0.5H,s), 7.18(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.70(1H,d,J=2.0Hz), 8.05-8.28(1H,br), 8.38(0.5H,br.d,J=7.3Hz), 8.43(0.5H,br.d,J=8.3Hz), 10.80-11.25(1H,br), 11.84(1H,br.s).

MS (ESI) m/z: 571($M+H^+$).

[Example 151]

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



The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 154 in a similar manner to Example 150.

Melting point: 191°C (decomposed).

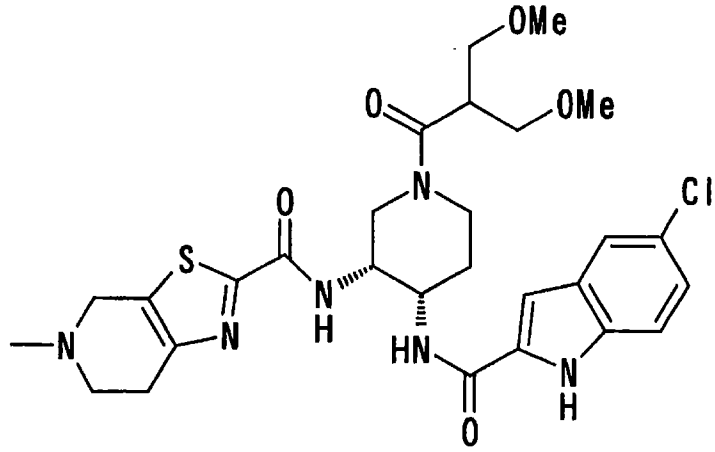
^{1}H-NMR (DMSO-d_6) δ: 1.69-2.23(4H,m), 2.25-2.40(1H,m), 2.71-2.84(0.5H,m), 2.89-3.93(9.5H,m), 2.91(3H,s), 3.01(1H,s), 3.14(2H,s), 4.05-4.80(5H,m), 7.09(1H,s), 7.18(1H,d,J=8.4Hz), 7.42(1H,d,J=8.4Hz), 7.70(1H,s), 8.00-8.30(1H,br), 8.36-8.53(1H,m), 11.25-11.75(1H,br),

11.85(1H,br.s).

MS (ESI) m/z: 585($M+H^+$).

[Example 152]

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



The title compound was obtained by condensing a carboxylic acid obtained by hydrolysis of the compound obtained in Referential Example 155 with the compound obtained in Example 118 in a similar manner to Example 150.

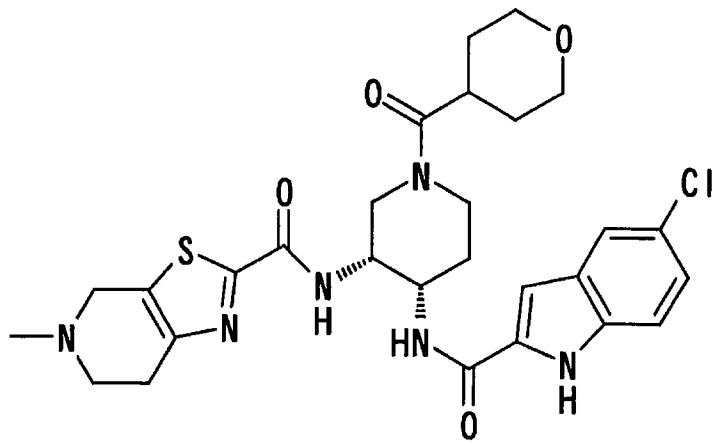
Melting point: 178-184°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.69-1.82(1H,m), 1.84-2.04(1H,m), 2.91(3H,s), 3.00-3.75(17H,m), 3.95-4.55(5H,m), 4.60-4.80(1H,m), 7.10(1H,br.s), 7.18(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.69(0.5H,br.s), 7.71(1H,br.s), 8.18-8.28(1H,br), 8.35-8.50(1H,br), 11.83(1H,br.s).

MS (ESI) m/z: 603($M+H^+$).

[Example 153]

N-[(3R*,4S*)-4-{[(5-Chloroindol-2-yl)carbonyl]amino}-(tetrahydro-2H-pyran-4-ylcarbonyl)piperidin-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and the compound obtained in Referential Example 156 in a similar manner to Example 150.

Melting point: 225-248°C (decomposed).

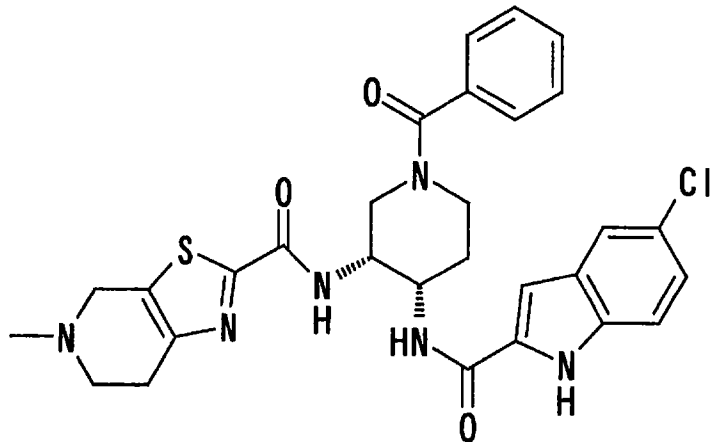
^{1}H-NMR (DMSO-d_6) δ: 1.55-1.68(4H,m), 1.70-1.85(1H,m), 1.85-2.05(1H,m), 2.60-2.95(1H,m), 2.89(3H,s), 2.95-3.20(3H,m), 3.20-4.00(9H,m), 4.00-4.80(4H,m), 7.08(1H,s), 7.17(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.71(1H,s), 8.00-8.30(1H,m), 8.35-8.50(1H,m), 11.16(1H,br.s), 11.85(1H,s).

MS (ESI) m/z: 585($M+H^+$).

[Example 154]

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

hydrochloride:



The title compound was obtained from the compound obtained in Example 118 and benzoyl chloride in a similar manner to Example 100.

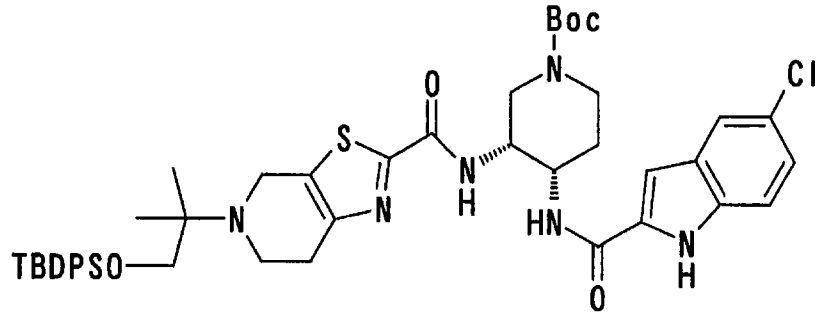
Melting point: 215-225°C (decomposed).

^{1}H-NMR (DMSO-d_6) δ: 1.75-1.90(1H,m), 1.90-2.20(1H,m), 2.93(3H,s), 3.10-4.00(8H,m), 4.05-4.80(4H,m), 7.00-7.60(5H,m), 7.08(1H,s), 7.16(1H,dd,J=8.8,1.6Hz), 7.40(1H,d,J=8.8Hz), 7.71(1H,d,J=1.6Hz), 8.31(1H,br.s), 8.46(1H,br.s), 11.39(1H,br.s),11.86(1H,s).

MS (FAB) m/z: 577($M+H^+$).

[Example 155]

tert-Butyl (3R*,4S*)-3-({[5-(2-{[tert-butyl(diphenyl)-silyl]oxy}-1,1-dimethylethyl)-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridin-2-yl]carbonyl}amino)-4-{[(5-chloroindol-2-yl)carbonyl]amino}piperidine-1-carboxylate:



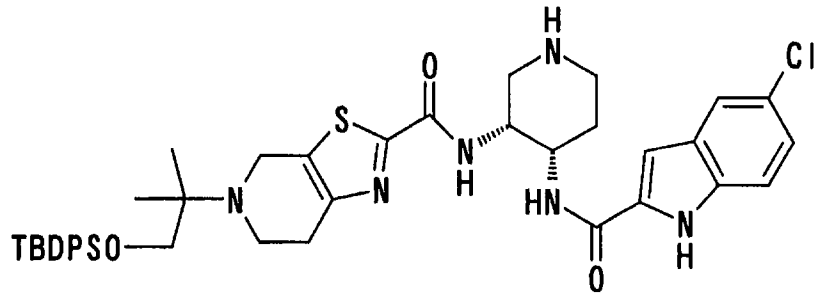
The title compound was obtained from the compound obtained in Referential Example 207 and the compound obtained in Referential Example 42 in a similar manner to Example 91.

^{1}H-NMR (DMSO-d_6) δ: 1.00(9H,s), 1.12(6H,s), 1.15-1.50(9H,m), 1.63-1.75(1H,m), 1.82-2.00(1H,m), 2.60-2.80(3H,m), 2.83-2.95(2H,m), 3.12-3.30(1H,m), 3.30(2H,s), 3.58(2H,s), 3.85-4.10(2H,m), 4.19(1H,br.s), 4.37(1H,br.s), 7.04(1H,s), 7.16(1H,d,J=9.0Hz), 7.30-7.50(7H,m), 7.50-7.65(4H,m), 7.70(1H,s), 7.99(1H,d,J=6.8Hz), 8.45(1H,br.s), 11.82(1H,s).

MS(ESI)m/z:869$(M+H)^+$

[Example 156]

5-(2-{[tert-Butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-N-((3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-piperidin-3-yl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide dihydrochloride:



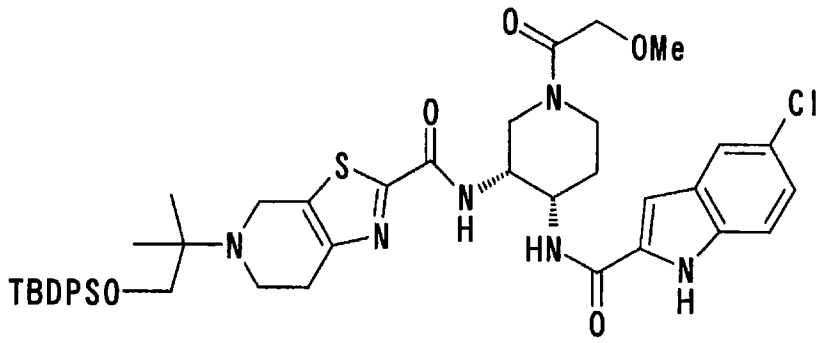
The title compound was obtained by treating the compound obtained in Example 155 in a similar manner to Example 95.

^{1}H-NMR (DMSO-d_6) δ: 1.04(9H,s), 1.43, 1.48(total 6H,each s), 1.85-2.00(1H,m), 2.05-2.20(1H,m), 2.95-3.20(2H,m), 3.25-3.60(6H,m), 3.80-3.90(1H,m), 3.95-4.05(1H,m), 4.45-4.55(1H,m), 4.60-4.85(3H,m), 7.10-7.20(2H,m), 7.35-7.55(7H,m), 7.55-7.75(5H,m), 8.52(1H,dd,J=14.4,7.8Hz), 8.93(1H,br), 9.20-9.40(2H,m), 11.30-11.50(1H,m), 11.87,11.92(total 1H,each s).

MS (ESI) m/z: 769($M+H^+$).

[Example 157]

5-(2-{[tert-Butyl(diphenyl)silyl]oxy}-1,1-dimethylethyl)-N-[(3R*,4S*)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-yl]-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine-2-carboxamide:



The title compound was obtained from the compound obtained in Example 156 and methoxyacetyl chloride in a similar manner to Example 100.

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.20(6H,s), 1.60-1.85(1H,m), 2.25-2.40(1H,m), 2.36(2H,s), 2.70-3.20(4H,m), 3.20-3.55(4H,m), 3.55-3.70(2H,m), 3.95-4.10(3H,m), 4.10-4.90(4H,m), 6.90(1H,d,J=1.5Hz), 7.15-7.30(2H,m), 7.30-7.50(6H,m), 7.60-7.70(5H,m), 8.15-8.22(1H,m), 8.46(1H,d,J=5.1Hz), 9.28(1H,s).

MS (ESI) m/z: 842($M+H^+$).

[Example 158]

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

