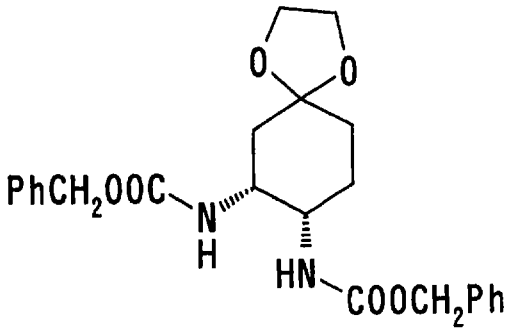
Benzyl (7R*,8S*)-7-{[(benzyloxy)carbony]amino}-1,4-dioxaspiro[4.5]dec-8-ylcarbamate:



The compound (4.0 g) obtained in Referential Example 116 was dissolved in absolute tetrahydrofuran (30 ml), and ethylene glycol (5.6 ml) and p-toluenesulfonic acid (192 mg) were added to stir the mixture at room temperature for 17 hours. The reaction mixture was poured into a saturated aqueous solution of sodium hydrogencarbonate and extracted with ethyl acetate. The resultant 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 (ethyl acetate:hexane = 1:1) to obtain the title compound (4.23 g).

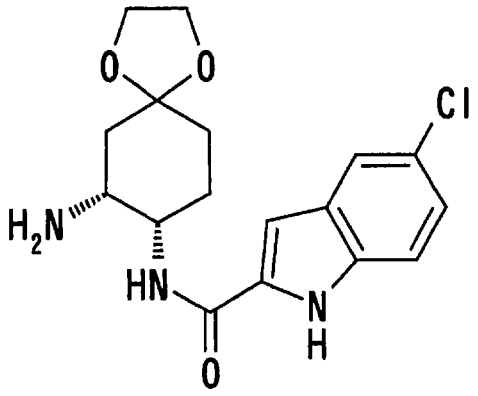
^{1}H-NMR ($CDCl_3$) δ: 1.65-1.71(4H,m), 2.00(1H,m), 2.11(1H,m), 3.49(1H,m), 3.73(1H,m), 3.93(4H,s), 5.03(2H,q,J=12.2Hz), 5.08(2H,q,J=12.2Hz), 7.32(10H,s).

MS (ESI) m/z: 441$(M+H)^+$.

[Referential Example 120]

N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-

chloroindole-2-carboxamide and N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide:



N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide) and N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-7-amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide) were obtained from the compound obtained in Referential Example 119 in a similar manner to Referential Example 118.

N-[(7R*,8S*)-7-Amino-1,4-dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-8-amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide:

^{1}H-NMR ($CDCl_3$) δ: 1.68-1.81(4H,m), 2.11(2H,m), 2.87(1H,td,J=3.9,11.2Hz), 3.77(1H,m), 3.97(4H,s), 6.27(1H,d,J=7.6Hz), 6.80(1H,s), 7.24(1H,d,J=9.0Hz), 7.35(1H,d,J=9.0Hz), 7.61(1H,s), 9.47(br.s,1H).

MS (ESI) m/z: 350$(M+H)^+$.

N-[(7R*,8S*)-8-Amino-1,4-dioxaspiro[4.5]dec-7-yl]-5-chloroindole-2-carboxamide (or N-[(7R*,8S*)-7-amino-1,4-

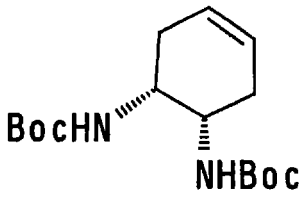
dioxaspiro[4.5]dec-8-yl]-5-chloroindole-2-carboxamide):

^{1}H-NMR ($CDCl_3$) δ: 1.65(2H,m), 1.88(1H,m), 1.96(1H,m), 2.31(1H,dd,J=12.9,3.2Hz), 2.96(1H,m), 3.98(1H,m), 4.02(4H,s), 4.12(1H,m), 6.77(1H,s), 7.06(1H,br.s), 7.23(1H,dd,J=8.8,2.0Hz), 7.37(1H,d,J=8.8Hz), 7.62(1H,d,J=2.0Hz), 9.49(1H,br.s).

MS (ESI) m/z: 350$(M+H)^+$.

[Referential Example 121]

tert-Butyl (1R,6S)-6-[(tert-butoxycarbonyl)amino]-3-cyclohexene-1-ylcarbamate:

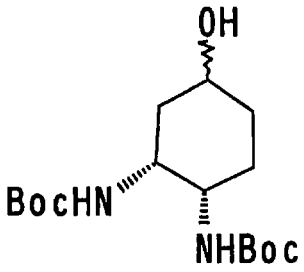


cis-4-Cyclohexene-1,2-diamine hydrochloride (4.0 g) was dissolved in a mixed solvent of water (40 ml) and acetonitrile (40 ml), and di-tert-butoxy carbonate (11.8 g) and triethylamine (12 ml) were added, and the mixture was stirred at room temperature for 4.5 hours. The reaction mixture was poured into water to conduct extraction with methylene chloride, and the resultant methylene chloride 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 (ethyl acetate:hexane = 1:4) to obtain the title compound (6.12 g).

^{1}H-NMR ($CDCl_3$) δ: 1.44(18H,s), 1.98(2H,dd,J=9.3,15.9Hz), 2.48(2H,br.d,J=15.9Hz), 3.66(2H,br.s), 4.88(2H,br.s), 5.58(2H,d,J=2.7Hz).

[Referential Example 122]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-hydroxycyclohexylcarbamate (mixture of stereoisomers):



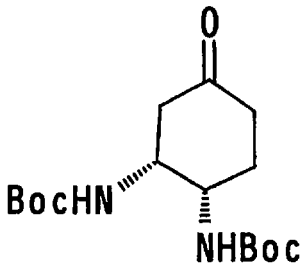
The compound (6.1 g) obtained in Referential Example 121 was dissolved in absolute tetrahydrofuran (40 ml), and borane-dimethyl sulfide complex (2.22 ml) was added under ice cooling. The mixture was stirred for 16 hours while gradually heating the mixture to room temperature as it is. Ice was added to the reaction mixture, and a 1N aqueous solution of sodium hydroxide and 30% aqueous hydrogen peroxide (50 ml) were added to stir the mixture at room temperature for 2 hours as it is. The reaction mixture was extracted with ethyl acetate, and 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 (ethyl acetate:hexane = 1:2 → 2:1) to obtain the title compound (6.1 g).

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 1.43(9H,s), 1.83-1.67(5H,m), 2.15(1H,m), 2.22(1H,s), 3.34(1H,m), 3.78(1H,m), 4.15(1H,s), 4.98(1H,q,J=9.0Hz), 5.02(1H,q,J=9.0Hz).

MS (ESI) m/z: 331$(M+H)^+$.

[Referential Example 123]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-oxocyclohexylcarbamate:



Oxalyl chloride (8.2 ml) and dimethyl sulfoxide (6.8 ml) were dissolved in methylene chloride (100 ml) at -60°C, and a solution of the compound (mixture of stereoisomers) (6.32 g) obtained in Referential Example 122 in tetrahydrofuran (80 ml) was added at a time, and the mixture was stirred for 1 hour. The temperature of the mixture was raised to -40°C, and triethylamine (21 ml) was added. The mixture was heated to room temperature. After 3 hours, the reaction mixture was poured into water and extracted with methylene chloride. The resultant 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 (ethyl acetate: hexane = 1:1) to obtain the title

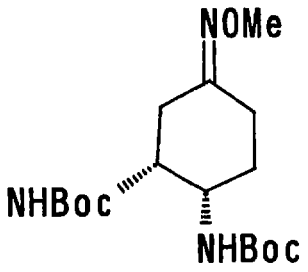
compound (3.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.44(9H,s), 2.24-2.36(3H,m), 2.39-2.44(2H,m), 2.75(1H,dd,J=14.6,2.9Hz), 3.66-3.81(2H,m), 4.95-4.90(1H,m), 4.97-5.03(1H,m).

MS (ESI) m/z: 329$(M+H)^+$.

[Referential Example 124]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-(methoxyimino)cyclohexylcarbamate:



The compound (1.5 g) obtained in Referential Example 123 was dissolved in methanol (30 ml), and O-methylhydroxyamine hydrochloride (572 mg) and pyridine (737 ml) were added to stir the mixture at room temperature for 17 hours. After the reaction mixture was concentrated, water was added to conduct extraction with ethyl acetate. The resultant 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 (ethyl acetate:hexane = 1:4) to obtain the title compound (1.52 g).

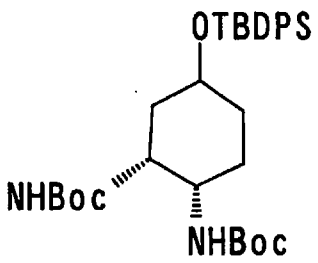
^{1}H-NMR ($CDCl_3$) δ: 1.44(18H,s), 1.64(1H,m), 2.16(2H,m),

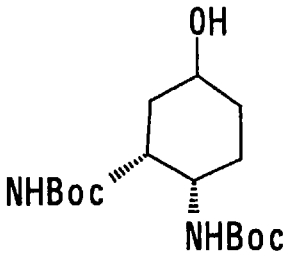
2.44(1H,m), 3.45-3.63(3H,m), 3.82(3H,s), 4.93(1H,m).

MS (ESI) m/z: 358$(M+H)^+$.

[Referential Example 125]

tert-Butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}cyclohexylcarbamate (Stereoisomer A):



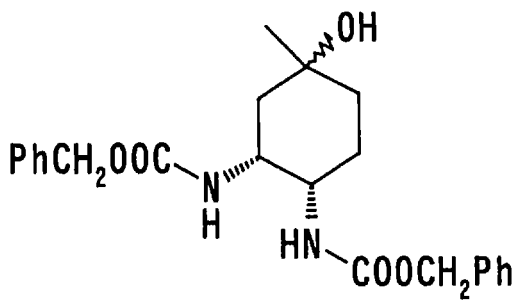


The title compound was obtained from the compound (mixture of stereoisomers) obtained in Referential Example 122 in a similar manner to Referential Example 58, and tert-butyl (1R*,2S*)-2-[(tert-butoxycarbonyl)amino]-5-hydroxycyclohexylcarbamate (Stereoisomer B) was recovered.

^{1}H-NMR ($CDCl_3$) δ: 1.03(9H,s), 1.39(9H,s), 1.40(9H,s), 1.72(1H,m), 1.86(1H,m), 2.13(1H,m), 3.24(2H,m), 3.65(1H,m), 4.83(1H,m), 7.37(10H,m).

[Referential Example 126]

Benzyl (1R*,2S*)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-5-methylcyclohexylcarbamate:



Anhydrous cerium chloride (6.4 g) was suspended in tetrahydrofuran (50 ml), and the suspension was cooled to -78°C in an argon atmosphere. A methyllithium solution (1.14N diethyl ether solution, 22.5 ml) was added to the suspension, and the mixture was stirred at -78°C for 30 minutes. A tetrahydrofuran solution (50 ml) of the compound (3.0 g) obtained in Referential Example 116 was added dropwise at -78°C, and the mixture was stirred for 30 minutes. The reaction mixture was poured into a 3% aqueous solution (100 ml) of acetic acid, and diethyl ether (50 ml) was added to stir the mixture at room temperature for 10 minutes. The reaction mixture was extracted with ethyl acetate, and the resultant 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 twice by column chromatography on silica gel (methanol:chloroform = 0:100 - 1:19) to obtain the title compound (Stereoisomer A) (780 mg) and the title compound (Stereoisomer B) (1.1 g).

Stereoisomer A:

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,s), 1.27-2.08(6H,m), 3.48(1H,br.s), 3.59(1H,br.s), 5.02-5.09(5H,m), 5.33(1H,br.s), 7.30-7.32(10H,s)

MS (FAB) m/z: 413$(M+H)^+$.

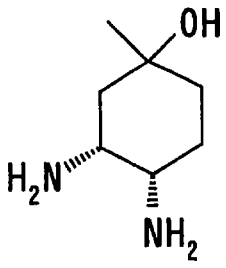
Stereoisomer B:

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,s), 1.29-2.07(6H,m), 3.39(1H,br.s), 3.82(1H,br.s), 5.02-5.23(6H,m), 7.30(10H,s)

MS(FAB) m/z: 413$(M+H)^+$.

[Referential Example 127]

($3R^*$,$4S^*$)-3,4-Diamino-1-methylcyclohexanol (Stereoisomer A)



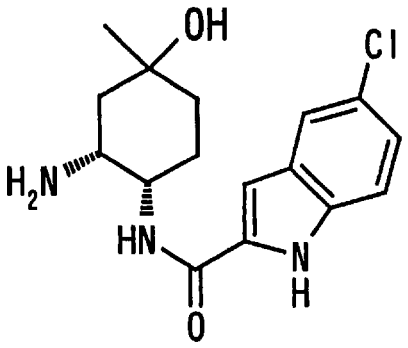
10% Palladium on carbon (350 mg) was suspended in a methanol solution (100 ml) of the compound (Stereoisomer A) (780 mg) obtained in Referential Example 126, and the suspension was stirred for 5 hours in a hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. After the residue was dissolved in methylene chloride (100 ml), and the solution was dried over anhydrous sodium sulfate, the solvent was distilled off to obtain the title compound (Stereoisomer A) (190 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.22(3H,s), 1.25-2.48(11H,m),

2.62(1H,br.s), 2.78(1H,br.s).

[Referential Example 128]

Mixture of N-[(1R*,2S*)-2-Amino-4-hydroxy-4-methylcyclohexyl]-5-chloroindole-2-carboxamide (Stereoisomer A) and N-[(1R*,2S*)-2-amino-5-hydroxy-5-methylcyclohexyl]-5-chloroindole-2-carboxamide (Stereoisomer A):

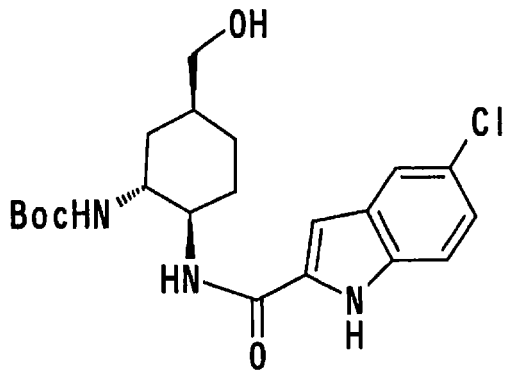


The title compound was obtained from the compound (Stereoisomer A) obtained in Referential Example 127 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 59.

^{1}H-NMR ($CDCl_3$) δ: 1.32(3H,s), 1.34-2.29(6H,m), 4.42-4.70(4H,br), 7.13(2H,s), 7.50(2H,s), 8.00(1H,s), 11.0(1H,br).

[Referential Example 129]

tert-Butyl (1R*,2R*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexylcarbamate:



1) Ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)-amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}-cyclohexanecarboxylate was obtained from the (1R*,3S*,4S*)-form obtained in Referential Example 89 in a similar manner to the process described in Referential Examples 90 and 91.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.72(6H,m), 2.15-2.28(2H,m), 2.41-2.49(1H,m), 2.85(1H,brs), 3.62-3.75(1H,m), 3.78-3.92(1H,m), 4.12-4.28(2H,m), 4.56-4.63(1H,m), 6.88(1H,brs), 7.20(1H,dd,J=8.8 and 2.0Hz), 7.33(1H,d,J=8.8Hz), 7.52-7.57(1H,m), 7.59(1H,d,J=2.0Hz), 9.24(1H,s).

MS (ESI) m/z: 464$(M+H)^+$.

2) The product (735 mg) obtained above was dissolved in methylene chloride (10 ml), a 1N hexane solution (5 ml) of diisobutylalminium hydride was added at -78°C, and the mixture was stirred for 3 hours and then 30 minutes at 0°C. A saturated aqueous solution of ammonium chloride was added at -78°C, the mixture was extracted with methylene chloride, and the resultant organic layer was washed with

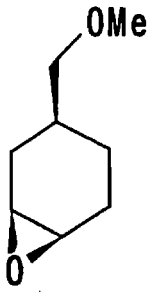
a saturated aqueous solution of sodium bicarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 19:1) to obtain the title compound (480 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.20-2.30(7H,m), 3.60-3.86(4H,m), 4.64(1H,br.s), 6.87(1H,s), 7.20-7.48(3H,m), 9.15(1H,br.s).

MS(ESI) m/z: 422$(M+H)^+$.

[Referential Example 130]

(1R*,3R*,6S*)-3-(Methoxymethyl)oxabicyclo[4.1.0]heptane:



1) (1R*,4R*,5R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (2.8 g) was dissolved in a mixed solvent of tetrahydrofuran (27 ml) and water (3 ml), concentrated hydrochloric acid (0.1 ml) was added, and the mixture was heated under reflux for 1 hour. The solvent was distilled off under reduced pressure to obtain (1R*,3R*,4R*)-3-hydroxy-4-iodocyclohexanecarboxylic acid (3.23 g) as a colorless solid.

2) The product (3.22 g) obtained by the reaction described above was dissolved in tetrahydrofuran (50 ml), borane-dimethyl sulfide complex (2 M tetrahydrofuran solution, 47 ml) was added under ice cooling, and the mixture was stirred at room temperature for 12 hours. The solvent was distilled off under reduced pressure, the residue was dissolved in isopropanol (10 ml), a 1N aqueous solution (12 ml) of sodium hydroxide was added, and the mixture was stirred for 12 hours. After the solvent was concentrated to about 1/5, the reaction mixture was diluted

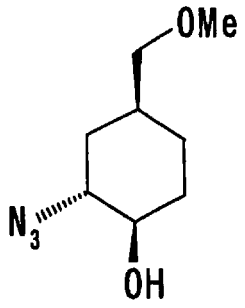
with water and methylene chloride to stir it for 10 minutes. An organic layer was separated, successively washed with a saturated aqueous solution of ammonium chloride and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2) to obtain (1R*,3R*,6S*)-7-oxabicyclo[4.1.0]hept-3-ylmethanol (1.25 g) as a colorless oil.

3) The product (4.63 g) obtained by the reaction in 2) was dissolved in tetrahydrofuran (50 ml), potassium bis(trimethylsilyl)amide (0.5N toluene solution, 80 ml) was added to the solution at -78°C. After stirring at same temperature for 10 minutes, methyl iodide (2.93 ml) was added. After heating the mixture to 0°C, it was stirred for 1 hour, quenched with a saturated aqueous solution of ammonium chloride and then diluted with diethyl ether. An organic layer was separated, washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (3.7 g).

^{1}H-NMR ($CDCl_3$) δ: 0.89-1.63(5H,m), 1.80-2.05(2H,m), 1.89-3.06(4H,m), 3.16(3H,s).

[Referential Example 131]

(1R*,2R*,4S*)-2-Azido-4-(methoxymethyl)cyclohexanol:

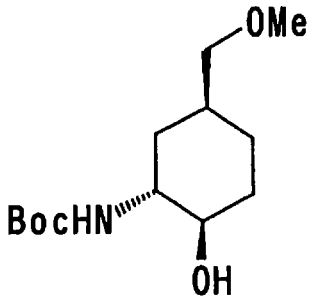


The title compound was obtained from the compound obtained in Referential Example 130 in a similar manner to Referential Example 87.

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.70(5H,m), 1.77-1.95(2H,m), 1.98-2.08(1H,m), 3.30(2H,d,J=6.8Hz), 3.35(3H,s), 3.45-3.65(2H,m).

[Referential Example 132]

tert-Butyl (1R*,2R*,5S*)-2-hydroxy-5-(methoxymethyl)-cyclohexylcarbamate:



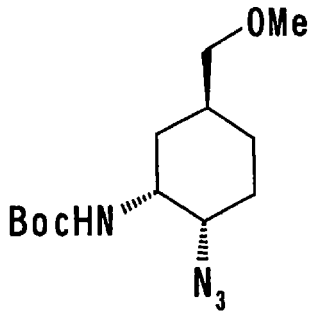
The title compound was obtained from the compound obtained in Referential Example 131 in a similar manner to Referential Example 88.

^{1}H-NMR ($CDCl_3$) δ: 1.35-2.01(16H,m), 3.05(1H,br.s), 3.32(2H,d,J=7.1Hz), 3.34(3H,s), 3.44-3.62(2H,m),

4.59(1H,br.s).

[Referential Example 133]

tert-Butyl (1R*,2S*,5S*)-2-azido-5-(methoxymethyl)-cyclohexylcarbamate:

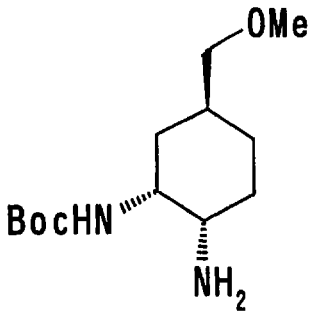


The title compound was obtained from the compound obtained in Referential Example 132 through the methansulfonate thereof in a similar manner to Referential Example 89.

^{1}H-NMR ($CDCl_3$) δ: 1.31-1.93(16H,m), 3.27(2H,d,J=6.4Hz), 3.32(3H,s), 3.57-3.70(1H,m), 3.67(1H,br.s), 3.95(1H,br.s).

[Referential Example 134]

tert-Butyl (1R*,2S*,5S*)-2-amino-5-(methoxymethyl)-cyclohexylcarbamate:

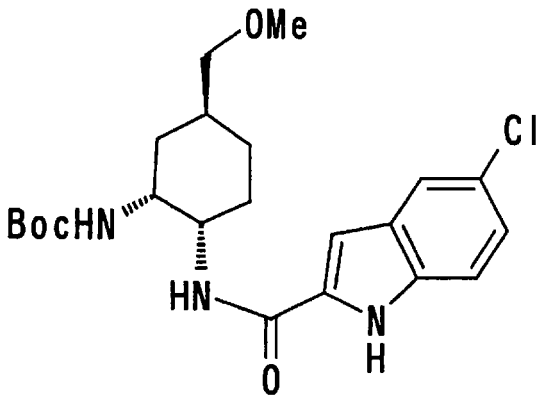


The title compound was obtained from the compound obtained in Referential Example 133 in a similar manner to

Referential Example 90.

[Referential Example 135]

tert-Butyl (1R*,2S*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(methoxymethyl)cyclohexylcarbamate:



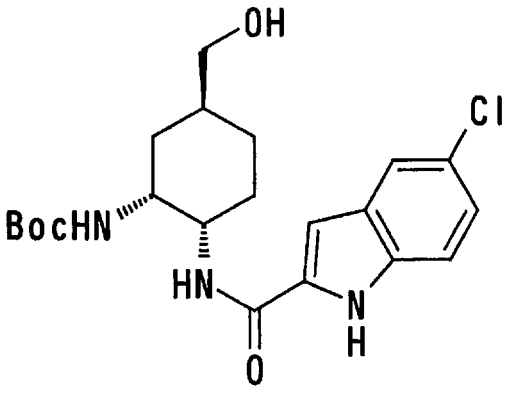
The title compound was obtained from the compound obtained in Referential Example 134 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.12-2.31(16H,m), 3.14-3.30(2H,m), 3.34(3H,s), 3.92(1H,br.s), 4.13(1H,br.s), 4.88(1H,br.s), 6.82(1H,s), 7.21(1H,br.d,J=8.8Hz), 7.33(1H,d,J=8.8Hz), 7.60(1H,s), 8.09(1H,br.s), 9.42(1H,br.s).

MS (ESI) m/z: 436$(M+H)^+$.

[Referential Example 136]

tert-Butyl (1R*,2S*,5S*)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexylcarbamate:



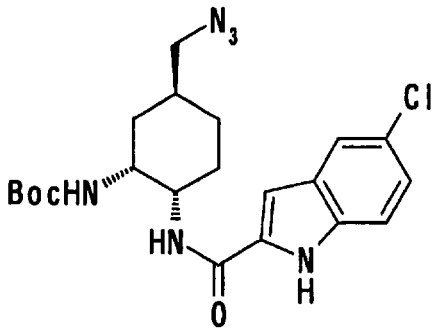
The title compound was obtained from the compound obtained in Referential Example 91 in a similar manner to Referential Example 129.

^{1}H-NMR ($CDCl_3$) δ: 0.78-2.30(16H,m), 3.41-3.59(3H,m), 3.86-3.95(1H,m), 4.12-4.20(1H,m), 4.82-4.91(1H,m), 6.81(1H,s), 7.17-7.40(2H,m), 7.60(1H,s), 8.03(1H,br.s), 9.18(1H,br.s).

MS (ESI) m/z: 422$(M+H)^+$.

[Referential Example 137]

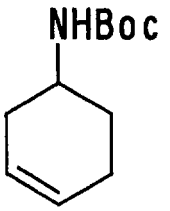
tert-Butyl (1R*,2S*,5S*)-5-(azidomethyl)-2-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexylcarbamate:



The title compound was obtained from the compound obtained in Referential Example 136 in a similar manner to Referential Example 80.

[Referential Example 138]

tert-Butyl 3-cyclohexen-1-ylcarbamate:

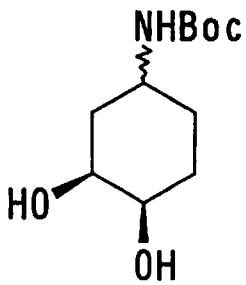


3-Cyclohexene-1-carboxylic acid (25.3 g) was dissolved in tert-butanol (250 ml), triethylamine (28 ml) and diphenylphosphorylazide (43.0 ml) were added, and the mixture was stirred for 1 hour at room temperature and 2 days at 90°C. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride) and then repurified by column chromatography on silica gel (hexane:ethyl acetate = 20:1) to obtain the title compound (24.9 g).

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.45-1.60(1H,m), 1.80-1.90(2H,m), 2.05-2.20(2H,m), 2.35-2.45(1H,m), 3.78(1H,br), 4.56(1H,br), 5.55-5.65(1H,m), 5.65-5.75(1H,m).

[Referential Example 139]

tert-Butyl (3R*,4S*)-3,4-dihydroxycyclohexylcarbamate:



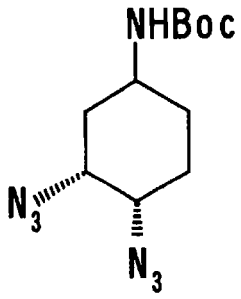
The compound (1.24 g) obtained in Referential Example 138 was dissolved in a mixed solvent of acetonitrile (15 ml) and water (5 ml), N-methylmorpholine N-oxide (0.90 g) and microcapsulated 10% osmium tetroxide(1 g) were added, and the mixture was stirred at about 80°C for a day. After insoluble matter was removed by filtration, the filtrate was concentrated under reduced pressure. The thus-obtained residue was purified by column chromatography on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (1.28 g).

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.30(1/2H,m), 1.35-2.00(15H,m), 2.15-2.30(3/2H,m), 2.40-2.60(1H,m), 3.64(1H,br), 3.75-3.90(3/2H,m), 4.00(1/2H,br).

MS (FAB) m/z: 232$(M+H)^+$.

[Referential Example 140]

tert-Butyl ($3R^*$,$4S^*$)-3,4-diazidocyclohexylcarbamate (Stereoisomer A and Stereoisomer B):



The title compounds (Stereoisomer A and Stereoisomer B) were obtained from the compound obtained in Referential Example 139 in a similar manner to Referential Example 80.

Stereoisomer A:

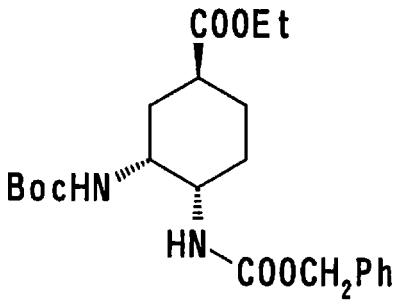
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.40-1.55(1H,m), 1.55-1.80(3H,m), 1.95-2.15(2H,m), 3.53(1H,m), 3.59(1H,br), 3.80(1H,m), 4.70(1H,br).

Stereoisomer B:

^{1}H-NMR ($CDCl_3$) δ: 1.27(1H,m), 1.44(9H,s), 1.40-1.55(1H,m), 1.80-2.00(2H,m), 2.00-2.15(1H,m), 2.21(1H,m), 3.48(1H,m), 3.77(1H,br), 3.89(1H,br), 4.34(1H,br).

[Referential Example 141]

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



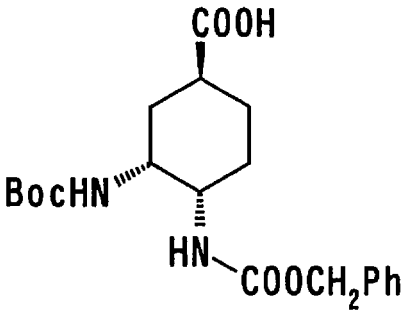
The compound (3.10 g) obtained in Referential Example 96 was dissolved in tetrahydrofuran (50 ml), and a saturated aqueous solution (50 ml) of sodium hydrogencarbonate was added. After benzyloxycarbonyl chloride (1.71 ml) was added dropwise to the reaction mixture under ice cooling, the mixture was stirred at room temperature for 4 days. Ethyl acetate (200 ml) and water (200 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. Solids deposited

were collected by filtration to obtain the title compound (3.24 g).

^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t,J=7.1Hz), 1.29-1.44(1H,m), 1.44(9H,s), 1.51-1.64(1H,m), 1.72-2.10(4H,m), 2.27-2.43(1H,m), 3.60-3.73(1H, m), 4.00-4.18(3H, m), 4.62(1H,br.s), 5.01-5.13(2H,m), 5.26(1H, br.s), 7.27-7.38(5H, m).

[Referential Example 142]

(1S,3R,4S)-4-{[(Benzyloxy)carbonyl]amino}-3-[(tert-butoxycarbonyl)amino] cyclohexanecarboxylic acid:



The compound (620 mg) obtained in Referential Example 141 was dissolved in tetrahydrofuran (20 ml), and an aqueous solution (10 ml) of lithium hydroxide monohydrate (93 mg) was added to stir the mixture at room temperature for 16 hours. After lithium hydroxide monohydrate (217 mg) was additionally added to the reaction mixture, and the mixture was stirred at room temperature for 2 hours, the reaction mixture was neutralized with 1N hydrochloric acid and extracted with methylene chloride. An organic layer was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The

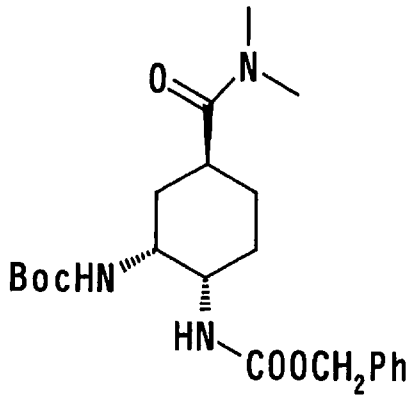
solvent was distilled off under reduced pressure to obtain the title compound (600 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.22-2.20(6H, m), 1.44(9H,s), 2.45(1H,br.s), 3.60-3.80(1H,br), 4.09(1H,br.s), 4.66 (1H,br.s), 5.00-5.20(2H,m), 5.26(1H,br.s), 7.20-7.40(5H,m).

MS (ESI) m/z: 393$(M+H)^+$.

[Referential Example 143]

Benzyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)amino]-4-[(dimethylamino)carbonyl]cyclohexylcarbamate:



After the compound (600 mg) obtained in Referential Example 142 and dimethylamine hydrochloride (240 mg) were suspended in methylene chloride (50 ml), a proper amount of tetrahydrofuran was added to the suspension to prepare a solution. To this solution were added triethylamine (0.41 ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (422 mg) and 1-hydroxybenzotriazole monohydrate (338 mg), and the mixture was stirred at room temperature for 1 hour. Dimethylamine hydrochloride (480 mg) and triethylamine (0.82 ml) were additionally added to the reaction mixture to stir the mixture at room

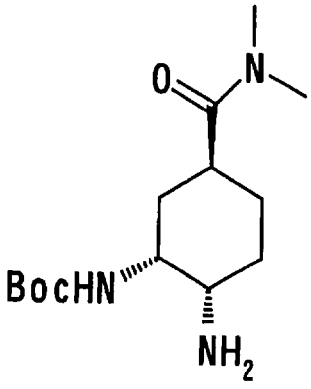
temperature for additional 18 hours. The reaction mixture was poured into water to separate an organic layer. After the organic layer was washed with 1N hydrochloric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 3:47 → 2:23) to obtain the title compound (620 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50(2H,m), 1.44(9H,s), 1.50-2.10(4H,m), 2.60(1H,br.t,J=11.6Hz), 2.93(3H,s), 3.02(3H,s), 3.70(1H,br.s), 4.14(1H,br.s), 4.65(1H,br.s), 5.00-5.30(3H,m), 7.26-7.40(5H,m).

MS (ESI) m/z = 420$(M+H)^+$.

[Referential Example 144]

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



10% Palladium on carbon (57 g) was added to a solution of the compound (190 g) obtained in Referential Example 143 in methanol (8000 ml), and the mixture was

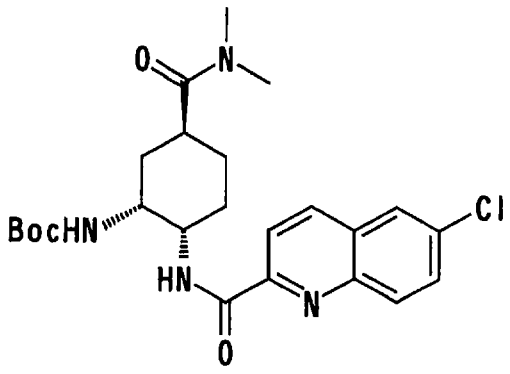
stirred for 3 hours under a hydrogen pressure (7 atm). After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. After toluene was added to the residue, and the mixture was concentrated under reduced pressure, hexane (2500 ml) was added to solidify a product. The product was collected by filtration and dried to obtain the title compound (121 g).

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.77(6H,m), 1.45(9H,s), 2.20-2.35(1H,br), 2.63-2.74(1H,m), 2.92(3H,s), 3.02(3H,s), 3.02-3.11(2H,m), 3.74-3.82(1H,m), 4.88-5.00(1H,br).

MS (ESI) m/z: 286$(M+H)^+$.

[Referential Example 145]

tert-Butyl (1R,2S,5S)-2-{[(6-chloroquinolin-2-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 54 in a similar manner to Referential Example 91.

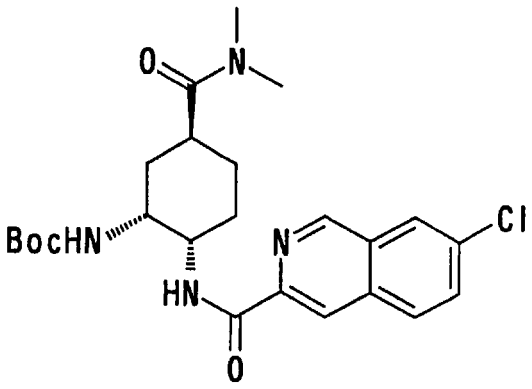
^{1}H-NMR ($CDCl_3$) δ: 1.41(9H,br), 1.50-1.70(1H,m), 1.75-

1.95(2H,m), 1.95-2.25(3H,m), 2.65-2.80(1H,m), 2.96(3H,s), 3.07(3H,s), 4.15-4.30(1H,m), 4.30-4.40(1H,m), 4.95(1H,br), 7.66(1H,d,J=8.8Hz), 7.84(1H,s), 8.00(1H,d,J=8.8Hz), 8.19(1H,d,J=8.6Hz), 8.30(1H,d,J=8.6Hz).

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

[Referential Example 146]

tert-Butyl (1R,2S,5S)-2-{[(7-chloroquinolin-3-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 57 in a similar manner to Referential Example 91.

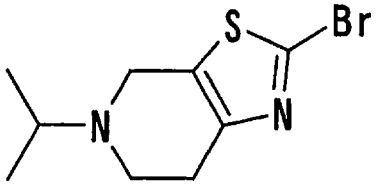
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.65(10H,br), 1.75-1.90(2H,m), 1.90-2.25(3H,m), 2.65-2.90(1H,br), 2.96(3H,s), 3.08(3H,s), 4.20-4.30(1H,m), 4.30-4.40(1H,m), 4.93(1H,br), 7.68(1H,m), 7.90(1H,br), 7.99(1H,s), 8.35-8.70(2H,m), 9.01(1H,br).

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

[Referential Example 147]

2-Bromo-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-

pyridine:

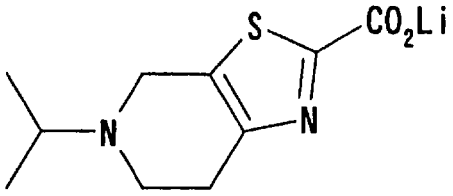


The title compound was obtained from the compound obtained in Referential Example 8 in a similar manner to Referential Example 9.

^{1}H-NMR ($CDCl_3$) δ: 1.13(6H,d,J=6.5Hz), 2.86(4H,s), 2.89-3.00(1H,m), 3.70(2H,s).

[Referential Example 148]

Lithium 5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:

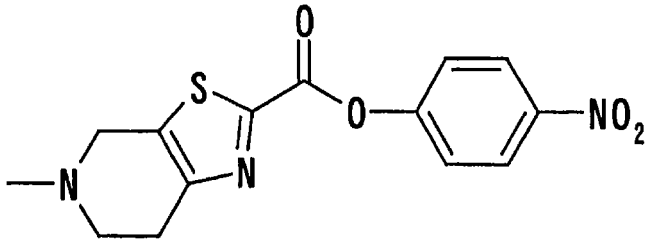


The title compound was obtained from the compound obtained in Referential Example 147 in a similar manner to Referential Example 10.

^{1}H-NMR (DMSO-d_6) δ: 1.05(6H,d,J=6.4Hz), 2.68-2.70(2H,m), 2.75-2.77(2H,m), 2.87-2.93(1H,m), 3.66(2H,s).

[Referential Example 149]

4-Nitrophenyl 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxylate:



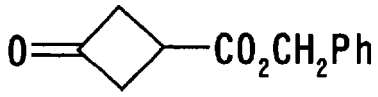
The title compound was obtained from the compound obtained in Referential Example 10 and p-nitrophenol in a similar manner to Referential Example 52.

^{1}H-NMR ($CDCl_3$) δ: 2.55(3H,s), 2.88(2H,t,J=5.7Hz), 3.06-3.12(2H,m), 3.80(2H,s), 7.46(2H,d,J=9.3Hz), 8.32(2H,d,J=9.3Hz).

MS (ESI) m/z: 320($M+H^+$).

[Referential Example 150]

Benzyl 3-oxocyclobutanecarboxylate:



Triethylamine (2.0 ml) and benzyl bromide (1.2 ml) were added to a solution of 3-oxocyclobutanecarboxylic acid (J. Org. Chem., Vol. 53, pp. 3841-3843, 1981) (995 mg) in tetrahydrofuran (5.0 ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate, and washed successively with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated saline and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was

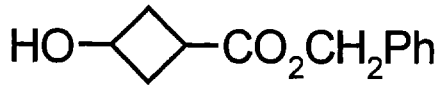
purified by column chromatography on silica gel (ethyl acetate:hexane = 1:6) to obtain the title compound (886 mg).

^{1}H-NMR ($CDCl_3$) δ: 3.22-3.33(3H,m), 3.37-3.48(2H,m), 5.19(2H,s), 7.31-7.42(5H,m).

MS (FAB) m/z: 205($M+H^+$).

[Referential Example 151]

Benzyl 3-hydroxycyclobutanecarboxylate:



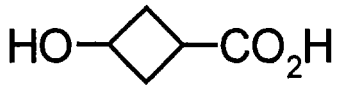
Sodium borohydride (76 mg) was added to a solution of the compound (781 mg) obtained in Referential Example 150 in a mixed solvent of tetrahydrofuran (10 ml) and methanol (0.5 ml) at 0°C, and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate, and washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:2) to obtain the title compound (770 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.13-2.27(3H,m), 2.55-2.71(3H,m), 4.14-4.23(1H,m), 5.12(2H,s), 7.28-7.39(5H,m).

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

[Referential Example 152]

3-Hydroxycyclobutanecarboxylic acid:

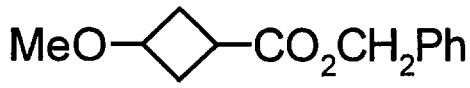


10% Palladium on carbon (108 mg) was added to a solution of the compound (706 mg) obtained in Referential Example 151 in ethanol (10 ml), and the mixture was stirred at room temperature for 2 hours in a hydrogen atmosphere. After the catalyst was removed by filtration through Celite, the filtrate was concentrated under reduced pressure to obtain the title compound (399 mg).

^{1}H-NMR (CD_3OD) δ: 2.00-2.21(2H,m), 2.41-2.61(3H,m), 4.01-4.13(1H,m).

[Referential Example 153]

Benzyl 3-methoxycyclobutanecarboxylate:



Methyl iodide (194 μl) and silver oxide (237 mg) were added to a solution of the compound (317 mg) obtained in Referential Example 151 in N,N-dimethylformamide (3.0 ml), and the mixture was stirred at 45°C for 1 hour. Methyl iodide (194 μl) and silver oxide (226 mg) were additionally added to the reaction mixture, and the mixture was stirred at 45°C for 16 hours. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by column

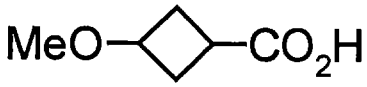
chromatography on silica gel (ethyl acetate:hexane = 1:10) to obtain the title compound (152 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.14-2.24(2H,m), 2.44-2.54(2H,m), 2.59-2.72(1H,m), 3.21(3H,s), 3.73-3.81(1H,m), 5.11(2H,s), 7.22-7.39(5H,m).

MS (ESI) m/z: 221($M+H^+$).

[Referential Example 154]

3-Methoxycyclobutanecarboxylic acid:

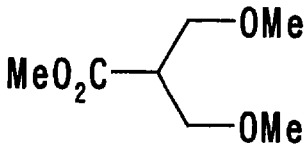


The title compound was obtained from the compound obtained in Referential Example 153 in a similar manner to Referential Example 152.

^{1}H-NMR ($CDCl_3$) δ: 2.17-2.27(2H,m), 2.48-2.58(2H,m), 2.62-2.73(1H,m), 3.25(3H,s), 3.76-3.86(1H,m), 8.60-9.30(1H,br).

[Referential Example 155]

Methyl 3-methoxy-2-(methoxymethyl)propionate:



Sodium methoxide (1.21 g) was added to a solution of methyl 2-(bromomethyl)acrylate (1.0 ml) in methanol (10 ml), and the mixture was heated under reflux for 26 hours. After cooling, the reaction mixture was diluted with diethyl ether, and precipitate was collected by filtration

and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (726 mg).

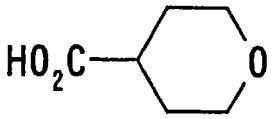
^{1}H-NMR ($CDCl_3$) δ: 2.90-2.96(1H,m), 3.34(6H,s), 3.57(2H,dd,J=9.3,5.9Hz), 3.64(2H,dd,J=9.3,6.6Hz), 3.73(3H,s).

^{13}C-NMR ($CDCl_3$) δ: 172.71, 70.31, 59.91, 46.49.

MS (ESI) m/z: 163($M+H^+$).

[Referential Example 156]

Tetrahydro-2H-pyrane-4-carboxylic acid:

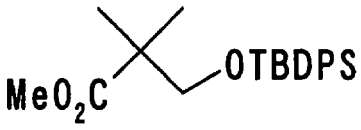


Dimethyl tetrahydro-4H-pyrane-4,4-dicarboxylate (4.04 g) was added to 20% hydrochloric acid (20 ml), and the mixture was heated under reflux for 19 hours. Water was added to the reaction mixture to conduct extraction with diethyl ether. After the resultant organic layer was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. After the resultant residue was solidified with hexane, the resultant solides were collected by filtration and washed to obtain the title compound (2.63 g).

^{1}H-NMR ($CDCl_3$) δ: 1.75-1.95(4H,m), 2.55-2.65(1H,m), 3.40-3.52(2H,m), 3.93-4.05(2H,m).

[Referential Example 157]

Methyl 3-{[tert-butyl(diphenyl)silyl]oxy}-2,2-dimethylpropionate:

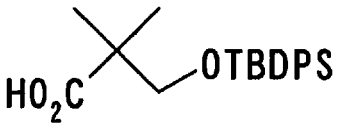


The title compound was obtained from methyl 2,2-dimethyl-3-hydroxypropionate in a similar manner to Referential Example 41.

^{1}H-NMR ($CDCl_3$) δ: 1.03(9H,s), 1.20(6H,s), 3.64-3.68(5H,m), 7.38-7.44(6H,m), 7.63-7.65(4H,m).

[Referential Example 158]

3-{[tert-Butyl(diphenyl)silyl]oxy}-2,2-dimethylpropionic acid:



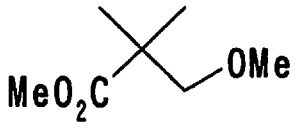
Water (0.24 ml) was added to a suspension composed of potassium tert-butoxide (5.32 g) and diethyl ether (100 ml) under ice cooling, and the mixture was stirred for 5 minutes. The compound (2.22 g) obtained in Referential Example 157 was added thereto, and the resultant mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was acidified with 1N hydrochloric acid and extracted 3 times with diethyl ether. After 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 (ethyl acetate:hexane = 1:6) to obtain the title compound (735 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.04(9H,d,J=0.7Hz), 1.22(6H,s), 3.65(2H,s), 7.36-7.45(6H,m), 7.64-7.66(4H,m).

[Referential Example 159]

Methyl 3-methoxy-2,2-dimethylpropionate:



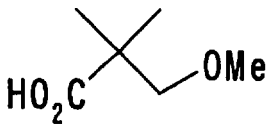
A solution of methyl 3-hydroxy-2,2-dimethylpropionate (25.0 g) in tetrahydrofuran (300 ml) was added dropwise to a suspension composed of a 60% oil suspension of sodium hydride (8.32 g) and tetrahydrofuran (100 ml) under ice cooling, and the mixture was stirred at 60°C for 1 hour. Methyl iodide (53.7 g) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 hours. Water was carefully added to conduct extraction twice with methylene chloride. After the resultant 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 resultant oil was distilled to obtain the title compound (12.8 g).

Boiling point: 140-142°C (ordinary pressure).

^{1}H-NMR ($CDCl_3$) δ: 1.19(6H,d,J=1.0Hz), 3.33(3H,d,J=1.0Hz), 3.38(2H,d,J=1.0Hz), 3.69(3H,d,J=1.0Hz).

[Referential Example 160]

3-Methoxy-2,2-dimethylpropionic acid:

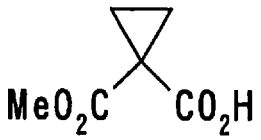


The title compound was obtained from the compound obtained in Referential Example 159 in a similar manner to Referential Example 158.

^{1}H-NMR ($CDCl_3$) δ: 1.22(6H,d,J=0.7Hz), 3.38(3H,d,J=0.7Hz), 3.40(2H,d,J=0.7Hz).

[Referential Example 161]

1-(Methoxycarbonyl)cyclopropanecarboxylic acid:



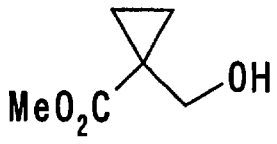
Dimethyl 1,1-cyclopropanecarboxylate (25 g) was dissloved in methanol (250 ml), and the solution was cooled with ice. A 1N aqueous solution of sodium hydroxide (158 ml) was then added dropwise, and the resultant mixture was warmed to room temperature and stirred overnight. After methanol was distilled off, the residue was washed with chloroform, and a water layer was cooled with ice, adjusted to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to obtain the title compound (16.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.76-1.80(2H,m), 1.82-1.88(2H,m),

3.79(3H,s), 12.73(1H,br).

[Referential Example 162]

Methyl 1-(hydroxymethyl)cyclopropanecarboxylate:



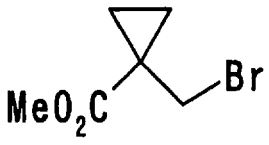
The compound (9.0 g) obtained in Referential Example 161 and triethylamine (9.7 ml) were dissolved in tetrahydrofuran (180 ml), and the solution was cooled to -10°C, to which isobutyl chloroformate (9.1 ml) was added dropwise, and the resultant mixture was stirred for 1 hour. On the other hand, sodium borohydride (7.1 g) was dissolved in tetrahydrofuran (100 ml)-water (25 ml) and cooled with ice. While removing insoluble matter by filtration, the solution prepared previously was added dropwise, and the resultant mixture was stirred at the same temperature for 1 hour. The reaction mixture was poured into a cooled 10% aqueous solution of citric acid to conduct extraction with ethyl acetate. After the extract was washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:9 - 2:1) to obtain the title compound (4.25 g).

^{1}H-NMR ($CDCl_3$) δ: 0.87-0.93(2H,m), 1.28-1.30(2H,m),

3.63(2H,s), 3.70(3H,s).

[Referential Example 163]

Methyl 1-(bromomethyl)cyclopropanecarboxylate:

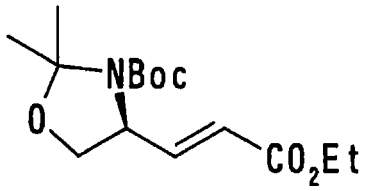


Triphenylphosphine (10 g) and carbon tetrabromide (16 g) were added to a solution of the compound (4.20 g) obtained in Referential Example 162 in methylene chloride (168 ml) at room temperature under a nitrogen atmosphere. After 2 minutes, a saturated aqueous solution of sodium hydrogencarbonate was added thereto. 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 resultant residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 1:19) to obtain the title compound (2.15 g).

^{1}H-NMR ($CDCl_3$) δ: 1.00-1.05(2H,m), 1.52-1.59(2H,m), 3.61(2H,s), 3.73(3H,s).

[Referential Example 164]

tert-Butyl (4S)-4-[(E)-3-ethoxy-3-oxo-1-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

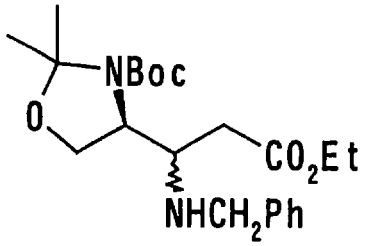


A mixture solution composed of tert-Butyl (4R)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (11.7 g), (carboethoxymethylene)triphenylphosphorane (20.7 g) and toluene (100 ml) was heated and stirred at 100°C for 18 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (17 g).

^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=6.6Hz), 1.43-1.56(15H,m), 3.80(1H,dd,J=9.0,2.4Hz), 4.09(1H,dd,J=9.0,6.6Hz), 4.11-4.23(2H,m), 4.30-4.61(1H,m), 5.83-6.02(1H,m), 6.74-6.89(1H,m).

[Referential Example 165]

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



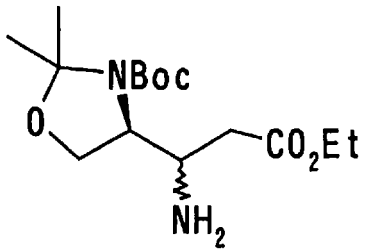
A mixture solution composed of the compound (22.2 g) obtained in Referential Example 164, benzylamine (16 g) and ethanol (100 ml) was heated under reflux for 2 days. The

reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (26 g).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=6.6Hz), 1.42-1.63(15H,m), 2.24-2.33(0.5H,m), 2.40-2.50(1H,m), 2.63-2.74(0.5H,m), 3.41-3.52(1H,m), 3.67-3.80(1H,m), 3.83(2H,s), 3.89-4.00(1H,m), 4.03-4.22(4H,m), 7.23-7.45(5H,m).

[Referential Example 166]

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

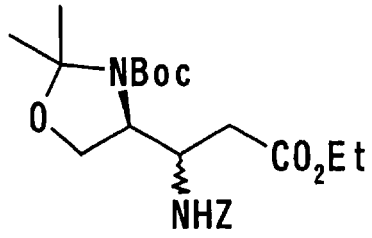


10% Palladium on carbon (10 g) was added to a solution of the compound (13.6 g) obtained in Referential Example 165 in ethanol (200 ml), and the mixture was stirred for 2 days under a hydrogen atmosphere. Insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure to obtain the title compound (10.5 g).

^{1}H-NMR (DMSO-d_6) δ: 1.19(1.5H,t,J=6.6Hz), 1.20(1.5H,t,J=6.6Hz), 1.32-1.50(15H,m), 2.63-2.81(2H,m), 3.22-3.34(2H,m), 3.93(1H,dd,J=10.0,6.8Hz), 4.08(2H,q,J=6.6Hz), 4.20-4.30(1H,m).

[Referential Example 167]

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

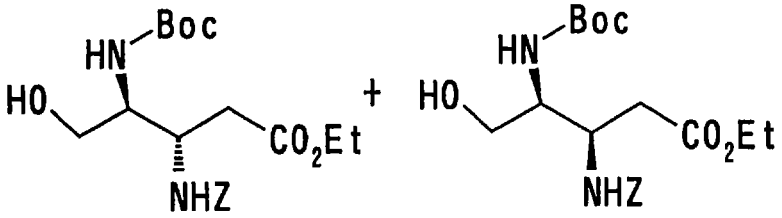


The compound (3.0 g) obtained in Referential Example 166 was suspended in a 9% aqueous solution (56 ml) of sodium hydrogencarbonate, and a solution of N-(benzyloxycarbonyloxy)succinimide (2.3 g) in dioxane (12 ml) was added dropwise to the suspension under ice cooling. The resultant mixture was stirred for 3 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water, a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform) to obtain the title compound (3.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t,J=6.6Hz), 1.48(9H,s), 1.56(6H,s),2.40-2.51(2H,m), 2.63-2.70(2H,m), 3.92-4.04(1H,m), 4.06-4.10(2H,m), 4.14-4.22(1H,m), 5.09(2H,s), 7.30-7.43(5H,m).

[Referential Example 168]

Ethyl (3S,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-hydroxyvalerate (low-polar compound) and ethyl (3R,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-hydroxyvalerate (high-polar compound):



Low-polar compound High-polar compound

Trifluoroacetic acid (100 ml) was added dropwise to a solution of the compound (30 g) obtained in Referential Example 167 in methylene chloride (100 ml) under ice cooling, and the mixture was stirred for 3 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in methylene chloride (100 ml). Triethylamine (20 ml) and a solution of di-tert-butyl dicarbonate (19 g) in methylene chloride (100 ml) were successively added dropwise to this solution under ice cooling, and the mixture was stirred for 4 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain the title low-polar

compound (7.6 g) and the title high-polar compound (10 g).

Low-polar compound:

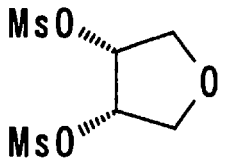
^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t,J=6.6Hz), 1.42(9H,s), 2.63(2H,d,J=4.4Hz), 3.30-3.41(1H,m), 3.50(1H,t,J=9.7Hz), 3.65(1H,t,J=9.7Hz),3.75(1H,d,J=11.7Hz),3.90-4.00(1H,m), 4.03-4.23(2H,m), 5.12(2H,s), 5.13-5.25(1H,m), 5.79-6.02(1H,m), 7.32-7.41(5H,m).

High-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.22(3H,t,J=6.6Hz), 1.41(9H,s), 2.50-2.70(2H,m), 3.20-3.31(1H,m), 3.43-3.51(1H,m), 3.56-3.70(1H,m), 3.74-3.78(1H,m), 4.00-4.19(2H,m), 4.23-4.30(1H,m), 4.78-4.89(1H,m), 5.10(2H,s), 5.56-5.67(1H,m), 7.31-7.40(5H,m).

[Referential Example 169]

(3R,4S)-4-[(Methylsulfonyl)oxy]tetrahydro-3-furanyl methanesulfonate:



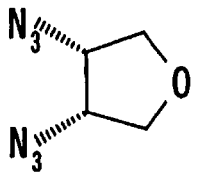
Triethylamine (12.0 ml) and methanesulfonyl chloride (3.6 ml) were successively added dropwise to a solution of 1,4-anhydroerythritol (5.0 g) in methylene chloride (50 ml) under ice cooling, and the mixture was stirred for 10 minutes under ice cooling. The reaction mixture was diluted with methylene chloride and washed with 10%

hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate 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 (9.2 g).

^{1}H-NMR ($CDCl_3$) δ: 3.15(6H,s), 3.99(2H,dd,J=11.2,2.5Hz), 4.16(2H,dd,J=11.2,4.6Hz), 5.10-5.20(2H,m).

[Referential Example 170]

(3R,4S)-3,4-Diazidotetrahydrofuran:

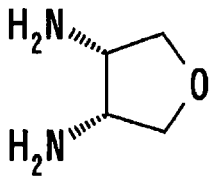


The compound (9.2 g) obtained in Referential Example 169 was dissolved in N,N-dimethylformamide (50 ml), sodium azide (18 g) was added, and the resultant mixture was heated and stirred at 100°C for 18 hours. The reaction mixture was diluted with ethyl acetate and washed with water and saturated aqueous 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 (3.8 g).

^{1}H-NMR ($CDCl_3$) δ: 3.83(2H,dd,J=8.6,2.0Hz), 3.96-4.12(4H,m).

[Referential Example 171]

(3R,4S)-Tetrahydro-3,4-furandiamine dihydrochloride:

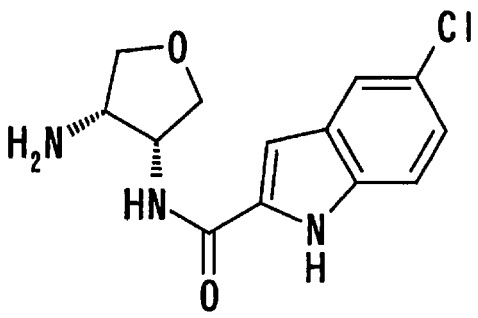


The compound (3.8 g) obtained in Referential Example 170 was dissolved in ethanol (50 ml), 10% palladium on carbon (1.0 g) was added to the solution, and the mixture was stirred for 18 hours under a hydrogen atmosphere. Insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure. A 1N ethanol solution of hydrochloric acid was added to the resultant residue, giving the hydrochloride salt. The hydrochloride was recrystallized from a mixed solvent of ethanol and diethyl ether to obtain the title compound (2.0 g).

^{1}H-NMR ($CDCl_3$) δ: 3.90(2H,dd,J=9.0,3.7Hz), 4.01-4.13(4H,m), 8.84(6H,s).

[Referential Example 172]

N-[(3R*,4S*)-4-Aminotetrahydro-3-furanyl]-5-chloroindole-2-carboxamide:



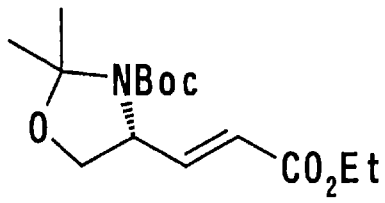
5-Chloroindole-2-carboxylic acid (0.29 g), 1-

hydroxybenzotriazole monohydrate (0.2 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.6 g) were successively added to a solution of the compound (0.5 g) obtained in Referential Example 171 in N,N-dimethylformamide (10 ml), and the mixture was heated and stirred at 50°C for a day. The reaction mixture was concentrated, and the resultant residue was diluted with a mixed solvent composed of chloroform and methanol (9:1) and washed with a saturated aqueous solution of sodium hydrogencarbonate 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, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 95:5) to obtain the title compound (0.2 g).

^{1}H-NMR ($CDCl_3$) δ: 1.80-1.92(1H,m), 3.62(1H,dd,J=9.3,4.2Hz), 3.68-3.80(2H,m), 4.06(1H,dd,J=9.3,5.6Hz), 4.21(1H,dd,J=9.3,6.8Hz), 4.36-4.52(2H,m), 6.87(1H,s), 7.24(1H,dd,J=8.8,2.0Hz), 7.36(1H,d,J=8.8Hz), 7.44-7.56(1H,m), 7.62(1H,d,J=2.0Hz), 9.41(1H,s).

[Referential Example 173]

tert-Buthyl (4R)-4-[(E)-3-ethoxy-3-oxo-1-propenyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

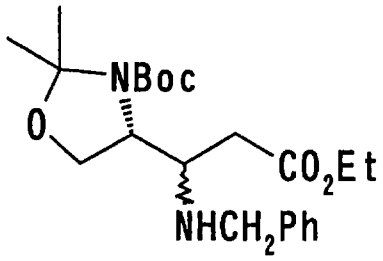


The title compound was obtained from tert-Butyl (4S)-4-formyl-2,2-dimethyl-1,3-oxazolidine-3-carboxylate in a similar manner to Referential Example 164.

^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=6.6Hz), 1.40-1.60(15H,m), 3.80(1H,dd,J=9.0,2.4Hz), 4.09(1H,dd,J=9.0,6.6Hz), 4.11-4.21(2H,m), 4.32-4.64(1H,m), 5.78-6.01(1H,m), 6.67-6.89(1H,m).

[Referential Example 174]

tert-Butyl (4R)-4-[1-(benzylamino)-3-ethoxy-3-oxopropyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:

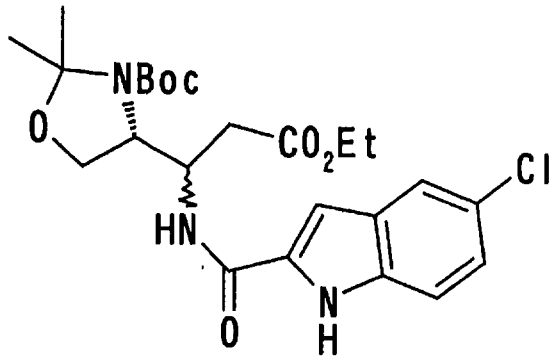


The title compound was obtained from the compound obtained in Referential Example 173 in a similar manner to Referential Example 165.

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=6.6Hz), 1.40-1.61(15H,m), 2.21-2.32(0.5H,m), 2.40-2.51(1H,m), 2.61-2.72(0.5H,m), 3.43-3.50(1H,m), 3.67-3.80(1H,m), 3.83(2H,s), 3.90-4.03(1H,m), 4.04-4.22(4H,m), 7.20-7.40(5H,m).

[Referential Example 175]

tert-Butyl (4R)-4-(1-{[(5-chloroindol-2-yl)carbonyl]amino}-3-ethoxy-3-oxopropyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate:



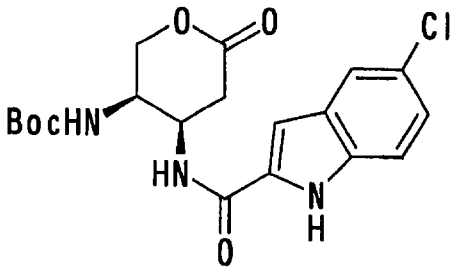
The title compound was obtained by reducing the compound obtained in Referential Example 174 in a similar manner to Referential Example 166 to remove a benzyl group and then condensing it with 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 172.

^{1}H-NMR ($CDCl_3$) δ:1.23(1.5H,t,J=6.6Hz), 1.25(1.5H,t,J=6.6Hz), 1.50(4.5H,s), 1.54(4.5H,s), 1.62(6H,s), 2.50-2.70(1.5H,m), 2.86(0.5H,dd,J=16.4,5.5Hz), 3.80-3.90(0.5H,m), 4.00-4.31(5H,m), 4.41-4.67(0.5H,m), 6.85(0.5H,s), 6.87(0.5H,s), 7.10-7.20(1H,m), 7.34(0.5H,d,J=8.8Hz), 7.38(0.5H,d,J=8.8Hz), 7.57(0.5H,s), 7.63(0.5H,s), 7.88(0.5H,d,J=7.6Hz), 8.54(0.5H,d,J=7.6Hz), 9.40(0.5H,s), 9.54(0.5H,s).

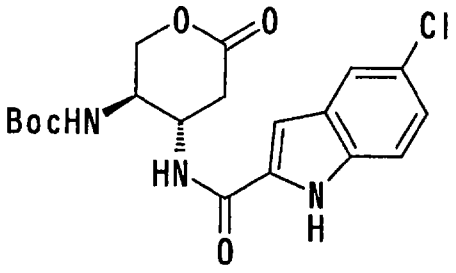
[Referential Example 176]

tert-Butyl (3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-6-oxotetrahydro-2H-pyran-3-ylcarbamate (low-polar compound) and tert-butyl; (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-6-oxotetrahydro-2H-pyran-3-ylcarbamate (high-polar

compound):



+



Low-polar compound High-polar compound

A 1N aqueous solution (4.0 ml) of sodium hydroxide was added to a solution of the compound (1.0 g) obtained in Referential Example 175 in ethanol (20 ml), and the mixture was stirred for 4 hours. Citric acid was added to the reaction mixture to adjust the pH of the reaction mixture to 4.0. The reaction mixture was extracted with ethyl acetate, and the resultant 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. The resultant residue was dissolved in methanol (50 ml), and toluenesulfonic acid monohydrate (0.1 g) was added to the solution to stir the resultant mixture for 18 hours. The reaction mixture was diluted with ethyl acetate 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 resultant residue was purified

by column chromatagraphy on silica gel (chloroform:methanol = 99:1) to obtain the title low-polar compound (0.3 g) and the title high-polar compound (0.3 g).

Low-polar compound:

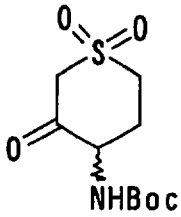
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.70(1H,dd,J=16.5,4.9Hz), 2.85(1H,dd,J=16.5,4.6Hz), 3.50-3.61(1H,m), 3.71-3.81(2H,m), 4.30-4.40(1H,m), 5.30(1H,d,J=9.5Hz), 6.89(1H,s), 7.23(1H,dd,J=8.8,2.0Hz), 7.38(1H,d,J=8.8Hz), 7.62(1H,d,J=2.0Hz), 7.93(1H,d,J=9.5Hz), 9.30(1H,s).

High-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.39(9H,s), 2.75(1H,dd,J=16.5,4.9Hz), 2.82(1H,dd,J=16.5,4.6Hz), 3.41-3.52(2H,m), 3.71-3.82(1H,m), 3.85-3.94(1H,m), 5.03(1H,d,J=9.3Hz), 6.99(1H,s), 7.22-7.31(1H,m), 7.34(1H,d,J=8.8Hz), 7.61(1H,d,J=2.0Hz), 7.83(1H,d,J=9.3Hz), 9.28(1H,s).

[Referential Example 177]

tert-Butyl 1,1,3-trioxohexahydro-1-thiopyran-4-ylcarbamate:



A solution of N-tert-butoxycarbonyl-L-methionine sulfone methyl ester (60.2 g) in tetrahydrofuran (900 ml) was cooled to -78°C, to which 0.5 M potassium bis-(trimethylsilyl)amide (toluene solution, 900 ml) was added dropwise, and the mixture was stirred for 2 hours at -78°C and for 4.5 hours at room temperature. A 1 M aqueous

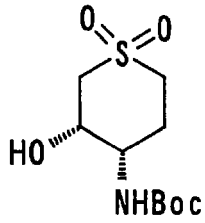
solution of ammonium chloride was added, and the mixture was stirred. The reaction mixture was subjected to liquid separation, and the resultant organic layer was then washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and solids formed were collected by filtration to obtain the title compound (12.4 g). The water layer separated previously was extracted twice with ethyl acetate, and the resultant organic layers were combined, washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The water layers used in the washing were further combined, and extracted again with ethyl acetate, and the extract was washed with saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The ethyl acetate extracts were combined, dried and then concentrated under reduced pressure to obtain the title compound (27.7 g) (total amount of the title compound: 40.1 g).

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.85-1.96(1H,m), 2.76-2.78(1H,m), 3.34-3.46(2H,m), 4.05(1H,dd,J=13.5,3.7Hz), 4.14(1H,d,J=13.5Hz), 4.38-4.44(1H,m), 5.46(1H,br).

MS (ESI) m/z: $262(M-H)^-$.

[Referential Example 178]

tert-Butyl (3R*,4R*)-3-hydroxy-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:



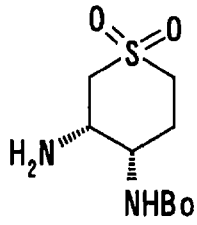
Sodium borohydride (2.17 g) was added to a suspension of the compound (10.1 g) obtained in Referential Example 177 in methanol (200 ml), and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. After ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue to conduct liquid separation, the resultant water layer was extracted twice with ethyl acetate. The resultant organic layers were combined, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain the title compound (9.96 g).

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.21-2.36(2H,m), 3.03-3.17(2H,m), 3.26-3.28(2H,m), 3.77-3.80(2H,m), 4.26-4.28(1H,m), 5.05-5.07(1H,m).

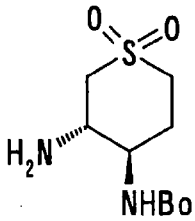
MS (ESI) m/z: 264$(M-H)^-$.

[Referential Example 179]

tert-Butyl (3R*,4R*)-3-amino-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate (low-polar compound) and tert-Butyl (3R*,4S*)-3-amino-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate (high-polar compound):



+



Low-polar compound (racemic modification)

High-polar compound (racemic modification)

Diethyl azodicarboxylate (6.96 g) was added to a solution of the compound (9.66 g) obtained in Referential Example 178 and triphenylphosphine (10.5 g) in tetrahydrofuran (150 ml), and the mixture was stirred at room temperature for 4.5 hours. After the reaction mixture was concentrated under reduced pressure, diethyl ether was added to the residue, and solids formed were collected by filtration. The thus-collected solids were purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 7:3) to obtain a mixture (7.25 g) containing tert-butyl 1,1-dioxo-1,2,3,4-tetrahydropyran-4-ylcarbamate as a colorless solid. The mother liquor was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 7:3) to obtain a mixture (9.18 g) containing tert-butyl 1,1-dioxo-1,2,3,4-tetrahydropyran-4-ylcarbamate as a colorless solid (total amount: 16.4 g). The thus-obtained mixtures were dissolved in dioxane (60 ml), and 28% aqueous ammonia (60 ml) was added. The resultant mixture was stirred at 60°C for 4.5 hours in a sealed tube. After allowing to cool, the reaction mixture was concentrated

under reduced pressure. After dioxane was distilled off, the residue was extracted 5 times with methylene chloride. The resultant organic layers were combined and concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 96:4) to obtain the title low-polar compound (2.31 g) and the title high-polar compound (4.31 g).

Low-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.14-2.28(2H,m), 3.01-3.08(3H,m), 3.23(1H,dd,J=13.8,3.9Hz), 3.47-3.49(1H,m), 3.71-3.76(1H,m), 5.32(1H,d,J=7.3Hz).

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

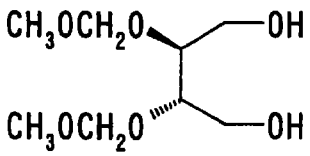
High-polar compound:

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.94-2.01(1H,m), 2.37-2.44(1H,m), 2.91(1H,dd,J=11.2,14.1Hz), 3.04-3.07(2H,m), 3.12-3.19(1H,m), 3.26-3.30(1H,m), 3.39-3.42(1H,m), 4.62(1H,br).

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

[Referential Example 180]

(2S,3S)-2,3-Bis(methoxymethoxy)-1,4-butanediol:



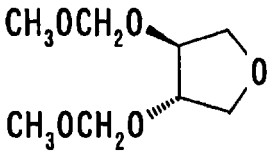
Chloromethyl methyl ether (4.8 ml) was added dropwise to a mixture solution composed of diethyl L-tartrate (8.6 g), diisopropylethylamine (40 ml) and methylene chloride

(40 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was concentrated, and the resultant residue was diluted with ethyl acetate and washed with 10% hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate 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, and the resultant residue was dissolved in tetrahydrofuran. The solution was added dropwise to a tetrahydrofuran suspension of lithium aluminum hydride (2.2 g) under ice cooling, and the mixture was stirred for 2 hours under ice cooling. After a 10% aqueous solution of sodium hydrogensulfate was carefully added under ice cooling, and the mixture was stirred for 1 hour, the reaction mixture was diluted with saturated aqueous solution of sodium chloride and extracted with ethyl acetate. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure to obtain the title compound (3.0 g).

^{1}H-NMR ($CDCl_3$) δ: 1.55-1.64(2H,m), 3.44(6H,s), 3.70-3.81(6H,m), 4.70(2H,d,J=6.9Hz), 4.76(2H,d,J=6.9Hz).

[Referential Example 181]

(3S,4S)-3,4-Bis(methoxymethoxy)tetrahydrofuran:

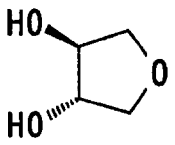


Diethyl azodicarboxylate (2.46 ml) was added dropwise to a mixture solution composed of the compound (3.0 g) obtained in Referential Example 180, triphenylphosphine (4.5 g), tetrahydrofuran (10 ml) and toluene (40 ml), and the mixture was stirred at room temperature for 4 days. The reaction mixture was concentrated under reduced pressure, a mixed solvent (160 ml) of hexane and diethyl ether (1:1) was added to the resultant residue, and the mixture was stirred for 3 hours. Insoluble matter deposited was then collected by filtration. The filtrate was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (1.95 g).

^{1}H-NMR ($CDCl_3$) δ: 3.38(6H,s), 3.80(2H,dd,J=9.2,1.7Hz), 4.00(2H,dd,J=9.2,4.4Hz), 4.23(2H,dd,J=4.4,1.7Hz), 4.67(2H,d,J=6.9Hz), 4.71(2H,d,J=6.9Hz).

[Referential Example 182]

(3S,4S)-Tetrahydro-3,4-furandiol:



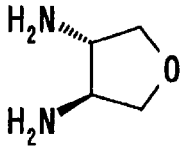
Concentrated hydrochloric acid (2.1 ml) was added to a solution of the compound (1.95 g) obtained in Referential Example 181 in methanol (6.0 ml), and the mixture was

stirred for 18 hours. After the reaction mixture was concentrated, and the resultant residue was diluted with chloroform and dried over potassium carbonate, the solvent was distilled off under reduced pressure to obtain the title compound (0.52 g).

^{1}H-NMR ($CDCl_3$) δ: 1.77(2H,d,J=4.7Hz), 3.73(2H,d,J=10.2Hz), 4.08(2H,dd,J=10.2,3.7Hz), 4.18-4.34(2H,m).

[Referential Example 183]

(3S,4S)-Tetrahydro-3,4-furandiamine:

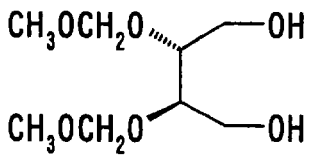


The title compound was obtained from the compound obtained in Referential Example 182 in a siminar manner to the processes described in Referential Examples 169 to 171.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.46(4H,m), 3.19(2H,dd,J=5.6,4.1Hz), 3.50(2H,dd,J=9.0,4.1Hz), 4.09(2H,dd,J=9.0,5.6Hz).

[Referential Example 184]

(2R,3R)-2,3-Bis(methoxymethoxy)-1,4-butanediol:

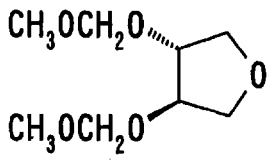


The title compound was obtained from diethyl D-tartrate in a similar manner to Referential Example 180.

^{1}H-NMR: The same as that of the enantiomer in Referential Example 180.

[Referential Example 185]

(3R,4R)-3,4-Bis(methoxymethoxy)tetrahydrofuran:

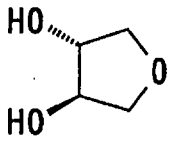


The title compound was obtained from the compound obtained in Referential Example 184 in a similar manner to Referential Example 181.

^{1}H-NMR: The same as that of the enantiomer in Referential Example 181.

[Referential Example 186]

(3R,4R)-Tetrahydro-3,4-furandiol:

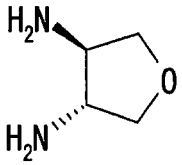


The title compound was obtained from the compound obtained in Referential Example 185 in a similar manner to Referential Example 182.

^{1}H-NMR: The same as that of the enantiomer in Referential Example 182.

[Referential Example 187]

(3R,4R)-Tetrahydro-3,4-furandiamine:

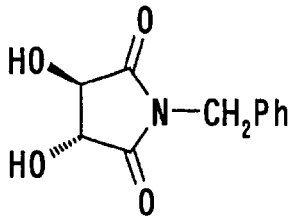


The title compound was obtained from the compound obtained in Referential Example 186 in a similar manner to Referential Example 183.

^{1}H-NMR ($CDCl_3$) δ: The same as that of the enantiomer in Referential Example 183.

[Referential Example 188]

(3R,4R)-1-Benzyl-3,4-dihydroxy-2,5-pyrrolidinedione:

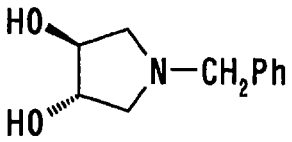


L-Tartaric acid (30 g) and benzylamine (22 ml) were added to xylene (150 ml), and the mixture was heated under reflux at 150°C for 3 hours using a Dean-Stark trap. After the reaction mixture was allowed to cool overnight, crystals were collected by filtration and washed with acetone. The resultant crude product was recrystallized from ethanol to obtain the title compound (23.2 g).

^{1}H-NMR (DMSO-d_6) δ: 4.36-4.40(2H,m), 4.55(each 1H,AB type d,J=15Hz), 6.26-6.30(2H,m), 7.25-7.35(5H,m).

[Referential Example 189]

(3S,4S)-1-Benzyl-3,4-pyrrolidinediol:



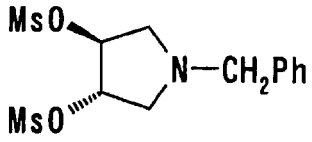
The compound (11 g) obtained in Referential Example 188 was dissolved in tetrahydrofuran (110 ml), and lithium aluminum hydride (5.69 g) was added portionwise to the solution under ice cooling. The mixture was heated to room temperature for 1 hour and heated under reflux and for

additional a night. After allowing the reaction mixture to cool, water (5.7 ml), a 15% aqueous solution (5.7 ml) of sodium hydroxide and water (17.1 ml) were added under ice cooling in that order, and the mixture was heated to room temperature and stirred for 1 hour. After deposits were filtered through Celite, and the mother liquor was concentrated under reduced pressure, the resultant residue was recrystallized from ethyl acetate to obtain title compound (6.35 g).

^{1}H-NMR ($CDCl_3$) δ: 2.40-2.44(2H,m), 2.88-2.92(2H,m), 3.58(each 1H,AB type d,J=7.8Hz), 4.04(2H,t,J=4.2Hz), 7.25-7.34(5H,m).

[Referential Example 190]

(3S,4S)-1-Benzyl-4-[(methylsulfonyl)oxy]pyrrolidinyl methanesulfonate:

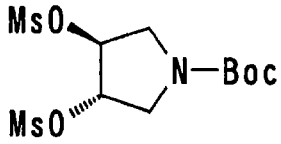


The title compound was obtained from the compound obtained in Referential Example 189 in a similar manner to Referential Example 169.

^{1}H-NMR ($CDCl_3$) δ: 2.76(2H,dd,J=11,4.6Hz), 3.08(6H,s), 3.64(2H,d,J=2.5Hz), 3.68-3.75(2H,m), 5.12-5.15(2H,m), 7.27-7.35(5H,m).

[Referential Example 191]

tert-Butyl (3S,4S)-3,4-bis[(methylsulfonyl)oxy]-1-pyrrolidinecarboxylate:



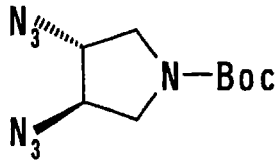
The compound (1.57 g) obtained in Referential Example 190 was dissolved in 1,2-dichloroethane (16 ml), 1-chloroethyl chloroformate (0.73 ml) was added at room temperature, and the resultant mixture was heated under reflux for 4 hours. After the solvent was distilled off under reduced pressure, methanol (16 ml) was added to the resultant residue, and the resultant mixture was heated under reflux for 1 hour, allowed to cool and concentrated. Crystals obtained by recrystallization from ethyl acetate were collected by filtration to obtain (3S,4S)-3,4-bis-[(methylsulfonyl)oxy]pyrrolidine hydrochloride (1.30 g) as colorless crystals. Di-tert-butyl dicarbonate (1.15 ml) was added to a solution of the hydrochloride thus obtained and triethylamine (1.40 ml) in methylene chloride (26 ml), and the mixture was stirred overnight at room temperature. After the reaction mixture was concentrated, the residue was diluted with ethyl acetate, 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 resultant residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:9 - 1:1) to obtain the title compound (1.40 g).

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.12(6H,s), 3.70-3.73(2H,m),

3.79(1H,d,J=4.5Hz), 3.82(1H,d,J=4.5Hz), 5.19(2H,br).

[Referential Example 192]

tert-Butyl (3R,4R)-3,4-diazido-1-pyrrolidinecarboxylate:

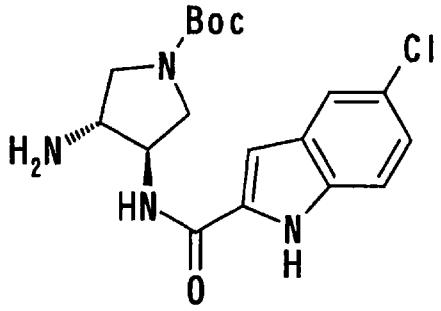


The title compound was obtained from the compound obtained in Referential Example 191 in a similar manner to Referential Example 170.

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 3.37-3.46(2H,m), 3.64-3.71(2H,m), 3.96(2H,t,J=3.2Hz).

[Referential Example 193]

tert-Butyl (3R,4R)-3-amino-4-{[(5-chloroindol-2-yl)carbonyl]amino}pyrrolidine-1-carboxylate:

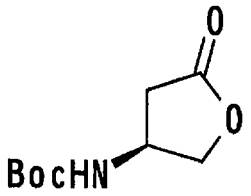


The title compound was obtained from the compound obtained in Referential Example 192 in a similar manner to Referential Examples 171 and 172.

^{1}H-NMR (DMSO-d_6) δ: 1.39(9H,s), 2.95-3.00(1H,m), 3.09-3.13(1H,m), 3.52(1H,dd,J=10,6.5Hz), 3.68(1H,dd,J=10,7.8Hz), 4.04-4.09(2H,m), 7.16(1H,s), 7.18(1H,s), 7.42(1H,d,J=8.5Hz), 7.69(1H,d,J=1.5Hz), 8.50(1H,d,J=6.5Hz), 11.77(1H,br).

[Referential Example 194]

tert-Butyl (3S)-5-oxotetrahydro-3-furanylcarbamate:

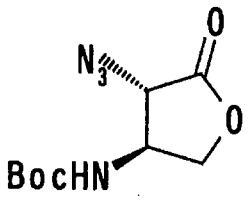


di-tert-Butyl dicarbonate (4.1 g) and 10% palladium on carbon (0.4 g) were added to a solution of benzyl (3S)-(-)-tetrahydro-5-oxo-3-furanylcarbamate (3.3 g) in tetrahydrofuran (20 ml), and the mixture was stirred for a day in a hydrogen atmosphere. After insoluble matter was filtered through Celite pad, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (1.5 g).

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 2.45(1H,dd,J=17.8,2.7Hz), 2.86(1H,dd,J=17.8,7.3Hz), 4.12-4.23(1H,m), 4.54-4.62(2H,m), 4.85-4.95(1H,m).

[Referential Example 195]

tert-Butyl (3S,4S)-4-azido-5-oxotetrahydro-3-furanylcarbamate:



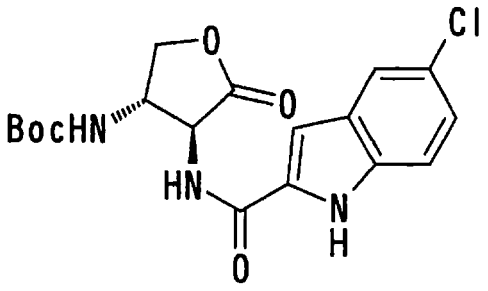
1 M Lithium bis(trimethylsilyl)amide (tetrahydrofuran solution, 8.65 ml) was added dropwise to a solution of the

compound (0.87 g) obtained in Referential Example 194 in tetrahydrofuran (20 ml) at -78°C, and the mixture was stirred for 30 minutes. After a solution of p-toluenesulfonylazide (1.02 g) in tetrahydrofuran (10 ml) was then added, and the mixture was stirred for 5 minutes, trimethylchlorosilane (1.7 ml) was added, and the mixture was stirred for 2 hours while the temperature of the system was gradually raised to room temperature. The reaction mixture was diluted with diethyl ether, washed with 10% hydrochloric acid, a 5% 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. The resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (0.62 g).

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 4.09(1H,dt,J=15.3,7.6Hz), 4.12-4.23(1H,m), 4.37-4.50(1H,m), 4.54(1H,dd,J=9.0,7.6Hz), 4.81-4.90(1H,m).

[Referential Example 196]

tert-Butyl (3S,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-oxotetrahydro-3-furanylcarbamate:

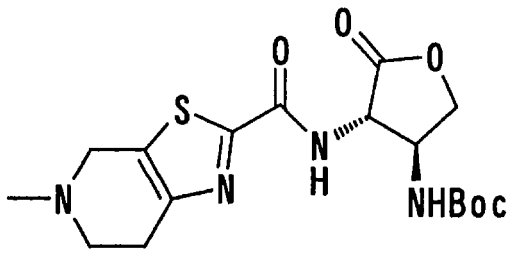


The title compound was obtained from the compound obtained in Referential Example 195 in a similar manner to Referential Examples 90 and 91.

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 4.01-4.13(1H,m), 4.20-4.36(1H,m), 4.78-4.93(2H,m), 6.15(1H,s), 6.93(1H,s), 7.03-7.11(1H,m), 7.20-7.28(1H,m), 7.30(1H,d,J=8.8Hz), 7.61(1H,s), 9.27(1H,s).

[Referential Example 197]

tert-Butyl (3S,4S)-4-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-5-oxotetrahydro-3-furanylcarbamate:



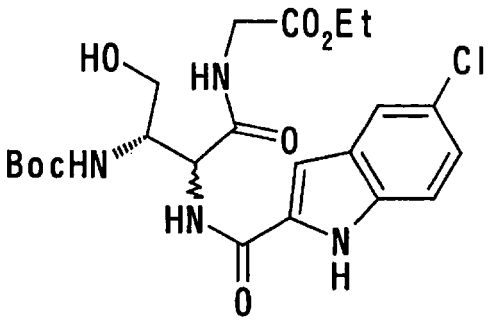
The title compound was obtained by getting tert-butyl (3S,4S)-4-amino-5-oxotetrahydro-3-furanylcarboxylate from the compound obtained in Referential Example 195 in a similar manner to Referential Example 90 and then reacting with the compound obtained in Referential Example 10 in

accordance with the reaction conditions of Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.52(3H,s), 2.83(2H,t,J=5.9Hz), 2.79-3.02(2H,m), 3.74(2H,s), 4.03-4.12(1H,m), 4.21-4.36(1H,m), 4.80-4.95(2H,m), 6.14-6.24(1H,m), 7.76-7.85(1H,m).

[Referential Example 198]

Ethyl 2-[((3S)-3-[(tert-butoxycarbonyl)amino]-2-{[(5-chloroindol-2-yl)carbonyl]amino}-4-hydroxybutanoyl)amino]-acetate:



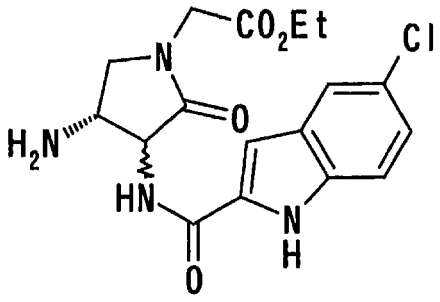
The compound (0.4 g) obtained in Referential Example 196, glycine ethyl ester hydrochloride (1.0 g) and triethylamine (1.0 ml) were added to ethanol (20 ml), and the mixture was heated and stirred at 60°C for 18 hours. The reaction mixture was diluted with chloroform and washed with a 10% aqueous solution of citric acid 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 resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 98:2) to obtain title

compound (0.31 g).

^{1}H-NMR (DMSO-d_6) δ: 1.17(3H,t,J=7.0Hz), 1.34(6H,s), 1.36(3H,s), 3.51-3.63(0.6H,m), 3.72-3.80(2H,m), 4.06(2H,q,J=7.0Hz), 4.11-4.23(1.4H,m), 4.67-4.82(1H,m), 4.85-4.91(1H,m), 6.48(0.4H,d,J=9.5Hz), 6.80(0.6H,d,J=9.5Hz), 7.10-7.22(2H,m), 7.42(1H,d,J=8.8Hz), 7.72(0.4H,d,J=2.0Hz), 7.73(0.6H,d,J=2.0Hz), 8.23-8.31(0.6H,m), 8.34-8.41(0.4H,m), 8.43-8.50(1H,m), 11.83(1H,s).

[Referential Example 199]

Ethyl 2-((4R)-4-amino-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-2-oxopyrrolidin-1-yl)acetate hydrochloride:



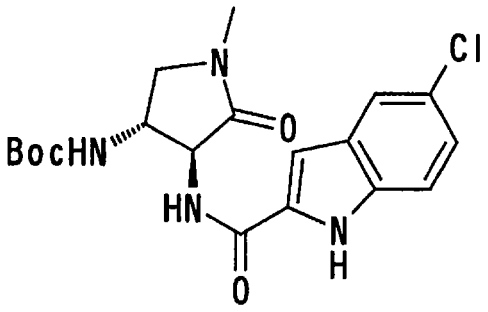
The title compound was obtained by converting the compound obtained in Referential Example 198 into a pyrrolidone derivative using the reaction conditions described in Referential Example 181 and then removing a tert-butoxycarbonyl group in a similar manner to Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.17(2H,t,J=7.0Hz), 1.23(1H,t,J=7.0Hz), 3.31-3.40(0.6H,m), 3.57(0.4H,d,J=11.2Hz), 3.90-4.23(4H,m), 4.42(0.6H,dd,J=12.0,6.1Hz), 4.50-4.60(0.4H,m), 4.62(0.6H,dd,J=12.0,3.9Hz), 5.12-5.23(0.4H,m), 7.17(0.4H,s),

7.20(0.4H,dd,J=8.8,2.0Hz), 7.28(0.6H,dd,J=8.8,2.0Hz), 7.30(0.6H,s), 7.44(0.4H,d,J=8.8Hz), 7.50(0.6H,d,J=8.8Hz), 7.75(1H,d,J=2.0Hz), 8.20-8.33(1H,m), 8.71-8.94(3.6H,m), 9.22-9.35(0.4H,m), 11.97(0.4H,s), 12.44(0.6H,s).

[Referential Example 200]

tert-Butyl (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]-amino}-1-methyl-5-oxopyrrolidin-3-ylcarbamate:

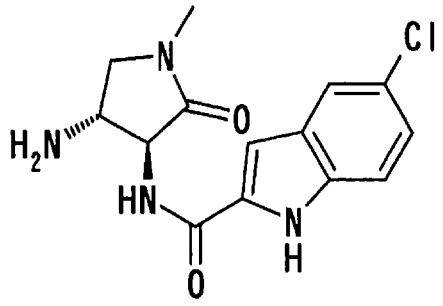


The title compound was obtained by treating a compound obtained by reaction of the compound obtained in Referential Example 196 with methylamine (40% methanol solution) in a similar manner to Referential Example 198 under the same conditions as those in Referential Example 181.

^{1}H-NMR ($CDCl_3$)δ: 1.43(9H,s), 2.90(3H,s), 4.26(1H,br.s), 4.36(2H,m), 4.51-4.52(1H,m), 5.35(1H,br.s), 6.95-6.99(2H,m), 7.22-7.32(3H,m), 7.63(1H,s), 8.95(1H,br.s).

[Referential Example 201]

N-[(3S,4R)-4-Amino-1-methyl-2-oxopyrrolidin-3-yl]-5-chloroindole-2-carboxamide:

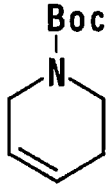


The title compound was obtained by treating the compound obtained in Referential Example 200 in a similar manner to Referential Example 69.

^{1}H-NMR ($CDCl_3$) δ: 2.95(3H,d,J=5.1Hz), 3.91-3.93(1H,m), 4.19(1H,d,J=3.7Hz), 4.36(1H,dd,J=11,1.7Hz), 4.48(1H,dd,J=11,2.0Hz), 6.90-6.97(2H,m), 7.21-7.33(2H,m), 7.62(1H,d,J=2.0Hz), 8.90(1H,s).

[Referential Example 202]

tert-Butyl 3,6-dihydro-1(2H)-pyridinecarboxylate:



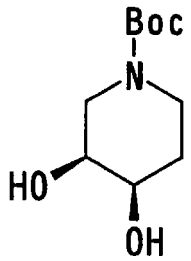
tert-Butyl dicarbonate (6.55 g) was added to a mixture of 1,2,3,6-tetrahydropyridine (2.50 g) and a 10% aqueous solution (3.0 ml) of sodium carbonate, and the mixture was stirred at room temperature for 20 hours. Water was added to the reaction mixture to conduct extraction with ethyl acetate. The resultant organic layer was washed with 0.5N hydrochloric acid, water, a saturated aqueous solution of sodium hydrogencarbonate and saturated

aqueous solution of sodium chloride in that order and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure to obtain the title compound (5.08 g).

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 2.12(2H,br.s), 3.48(2H,t,J=5.6Hz), 3.88(2H,br.s), 5.60(1H,br.s), 5.78-5.90(1H,m).

[Referential Example 203]

tert-Butyl (3R*,4S*)-3,4-dihydroxy-1-piperidinecarboxylate:



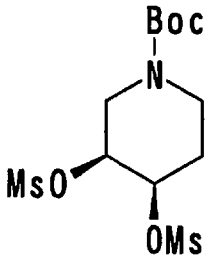
The compound (18.45 g) obtained in Referential Example 202 was dissolved in acetonitrile (200 ml), and water (38 ml), a 0.039 M aqueous solution (82 ml) of osmium tetroxide and N-methylmorpholine N-oxide (23.13 g) were added. The mixture was stirred at room temperature for 17 hours. An excessive oxidizing agent was treated with a saturated aqueous solution of sodium sulfite to conduct extraction with ethyl acetate. The resultant organic layer was washed with water, 0.5N hydrochloric acid, water, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified

by column chromatagraphy on silica gel (hexane:ethyl acetate = 1:3) to obtain the title compound (15.0 g).

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.60-1.73(1H,m), 1.77-1.90(1H,m), 2.68(1H,br.s), 2.80-3.20(1H,br), 3.22-3.32(1H,m), 3.42(1H,dd,J=14.3,3.4Hz), 3.50-3.62(2H,m), 3.77(1H,brs), 3.81-3.92(1H,m).

[Referential Example 204]

tert-Butyl (3R*,4S*)-3,4-bis[(methylsulfonyl)oxy]-1-piperidinecarboxylate:

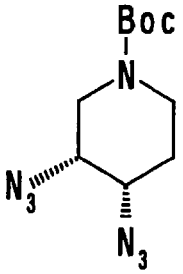


The title compound was obtained from the compound obtained in Referential Example 203 in a similar manner to Referential Example 169.

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.85-1.97(1H,m), 2.08-2.20(1H,m), 3.00-4.20(4H,m), 3.12(6H,s), 4.85(1H,br.s), 4.94(1H,br.s).

[Referential Example 205]

tert-Butyl (3R*,4S*)-3,4-diazido-1-piperidinecarboxylate:

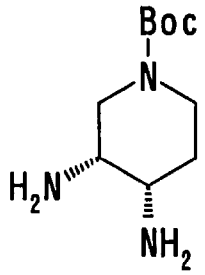


The title compound was obtained from the compound obtained in Referential Example 204 in a similar manner to Referential Example 170.

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.70-1.80(1H,m), 1.90-2.00(1H,m), 3.05-4.00(6H,m).

[Referential Example 206]

tert-Butyl (3R*,4S*)-3,4-diamino-1-piperidinecarboxylate:

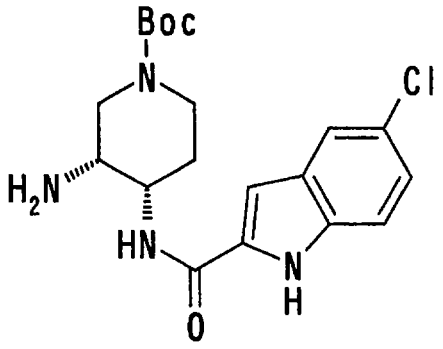


The title compound was obtained from the compound obtained in Referential Example 205 in a similar manner to Referential Example 171.

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.48-1.60(2H,m), 1.80-2.10(4H,br), 2.85-2.91(2H,m), 2.97(1H,br.s), 3.09(1H,dd,J=13.6,2.7Hz), 3.74(1H,dd,J=13.6,4.2Hz), 3.81(1H,s).

[Referential Example 207]

tert-Butyl (3R*,4S*)-3-amino-4-{[(5-chloroindol-2-yl)-carbonyl]amino}-1-piperidinecarboxylate:

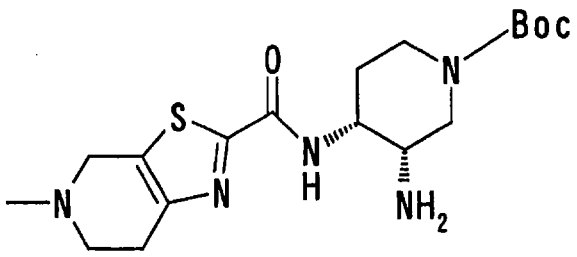


The compound (3.23 g) obtained in Referential Example 206 was dissolved in N,N-dimethylformamide (100 ml), and triethylamine (2.08 ml) and the compound (3.80 g) obtained in Referential Example 52 were added to the solution. The mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride. The resultant 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 resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 20:1 - 10:1) to obtain the title compound (2.70 g).

^{1}H-NMR (DMSO-d_6) δ: 1.40-1.58(3H,m), 1.41(9H,s), 1.75-1.90(1H,m), 2.95(1H,br.s), 2.98-3.05(1H,m), 3.19-3.28(1H,m), 3.74(1H,dd,J=19.5,15.4Hz), 3.79(1H,br.s), 4.04-4.12(1H,m), 7.17(1H,dd,J=8.7,1.9Hz), 7.21(1H,s), 7.42(1H,d,J=8.7Hz), 7.68(1H,d,J=1.9Hz), 8.00(1H,br.d,J=7.6Hz), 11.80(1H,s).

[Referential Example 208]

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

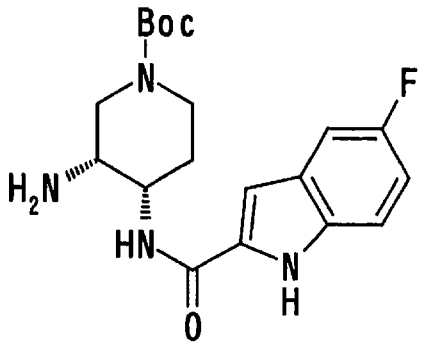


The compound (3.23 g) obtained in Referential Example 206 was dissolved in N,N-dimethylformamide (100 ml), and triethylamine (2.08 ml) was added. The compound (3.83 g) obtained in Referential Example 149 was then added, and the mixture was stirred at room temperature for 3 days. The reaction mixture was concentrated under reduced pressure, and water was added to the residue to conduct extraction with methylene chloride. 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 sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 10:1 - 5:1) to obtain the title compound (2.27 g).

^{1}H-NMR ($CDCl_3$) δ: 1.30-1.62(3H,m), 1.47(9H,s), 1.78-1.88(1H,m), 2.51(3H,s), 2.81(2H,t,J=5.9Hz), 2.85-2.98(3H,m), 3.00-3.15(2H,m), 3.71(2H,s), 3.80-4.15(3H,m), 7.79(1H,br.s).

[Referential Example 209]

tert-Butyl (3R*,4S*)-3-amino-4-{[(5-fluoroindol-2-yl)-carbonyl]amino}-1-piperidinecarboxylate:



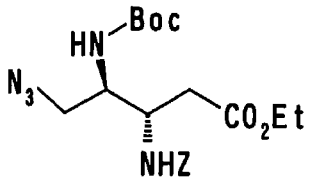
The title compound was obtained from the compound obtained in Referential Example 206 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 172.

^{1}H-NMR ($CDCl_3$) δ: 1.40-1.70(3H,m), 1.48(9H,s), 2.79-2.92(1H,m), 2.99-3.14(1H,m), 4.00-4.23(3H,m), 6.85(1H,s),7.04(1H,td,J=9.0,2.4Hz), 7.07-7.20(1H,br), 7.27(1H,dd,J=9.0,2.4Hz), 7.35(1H,d,J=9.0,4.4Hz), 9.25-9.50(1H,br).

MS (ESI)m/z: 377$(M+H)^+$.

[Referential Example 210]

Ethyl (3R,4R)-5-azido-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]valerate:



Triethylamine (4.80 ml) and methanesulfonyl chloride (1.55 ml) were successively added dropwise to a solution of

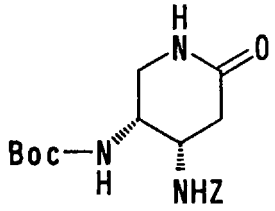
the (3S,4S)-compound obtained in Referential Example 168 (low-polar compound) (7.1 g) in methylene chloride (100 ml) under ice cooling, and the mixture was stirred for 30 minutes under ice cooling. The reaction mixture was diluted with chloroform and washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate 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 a methanesulfonyl derivative (9.20 g). A mixture solution composed of the thus-obtained methanesulfonyl derivative, sodium azide (5.64 g) and N,N-dimethylformamide (100 ml) was stirred at 80°C for 20 hours. The reaction mixture was diluted with ethyl acetate and washed with water 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, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform) to obtain the title compound (5.42 g).

^{1}H-NMR ($CDCl_3$) δ: 1.24(3H,t,J=7.1Hz), 1.43(9H,s), 2.56-2.68(2H,m), 3.48-3.60(2H,m), 3.88-3.97(1H,m), 4.04-4.20(3H,m), 4.88-4.97(1H,br), 5.10(2H,s), 5.60-5.75(1H,br), 7.30-7.40(5H,m).

MS (ESI) m/z: 436$(M+H)^+$.

[Referential Example 211]

Benzyl (4S,5R)-5-[(tert-butoxycarbonyl)amino]-2-oxo-piperidin-4-ylcarbamate:



A Lindlar catalyst (2.71 g) was added to a solution of the compound (5.42 g) obtained in Referential Example 210 in a mixed solvent of ethanol (150 ml) and tetrahydrofuran (10.0 ml), and the mixture was stirred for 3 hours under a hydrogen atmosphere and then for 14 hours under nitrogen conditions. After insoluble matter was removed through Celite pad, and the filtrate was concentrated under reduced pressure, the resultant residue was dissolved in tetrahydrofuran (30 ml), and triethylamine (3.0 ml) was added thereto. The mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate 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, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 25:1) to obtain the title compound (2.50 g).

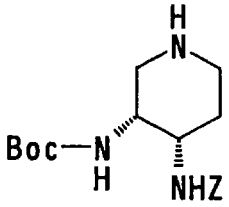
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 2.30-2.50(1H,br), 2.65-

2.90(1H,br), 3.15-3.30(1H,br), 3.35-3.65(1H,br), 4.00-4.25(2H,br), 5.11(2H,s), 5.55-5.60(1H,br), 5.65-5.90(1H,br), 6.25-6.55(1H,br), 7.28-7.40(5H,m).

MS (ESI) m/z: 364$(M+H)^+$.

[Referential Example 212]

Benzyl (3R,4S)-3-[(tert-butoxycarbonyl)amino]piperidin-4-ylcarbamate:



1 M Borane·tetrahydrofuran complex (tetrahydrofuran solution, 34.0 ml) was added dropwise to a Tetrahydrofuran solution (70 µl) of the compound (2.49 g) obtained in Referential Example 211 under ice cooling, and the mixture was stirred for 20 hours while the temperature of the system was gradually raised to room temperature. Methanol (100 ml) was added to the reaction mixture, and the solvent was distilled off under reduced pressure. Ethanol (45 ml), water (5 ml) and triethylamine (10 ml) were aded to the residue, and the mixture was heated under reflux for 24 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol: water = 7:3:1, lower layer) to obtain the title compound (1.61 g).

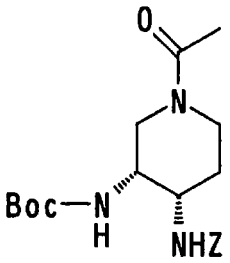
^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.65-1.72(2H,m), 2.67(1H,t,J=12.0Hz), 2.82(12H,d,J=12.0Hz), 2.90-3.10(1H,br),

3.60-3.80(2H,m), 3.90-4.00(1H,m), 5.00-5.20(2H,m), 5.40-5.60(2H,br), 7.25-7.74(5H,m).

MS (FAB) m/z: 350$(M+H)^+$.

[Referential Example 213]

tert-Butyl (3R,4S)-1-acetyl-4-{[(benzyloxy)carbonyl]amino}-piperidin-3-ylcarbamate:



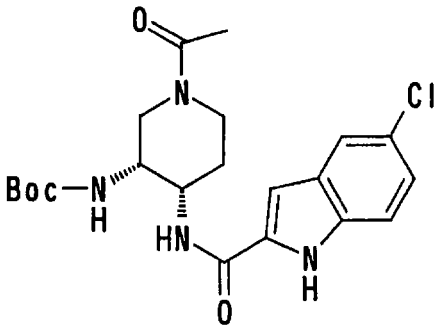
The title compound was obtained by reaction of the compound obtained in Referential Example 212 with acetyl chloride and triethylamine in methylene chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.85-2.15(2H,m), 2.07(1.5H,s), 2.14(1.5H,s), 2.75-2.90(1H,m), 3.10-3.20(0.5H,m), 3.25-3.35(0.5H,br.d,J=14.2Hz), 3.65-4.05(3H,m), 4.38-4.47(0.5H,br.d,J=13.0Hz), 4.5,4-4.63(0.5H,m), 4.69-4.83(1H,br), 4.98-5.20(2.5H,m), 5.90-6.05(0.5H,br), 7.30-7.40(5H,m).

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

[Referential Example 214]

tert-Butyl (3R,4S)-1-acetyl-4-{[(5-chloroindol-2-yl)-carbonyl]amino}piperidin-3-ylcarbamate:



10% Palladium on carbon (532 mg) was added to a solution of the compound (745 mg) obtained in Referential Example 213 in ethanol (50 ml), and the mixture was stirred at room temperature for 16 hours under a hydrogen atmosphere. Insoluble matter was removed by filtration through Celite, and the filtrate was then concentrated under reduced pressure. The resultant residue was treated with 5-chloroindole-2-carboxylic acid (467 mg) in a similar manner to Referential Example 68 to obtain the title compound (650 mg).

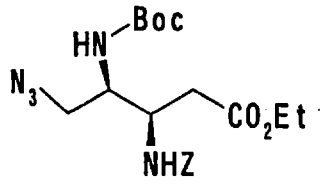
^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.60-1.80(2H,m), 2.12(1H,s), 2.16(2H,s), 2.30-2.45(0.5H,m), 2.67-2.82(0.3H,m), 2.89(0.7H,d,J=13.7Hz), 3.23(0.7H,t,J=12.9Hz), 3.37(0.3H,d,J=13.7Hz), 3.81-3.95(1H,m), 4.05-4.33(2H,m), 4.62-4.72(0.3H,br), 4.77(0.7H,d,J=13.7Hz), 5.10-5.27(1H,m), 6.81(0.3H,br.s), 6.85(0.7H,s), 7.21(1H,br.d,J=8.8Hz), 7.34(1H,d,J=8.8Hz), 7.57(0.3H,br.s), 7.61(0.7H,s), 8.55-8.65(0.5H,br), 9.43-9.53(0.7H,br), 9.60-9.70(0.3H,br).

MS (ESI) m/z: 435$(M+H)^+$.

[Referential Example 215]

Ethyl (3R,4R)-5-azido-3-{[(benzyloxy)carbonyl]amino}-4-

[(tert-butoxycarbonyl)amino]valerate:

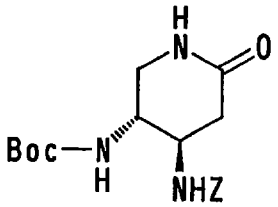


The title compound was obtained from the (3R,4S)-compound (high-polar compound) obtained in Referential Example 168 in a similar manner to Referential Example 210.

^{1}H-NMR ($CDCl_3$) δ: 1.23(3H,t,J=6.6Hz), 1.42(9H,s), 2.51-2.63(2H,m), 3.43-3.50(2H,m), 3.84-3.92(1H,m), 4.03-4.23(3H,m), 5.10(2H,s), 5.11-5.24(1H,m), 5.54-5.60(1H,m), 7.32-7.44(5H,m).

[Referential Example 216]

Benzyl (4R,5R)-5-[(tert-butoxycarbonyl)amino]-2-oxo-piperidin-4-ylcarbamate:

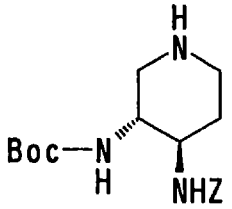


The title compound was obtained by treating the compound obtained in Referential Example 215 in a similar manner to Referential Example 211.

^{1}H-NMR (DMSO-d_6) δ: 1.35(9H,s), 2.19(1H,dd,J=17.4,9.1Hz), 2.41-2.51(1H,m), 2.97(1H,t,J=9.1Hz), 3.00-3.11(1H,m), 3.51-3.64(1H,m), 3.67-3.73(1H,m), 5.00(2H,s), 6.71-6.80(1H,m), 7.20-7.30(5H,m), 7.44-7.52(1H,m), 8.30(1H,s).

[Referential Example 217]

Benzyl (3R,4R)-3-[(tert-butoxycarbonyl)amino]piperidin-4-ylcarbamate:

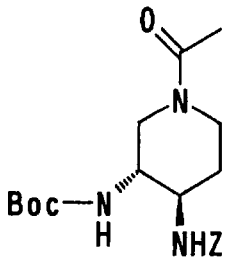


The title compound was obtained by treating the compound obtained in Referential Example 216 in a similar manner to Referential Example 212.

^{1}H-NMR ($CDCl_3$) δ: 1.39(9H,s), 2.05(2H,d,J=12.9Hz), 2.40(1H,t,J=11.0Hz), 2.63(1H,t,J=12.0Hz), 3.09(1H,d,J=12.0Hz), 3.31(1H,d,J=11.0Hz), 3.42-3.53(2H,m), 4.80-4.91(1H,m), 5.09(2H,s), 5.23-5.32(1H,m), 7.34-7.41(5H,m).

[Referential Example 218]

tert-Butyl (3R,4R)-1-acetyl-4-{[(benzyloxy)carbonyl]amino}-piperidin-3-ylcarbamate:



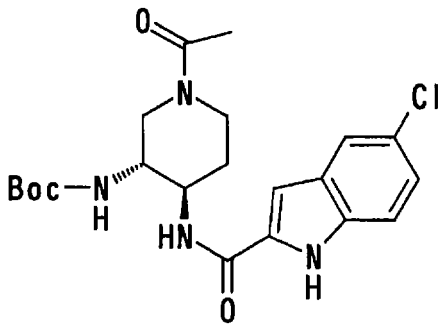
The title compound was obtained by treating the compound obtained in Referential Example 217 in a similar manner to Referential Example 213.

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 1.53-1.67(1H,m), 1.89-

2.00(1H,m), 2.09(1.5H,s), 2.15(1.5H,s), 2.57(1H,t,J=12.0Hz), 2.78(1H,t,J=12.0Hz), 3.20-3.30(1H,m), 3.40-3.56(2H,m), 4.23-4.31(1H,m), 4.45-4.56(1H,m), 5.01-5.08(1H,m), 5.10(2H,s), 7.32-7.44(5H,m).

[Referential Example 219]

tert-Butyl (3R,4R)-1-acetyl-4-{[(5-chloroindol-2-yl)-carbonyl]amino}piperidin-3-ylcarbamate:

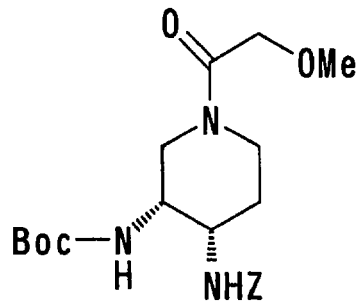


The title compound was obtained by treating the compound obtained in Referential Example 218 in a similar manner to Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.35(9H,s), 1.42-1.56(2H,m), 2.00-2.10(1H,m), 2.12(1.5H,s), 2.17(1.5H,s), 2.31-2.43(1H,m), 2.67-3.00(1H,m), 3.55-3.63(1H,m), 3.78-4.00(1H,m), 4.03-4.21(1H,m), 4.78-5.24(2H,m), 6.91(0.5H,s), 6.92(0.5H,s), 7.22-7.32(1H,m), 7.33(1H,d,J=8.8Hz), 7.58(1H,s), 9.45(0.5H,s), 9.51(0.5H,s).

[Referential Example 220]

Benzyl (3R,4S)-3-[(tert-butoxycarbonyl)amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:



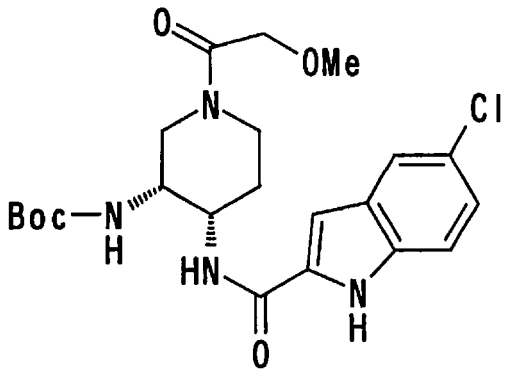
The title compound was obtained from the compound obtained in Referential Example 212 and methoxyacetyl chloride in a similar manner to Referential Example 213.

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.70-2.15(2H,m), 2.70-2.85(1H,m), 2.90-3.30(1H,m), 3.35-3.70(1H,m), 3.43(3H,s), 3.75-3.90(2H,m), 3.90-4.25(3H,m), 4.40-4.80(1H,m), 5.05-5.09(1H,m), 5.10(2H,br.s), 7.30-7.40(5H,m).

MS (ESI) m/z: 322($M+H^+$).

[Referential Example 221]

tert-Butyl (3R,4S)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:



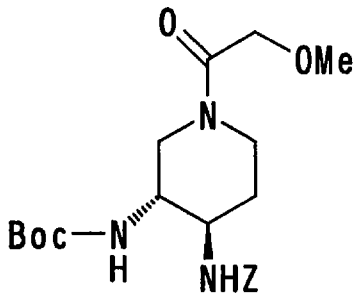
The title compound was obtained from the compound obtained in Referential Example 220 in a similar manner to Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.60-1.80(1H,m), 2.20-2.40(1H,m), 2.70-2.80(0.6H,m), 2.90-3.00(0.4H,m), 3.15-3.30(0.4H,m), 3.32-3.40(0.6H,m), 3.46,3.49(total 3H,each s), 3.85-4.30(5H,m), 4.55-4.80(1H,m), 5.11(0.4H,br.s), 6.05(0.6H,br.s), 6.86(1H,s), 7.20(1H,dd,J=8.7,2.0Hz), 7.33(1H,d,J=8.7Hz), 7.61(1H,s), 8.40-8.60(1H,m), 9.41(1H,br.s).

MS (FAB) m/z: 465$(M+H)^+$.

[Referential Example 222]

Benzyl (3R,4R)-3-[(tert-butoxycarbonyl)amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:



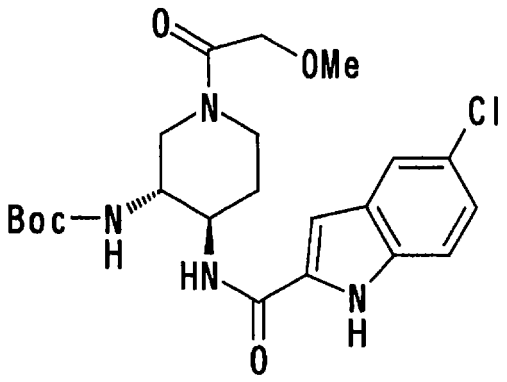
The title compound was obtained from the compound obtained in Referential Example 217 and methoxyacetyl chloride in a similar manner to Referential Example 213.

^{1}H-NMR ($CDCl_3$) δ: 1.41(9H,s), 1.45-1.67(1H,m), 2.01-2.14(1H,m), 2.63(1H,t,J=12.0Hz), 2.75(1H,t,J=12.0Hz), 3.20-3.30(1H,m), 3.32-3.41(5H,m), 3.44-3.56(2H,m), 4.21-4.32(1H,m), 4.50-4.63(1H,m), 5.03-5.08(1H,m), 5.09(2H,s), 7.32-7.40(5H,m).

[Referential Example 223]

tert-Butyl (3R,4R)-4-{[(5-chloroindol-2-yl)carbonyl]-

amino}-1-(2-methoxyacetyl)piperidin-3-ylcarbamate:

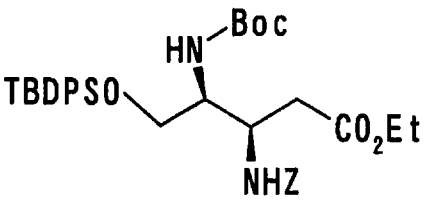


The title compound was obtained from the compound obtained in Referential Example 222 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.35(9H,s), 1.41-1.56(2H,m), 2.11-2.23(0.5H,m), 2.34-2.50(0.5H,m), 2.78-2.89(0.5H,m), 3.01-3.12(0.5H,m), 3.42(5H,s), 3.45-3.56(1H,m), 3.78-3.89(1H,m), 4.00-4.21(2H,m), 4.78-5.21(2H,m), 6.91(0.5H,s), 6.93(0.5H,s), 7.23(1H,dd,J=8.8,2.0Hz), 7.33(1H,d,J=8.8Hz), 7.59(1H,s), 9.37(0.5H,s), 9.54(0.5H,s).

[Referential Example 224]

Ethyl (3R,4S)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}-valerate:



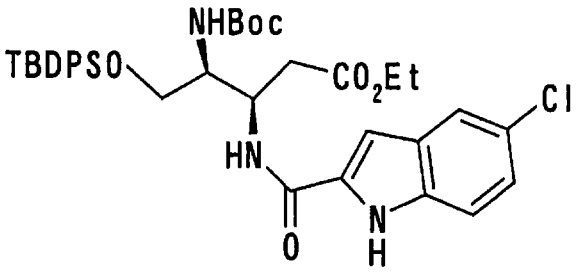
Triethylamine (0.47 ml), imidazole (0.19 g) and tert-

butylchlorodiphenylsilane (0.7 ml) were successively added to a solution of the (3R,4S)-compound (high-polar compound) (0.74 g) obtained in Referential Example 168 in N,N-dimethylformamide (30 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 a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 8:1) to obtain the title compound (0.85 g).

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.19(3H,t,J=7.4Hz), 1.40(9H,s), 2.40-2.50(1H,m), 2.60(1H,dd,J=15.9,4.5Hz), 3.56-3.67(1H,m), 3.74(1H,dd,J=11.2,4.5Hz), 3.78-3.89(1H,m), 4.08(2H,q,J=7.4Hz), 4.21-4.30(1H,m), 4.99-5.13(3H,m), 5.41-5.52(1H,m), 7.40-7.53(6H,m), 7.60-7.72(4H,m).

[Referential Example 225]

Ethyl (3R,4S)-4-[(tert-butoxycarbonyl)amino]-5-{[tert-butyl(diphenyl)silyl]oxy}-3-{[(5-chloroindol-2-yl)-carbonyl]amino}valerate:

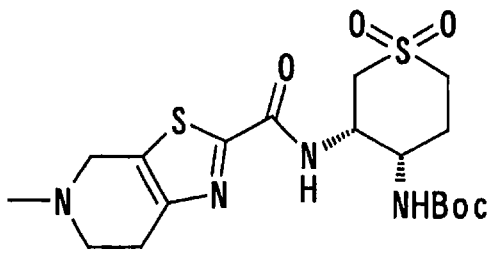


The title compound was obtained by removing the benzyloxycarbonyl group of the compound obtained in Referential Example 224 and condensing with 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.

^{1}H-NMR ($CDCl_3$) δ: 1.10(9H,s), 1.20(3H,t,J=7.4Hz), 1.32(9H,s), 2.40-2.52(1H,m), 2.71(1H,dd,J=15.9,4.5Hz), 3.67-3.81(2H,m), 4.00-4.20(2H,m), 4.56-4.74(1H,m), 5.00-5.11(1H,m), 6.81(1H,s), 7.21(1H,dd,J=8.8,2.0Hz), 7.32(1H,d,J=8.8Hz), 7.40-7.50(6H,m), 7.58(1H,d,J=8.5Hz), 7.63-7.74(5H,m), 9.01-9.14(1H,m).

[Referential Example 226]

tert-Butyl (3R*,4R*)-3-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:



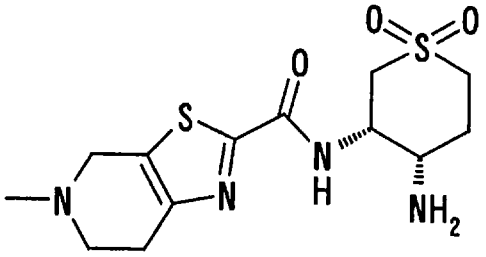
The title compound was obtained from the (3R*,4R*)-

compound (low-polar compound) obtained in Referential Example 179 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 68.

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 2.30-2.37(2H,m), 2.51(3H,s), 2.82-2.85(2H,m), 2.92-2.95(2H,m), 3.17-3.20(4H,m), 3.40-3.43(1H,m), 3.69-3.77(2H,m), 3.97-3.98(1H,m), 4.98(1H,br), 5.25(1H,br).

[Referential Example 227]

N-(3R*,4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



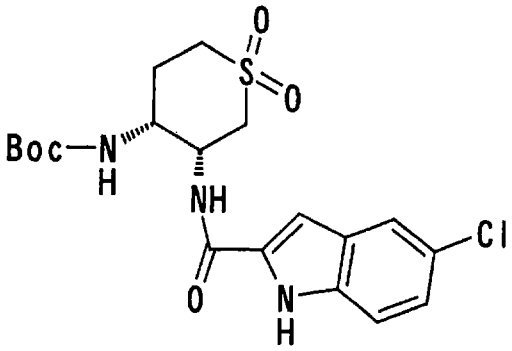
The title compound was obtained by treating the compound obtained in Referential Example 226 in a similar manner to Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 2.29-2.33(2H,m), 2.93(3H,s), 3.16(2H,br), 3.40(2H,br), 3.52(2H,br), 3.69-3.76(3H,m), 4.48(1H,br), 4.71-4.82(2H,m), 8.34(2H,br), 8.82(1H,br).

MS (ESI) m/z: 345$(M+H)^+$.

[Referential Example 228]

tert-Butyl (3R*,4R*)-3-{[(5-chloroindol-2-yl)carbonyl]-amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:



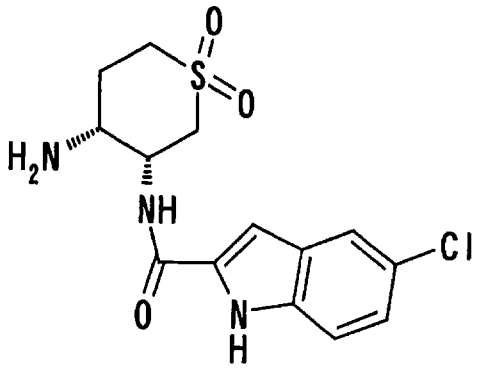
The title compound was obtained from the (3R*,4R*)-compound (low-polar compound) obtained in Referential Example 179 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 68.

^{1}H-NMR (DMSO-d_6) δ: 1.34(9H,s), 2.09(2H,br), 3.07(1H,d,J=12.6Hz), 3.24-3.28(1H,m), 3.48(2H,br), 4.12(1H,br), 4.53(1H,br), 7.04(1H,s), 7.16-7.18(2H,m), 7.44(1H,d,J=8.7Hz), 7.67(1H,s), 8.37(1H,br), 11.81(1H,s).

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

[Referential Example 229]

N-[(3R*,4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-chloroindole-2-carboxamide hydrochloride:



The title compound was obtained by treating the

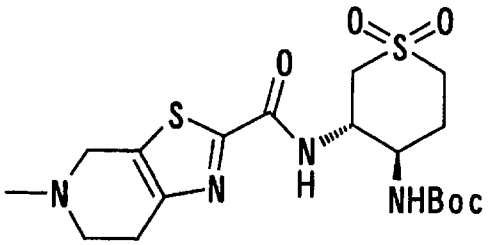
compound obtained in Referential Example 228 in a similar manner to Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 2.24-2.33(2H,m), 3.43-3.55(3H,m), 3.60-3.66(1H,m), 3.77(1H,br), 4.75-4.79(1H,m), 7.18-7.21(2H,m), 7.46(1H,d,J=8.8Hz), 7.72(1H,d,J=1.7Hz), 8.39(2H,br), 8.58(1H,d,J=6.8Hz), 11.93(1H,s).

MS (ESI) m/z: 342$(M+H)^+$.

[Referential Example 230]

tert-Butyl (3R*,4S*)-3-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:



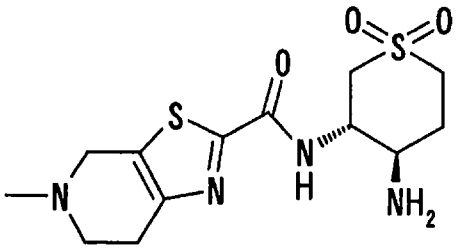
The title compound was obtained from the (3R*,4S*)-compound (high-polar compound) obtained in Referential Example 179 and the compound obtained in Referential Example 10 in a similar manner to Referential Example 98.

^{1}H-NMR ($CDCl_3$) δ: 1.32(9H,s), 2.14-2.24(1H,m), 2.33-2.38(1H,m), 2.50(3H,s), 2.78-2.83(2H,m), 2.86-2.95(2H,m), 3.08-3.14(3H,m), 3.55(1H,d,J=13.4Hz), 3.68(1H,d,J=15.5Hz), 3.72(1H,d,J=15.5Hz), 3.86-3.88(1H,m), 4.45-4.53(1H,m), 4.75(1H,d,J=8.5Hz), 7.76(1H,d,J=8.3Hz).

MS (ESI) m/z: 445$(M+H)^+$.

[Referential Example 231]

N-[(3R*,4S*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-2-carboxamide hydrochloride:



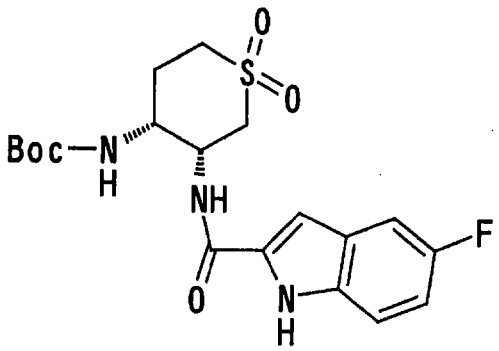
The title compound was obtained by treating the compound obtained in Referential Example 230 in a similar manner to Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 2.03-2.12(1H,m), 2.51(1H,br), 2.93(3H,s), 3.14(2H,d,J=12.2Hz), 3.28(2H,br), 3.33(2H,br), 3.48(3H,br),3.72(2H,br), 4.49(2H,br), 4.71-4.74(1H,m), 8.38(2H,br), 9.21-9.24(1H,m).

MS (ESI) m/z: 345$(M+H)^+$.

[Referential Example 232]

tert-Butyl (3R*,4R*)-3-{[(5-fluoroindol-2-yl)carbonyl]-amino}-1,1-dioxohexahydro-1-thiopyran-4-ylcarbamate:



The title compound was obtained from the (3R*,4R*)-compound (low-polar compound) obtained in Referential

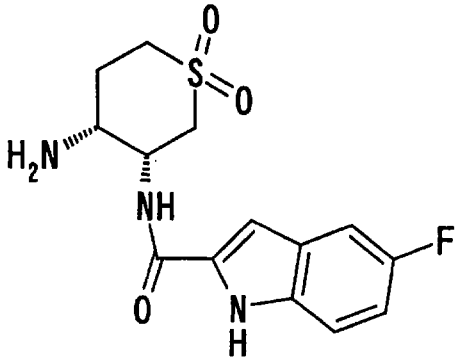
Example 179 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 68.

^{1}H-NMR (DMSO-d_6) δ: 1.37(9H,s), 2.10-2.13(2H,m), 3.06(1H,br), 3.37-3.49(3H,m), 4.13(1H,br), 4.57(1H,br), 6.95-7.01(2H,m), 7.14(1H,br), 7.30(1H,d,J=8.5Hz), 7.41(1H,dd,J=8.8,4.5Hz), 8.28(1H,br),11.68(1H,s).

MS (ESI) m/z: 426$(M+H)^+$.

[Referential Example 233]

N-[(3R*,4R*)-4-Amino-1,1-dioxohexahydro-1-thiopyran-3-yl]-5-fluoroindole-2-carboxamide hydrochloride:



The title compound was obtained by treating the compound obtained in Referential Example 232 in a similar manner to Referential Example 69.

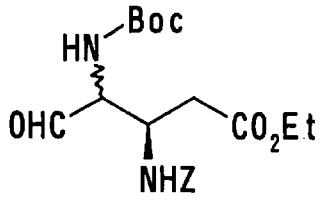
^{1}H-NMR (DMSO-d_6) δ: 2.25-2.31(1H,m), 2.47(1H,br), 3.30(1H,br), 3.49-3.53(2H,m), 3.60-3.66(1H,m), 3.78(1H,br), 4.79(1H,br),7.01-7.05(1H,m), 7.21(1H,s), 7.38(1H,d,J=9.0Hz), 7.44(1H,dd,J=8.8,4.4Hz), 8.40(2H,br), 8.56(1H,br), 11.81(1H,s).

MS (ESI) m/z: 326$(M+H)^+$.

[Referential Example 234]

Ethyl (3R)-3-{[(benzyloxy)carbonyl]amino}-4-[(tert-

butoxycarbonyl)amino]-5-oxovalerate:

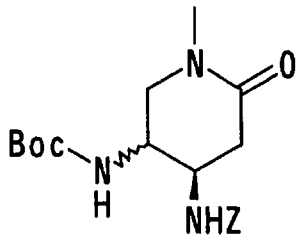


Sulfur trioxide-pyridine comples (1.5 g) was gradually added to a mixed solvent composed of the (3R,4S)-compound (high-polar compound) (0.5 g) obtained in Referential Example 168, dimethyl sulfoxide (6.8 ml) and triethylamine (2.6 ml), and the mixture was stirred for 20 minutes. The reaction mixture was poured into water and extracted with ethyl acetate. The resultant organic layer was washed with a saturated aqueous solution of ammonium chloride, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (0.51 g).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.4Hz), 1.44(9H,s), 2.51-2.70(2H,m), 4.01-4.23(2H,m), 4.45-4.67(1H,m), 5.00-5.23(2H,s), 5.24-5.42(1H,m), 7.23-7.43(5H,m), 9.63(0.5H,s), 9.67(0.5H,s).

[Referential Example 235]

Benzyl (4R)-5-[(tert-butoxycarbonyl)amino]-1-methyl-2-oxopiperidin-4-ylcarbamate:



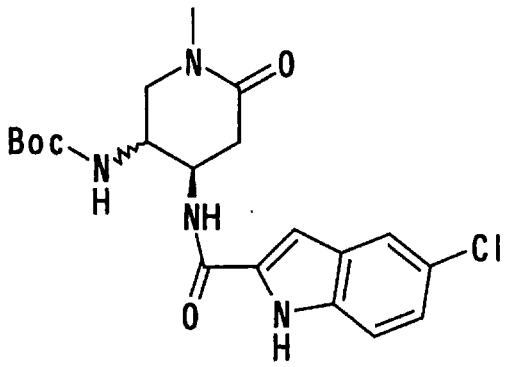
Acetic acid (0.27 ml) and 2 M methylamine (tetrahydrofuran solution, 1.0 ml) were successively added to a solution of the compound (0.51 g) obtained in Referential Example 234 in ethanol (10 ml) under ice cooling, and the mixture was stirred for 1 hour while the temperature of the system was gradually raised to room temperature. Sodium cyanoborohydride (0.15 g) was added to stir the mixture for 18 hours. The reaction mixture was diluted with chloroform 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, the solvent was distilled off under reduced pressure, and the resultant residue was dissolved in toluene (20 ml). Triethylamine (2 ml) was added to this solution, and the mixture was heated under reflux for 2 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was purified by column chromatagraphy on silica gel (chloroform:methanol = 98:2) to obtain the title compound (0.28 g).

^{1}H-NMR (DMSO-d_6) δ: 1.36(3.6H,s), 1.38(5.4H,s), 2.22-2.43(1H,m), 2.44-2.61(1H,m), 2.72(1.2H.s), 2.80(1.8H.s),

3.10(0.5H,dd,J=12.5,8.3Hz), 3.21-3.30(0.5H,m), 3.33-3.45(1H,m), 3.56-3.82(1H,m), 3.89-4.00(1H,m), 4.94(1H,d,J=8.1Hz), 5.00(1.2H.s), 5.01(0.8H,s), 6.89-7.02(0.5H,m), 7.23-7.44(5.5H,m).

[Referential Example 236]

tert-Butyl (4R)-4-{[(5-chloroindol-2-yl)carbonyl]amino}-1-methyl-6-oxopiperidin-3-ylcarbamate:

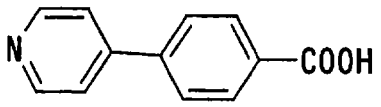


The title compound was obtained from the compound obtained in Referential Example 235 and 5-chloroindole-2-carboxylic acid in a similar manner to Referential Example 214.

^{1}H-NMR (DMSO-d_6) δ: 1.24(5.4H,s), 1.35(3.6H,s), 2.43-2.56(2H,m), 2.80(3H,s), 3.10-3.20(1H,m), 3.30-3.52(1H,m), 3.83-3.91(0.4H,m), 4.02-4.10(0.6H,m), 4.20-4.31(0.6H,m), 4.43-4.54(0.4H,m), 6.94(0.6H,d,J=8.1Hz), 7.08(1H,s), 7.16(1H,dd,J=8.8,2.0Hz), 7.42(1H,d,J=8.8Hz), 7.69(1H,d,J=2.0Hz), 8.30(0.4H,s), 8.36(0.4H,d,J=7.3Hz), 8.43(0.6H,d,J=8.3Hz), 11.75(0.6H,s), 11.78(0.4H,s).

[Referential Example 237]

4-(Pyridin-4-yl)benzoic acid hydrochloride:



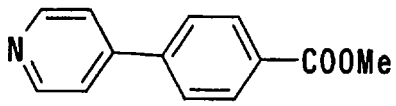
4-Bromopyridine hydrochloride (11.7 g) and 4-carboxyphenylboric acid (10.0 g) were dissolved in a mixed solvent of toluene (250 ml) and water (250 ml), tetrakis(triphenylphosphine)palladium(0) (5.0 g) and anhydrous sodium carbonate (25.4 g) were successively added, and the mixture was heated under reflux at 120°C for 19 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added to the reaction mixture to extract it with water. Concentrated hydrochloric acid was added to the water layer to acidify it. The water layer was washed with ethyl acetate and then concentrated, and solids deposited were collected to obtain the title compound (8.37 g).

^{1}H-NMR (DMSO-d_6) δ: 8.11(2H,d,J=8.8Hz), 8.14(2H,dJ=8.8Hz), 8.35(2H,d,J=6.6Hz), 8.97(2H,d,J=6.6Hz).

MS (FAB) m/z: 200$(M+H)^+$.

[Referential Example 238]

Methyl 4-(Pyridin-4-yl)benzoate:



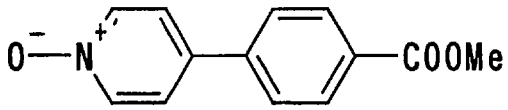
The compound (12.4 g) obtained in Referential Example 237 was dissolved in methanol (200 ml), concentrated sulfuric acid (5 ml) was added at room temperature, and the

mixture was heated under reflux for 3 hours. After completion of the reaction, the solvent was distilled off, and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue to extract it with ethyl acetate. The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and hexane was added to the residue to solidify it, thereby obtaining the title compound (9.86 g).

^{1}H-NMR ($CDCl_3$) δ: 3.96(3H,s), 7.54(2H,d,J=5.9Hz), 7.71(2H,dJ=8.3Hz), 8.16(2H,d,J=8.3Hz), 8.71(2H,d,J=5.9Hz).

[Referential Example 239]

4-[4-(Methoxycarbonyl)phenyl]pyridine N-oxide:



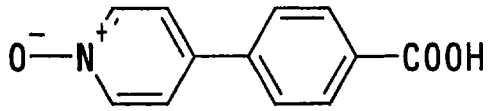
The compound (1.49 g) obtained in Referential Example 238 was dissolved in methylene chloride (30 ml), 70% m-chloroperbenzoic acid (3.46 g) was added, and the mixture was stirred at room temperature for 1 hour. An aqueous solution of sodium sulfite was added to conduct liquid separation. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain the title compound (1.33 g).

^{1}H-NMR (DMSO) δ: 3.88(3H,s), 7.86(2H,d,J=7.2Hz), 7.94(2H,d,J=8.3Hz), 8.05(2H,d,J=8.3Hz), 8.30(2H,d,J=7.2Hz).

MS (FAB) m/z: 230$(M+H)^+$.

[Referential Example 240]

4-(4-Carboxyphenyl)pyridine N-oxide:

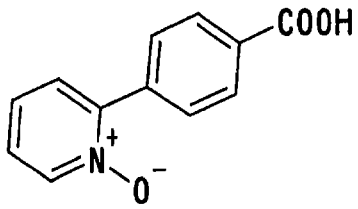


The compound (802 mg) obtained in Referential Example 239 was dissolved in dioxane (20 ml), a 1N aqueous solution (5 ml) of sodium hydroxide was added, and the mixture was refluxed for 1 hour and then stirred at room temperature for 2 hours. 1N Hydrochloric acid (5 ml) was added to neutralize it. Further, water (5 ml) was added, and precipitate formed was collected by filtration to obtain the title compound (627 mg).

^{1}H-NMR (DMSO) δ: 7.85(2H,d,J=7.2Hz), 7.91(2H,d,J=8.3Hz), 8.03(2H,d,J=8.3Hz), 8.30(2H,d,J=7.2Hz).

[Referential Example 241]

2-(4-Carboxyphenyl)-1-pyridine N-oxide:



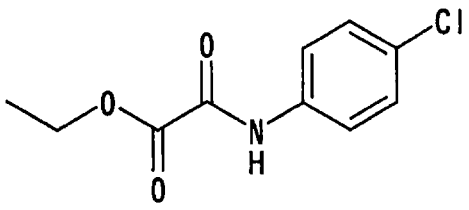
The title compound was obtained from 2-bromopyridine in similar manners to Referential Examples 237, 238, 239 and 240.

^{1}H-NMR (DMSO-d_6) δ: 7.41-7.45(2H,m), 7.65-7.69(1H,m), 7.94(2H,d,J=8.3Hz), 8.02(2H,d,J=8.3Hz), 8.34-8.38(1H,m), 13.09(1H,s).

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

[Referential Example 242]

Ethyl 2-(4-chloroanilino)-2-oxoacetate:



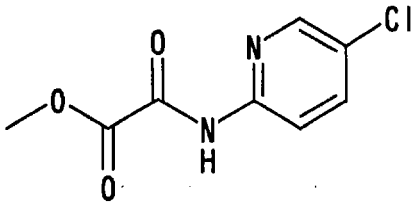
Triethylamine (1.52 ml) and ethyl chlorooxoacetate (1.11 ml) were successively added to a solution of 4-chloroaniline (1.16 g) in methylene chloride (26 ml), and the mixture was stirred at room temperature for 14 hours. After a saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation, the resultant organic layer was successively washed with a 10% aqueous solution of citric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, hexane was added to the residue to deposit crystals, and the crystals were collected by filtration and dried to obtain the title compound (1.89 g).

^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.1Hz), 4.42(2H,q,J=7.1Hz), 7.34(2H,d,J=8.8Hz), 7.60(2H,d,J=8.8Hz), 8.86(1H,br.s).

MS (ESI)m/z: 228$(M+H)^+$.

[Referential Example 243]

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



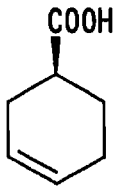
2-Amino-5-chloropyridine (1.16 g) and triethylamine (1.51 ml) were dissolved in methylene chloride (26 ml), ethyl chlorooxoacetate (1.10 ml) was added to the solution under ice cooling, and the mixture was stirred at room temperature for 14 hours. After a saturated aqueous solution of sodium hydrogencarbonate 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 chromatagraphy on silica gel (hexane:ethyl acetate = 3:1). The thus-obtained pale yellow solids were dissolved in methanol (20 ml), and the solution was stirred at 50°C for 11 hours. The reaction mixture was concentrated under reduced pressure, and crystals deposited were collected by filtration and dried to obtain the title compound (0.43 g).

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.73(1H,dd,J=8.8,2.2Hz), 8.24(1H,d,J=8.8Hz), 8.31(1H,d,J=2.2Hz), 9.39(1H,br.s).

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

[Referential Example 244]

(1S)-3-Cyclohexene-1-carboxylic acid:



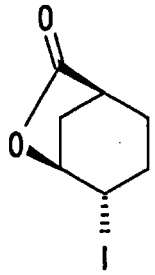
The (R)-(+)-α-methylbenzylamine salt (J. Am. Chem. Soc., Vol. 100, pp. 5199-5203, 1978) (95.0 g) of (1S)-3-cyclohexene-1-carboxylic acid was dissolved in a mixture of ethyl acetate (1.6 l) and 2N hydrochloric acid (1.6 l). After an organic layer was taken out, a water layer was extracted with ethyl acetate (500 ml x 2 times). The resultant organic layers were combined and washed with saturated aqueous solution of sodium chloride (300 ml x 2 times) to take out an organic layer. After a water layer was extracted with ethyl acetate (200 ml), the resultant organic layer was washed with saturated aqueous solution of sodium chloride (100 ml). All organic layers were combined and dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound (48.3 g).

$[\alpha]^{25}_{D}$ = -104° (c = 1, chloroform).

^{1}H-NMR ($CDCl_3$) δ: 1.66-1.77(1H,m), 2.00-2.20(3H,m), 2.20-2.38(2H,m), 2.57-2.65(1H,m), 5.65-5.75(2H,m).

[Referential Example 245]

(1S,4S,5S)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one:



Iodine (125.4 g) was added to a mixture of the compound (48.0 g) obtained in Referential Example 244, methylene chloride (580 ml), potassium iodide (82. 1 g), sodium hydrogencarbonate (42.0 g) and water (530 ml) at an internal temperature of 5°C, and the resultant mixture was stirred at room temperature for 3 hours. After a 1N aqueous solution (800 ml) of sodium thiosulfate was added to the reaction mixture, the resultant mixture was extracted with methylene chloride (1 L, 500 ml). The resultant organic layer was washed with an aqueous solution (300 ml) of sodium hydrogencarbonate, water (500 ml) and saturated aqueous solution of sodium chloride (300 ml), dried over anhydrous magnesium sulfate and then concentrated. Crystals deposited were collected by filtration, washed with hexane and then dried to obtain the title compound (89.5 g).

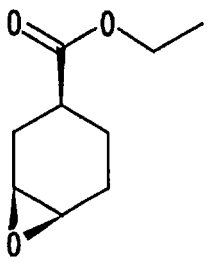
Mp. 130-131°C

$[\alpha]^{25}_{D}$ = -41° (c = 1, chloroform).

^{1}H-NMR ($CDCl_3$) δ: 1.78-1.96(2H,m), 2.12(1H,dd,J=16.5Hz,5.2Hz), 2.35-2.50(2H,m), 2.65-2.70(1H,m), 2.80(1H,d,J=12.2Hz), 4.45-4.55(1H,m), 4.77-4.87(1H,m).

[Referential Example 246]

Ethyl (1S,3S,6R)-7-oxabicyclo[4.1.0]heptane-3-carboxylate:



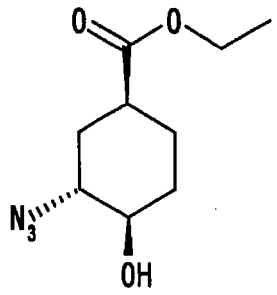
A 2N aqueous solution (213 ml) of sodium hydroxide was added to an ethanol (810 ml) suspension of the compound (89.3 g) obtained in Referential Example 245, and the mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure on a hot bath of 35°C, and water (500 ml) was added to the resultant oil to conduct extraction with methylene chloride (500 ml and 300 ml). The extract was washed with water (300 ml) and dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The resultant oil was purified by column chromatography on silica gel (hexane:ethyl acetate = 85:15) to obtain the title compound (41.3 g).

$[\alpha]^{25}_{D}$ = -58° (c = 1, chloroform).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.2Hz), 1.50-1.70(2H,m), 1.71-1.82(1H,m), 2.08-2.28(4H,m), 3.16(2H,s), 4.12(2H,q,J=7.2Hz).

[Referential Example 247]

Ethyl (1S,3R,4R)-3-azido-4-hydroxycyclohexanecarboxylate:



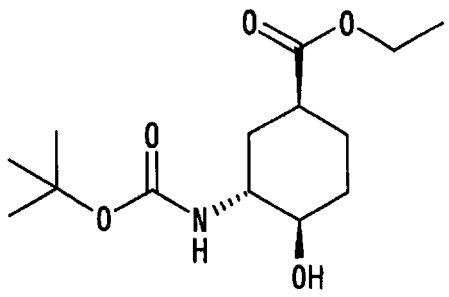
A mixture of the compound (41.0 g) obtained in Referential Example 246, N,N-dimethylformamide (300 ml), ammonium chloride (19.3 g) and sodium azide (23.5 g) was stirred at 76°C for 13 hours. After insoluble matter was taken out by filtration, the filtrate was concentrated under reduced pressure without solidifying, and the product previously taken out by filtration was added to the residue, and the mixture was dissolved in water (500 ml). The solution was extracted with ethyl acetate (500 ml and 300 ml), and the extract was washed with water and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then concentrated to obtain the title compound (51.5 g).

$[\alpha]^{25}_{D}$ = +8° (c = 1, chloroform).

^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.37-1.64(3H,m), 1.86-1.95(1H,m), 2.04-2.16(1H,m), 2.32-2.41(1H,m), 2.44(1H,br.s), 2.68-2.78(1H,m), 3.45-3.60(2H,m), 4.17(2H,q,J=7.1Hz).

[Referential Example 248]

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



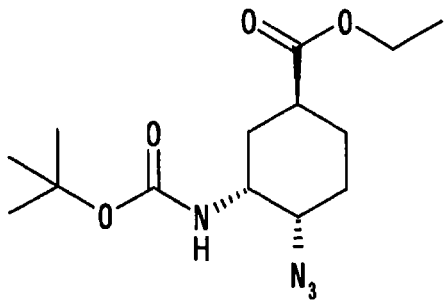
A mixture of the compound (51.2 g) obtained in Referential Example 247, di-tert-butyl dicarbonate (68.1 g), 5% palladium on carbon (5.0 g) and ethyl acetate (1000 ml) was stirred overnight at room temperature under a hydrogen pressure (7 kg/cm^2). An oil obtained by filtering the reaction mixture and concentrating the filtrate was purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1 → 3:1). The purified product was crystallized from hexane to obtain the title compound (46.9 g). The mother liquor was additionally purified by column chromatography on silica gel (chloroform:methanol = 100:1) to obtain the title compound (6.74 g).

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

^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.38-1.57(3H,m), 1.45(9H,s), 1.86-1.95(1H,m), 2.05-2.17(1H,m), 2.29-2.39(1H,m), 2.61-2.68(1H,m), 3.34(1H,br.s), 3.39-3.48(1H,m), 3.53-3.64(1H,m), 4.10-4.24(2H,m), 4.54(1H,br.s).

[Referential Example 249]

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



Methanesulfonyl chloride (42 ml) was added dropwise to a solution containing the compound (53.5 g) obtained in Referential Example 248, methylene chloride (500 ml) and triethylamine (130 ml) over 20 minutes at -10°C to -15°C. The mixture was heated to room temperature over 2 hours and stirred for 2 hours. 0.5N Hydrochloric acid (800 ml) was added dropwise to the reaction mixture at 0°C to acidify it, and extraction was conducted with methylene chloride (500 ml and 300 ml). The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The crystals thus obtained were dissolved in N,N-dimethylformamide (335 ml), sodium azide (60.5 g) was added, and the mixture was stirred at 67°C to 75°C for 16 hours. After the reaction mixture was filtered, the filtrate was concentrated under reduced pressure to distill off 250 ml of the solvent. The residue was combined with the product previously taken out by filtration, and the mixture was dissolved in water (500 ml). The solution was extracted with ethyl acetate (1 L and 300 ml), and the extract was washed with saturated

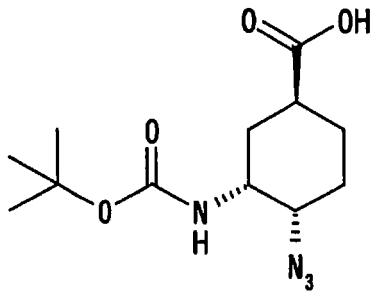
aqueous solution of sodium chloride (400 ml and 200 ml), dried over anhydrous magnesium sulfate and then concentrated. The crystals thus obtained were purified by column chromatography on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compounds (18.4 g).

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

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.35-2.00(15H,s), 2.60-2.68(1H,m), 3.80-3.96(2H,m), 4.15(2H,q,J=7.1Hz), 4.61(1H,br.s).

[Referential Example 250]

(1S,3R,4S)-4-Azido-3-[(tert-butoxycarbonyl)amino]-cyclohexanecarboxylic acid:



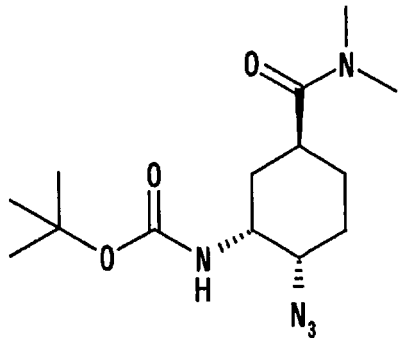
Lithium hydroxide (102 mg) and water (5 ml) were added to a solution of the compound (1.0 g) obtained in Referential Example 249 in tetrahydrofuran (25 ml). After stirring for 17 hours, lithium hydroxide (50 mg) was additionally added to stir the mixture for 4 hours. 1N Hydrochloric acid (6.3 ml) was added to the reaction mixture to conduct extraction with ethyl acetate. After the resultant organic layer was dried, the solvent was distilled off under reduced pressure to obtain the title

compound (980 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.30-2.20(6H,m), 1.45(9H,s), 2.70-2.80(1H,m), 3.94(2H,br.s), 4.73(1H,br.s).

[Referential Example 251]

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



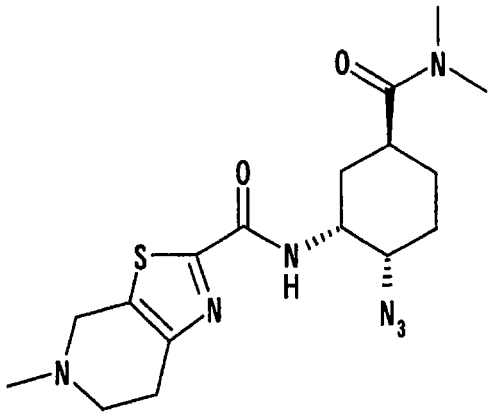
The compound (4.77 g) obtained in Referential Example 250 was dissolved in methylene chloride (150 ml), to which dimethylamine hydrochloride (3.26 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.60 g), 1-hydroxybenzotriazole monohydrate (3.24 g) and N-methylmorpholine (8.09 g) were added, and the mixture was stirred at room temperature for 18 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct liquid separation. The resultant organic layer was then dried, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methanol:methylene chloride = 1:50) to obtain the title compound (4.90 g).

^{1}H-NMR ($CDCl_3$) δ: 1.30-1.90(4H,m), 1.45(9H,s), 1.97-

2.18(2H,m), 2.75-2.85(1H,m), 2.92(3H,s), 3.02(3H,s), 3.68-3.80(1H,m), 4.05-4.20(1H,m), 4.55-4.75(1H,m).

[Referential Example 252]

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



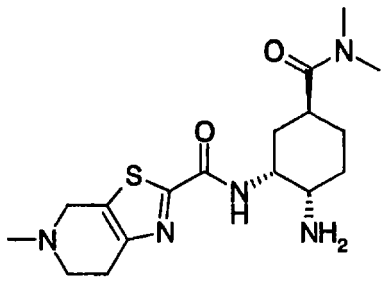
The compound (9.13 g) obtained in Referential Example 251 was dissolved in methylene chloride (100 ml), and an ethanol solution (100 ml) of hydrochloric acid was added to stir the mixture at room temperature for 1 minute. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in N,N-dimethylformamide (200 ml). To the solution were added the compound (7.75 g) obtained in Referential Example 10, 1-hydroxybenzotriazole monohydrate (4.47 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.2 g) and triethylamine (2.02 ml), and the mixture was stirred overnight at room temperature. The compound (2.38 g) obtained in Referential Example 10 and 1-(3-

dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.60 g) were additionally added to stir the mixture for 3 days. The reaction mixture was concentrated 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 dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was then purified by column chromatagraphy on silica gel (methylene chloride:methanol = 47:3) to obtain the title compound (7.38 g).

^{1}H-NMR ($CDCl_3$) δ: 1.72-1.97(4H,m), 2.10-2.27(2H,m), 2.51(3H,s), 2.77-3.05(11H,m), 3.68(1H,d,J=15.4Hz), 3.74(1H,d,J=15.4Hz), 3.86-3.93(1H,m), 4.54-4.60(1H,m), 7.25(1H,d,J=7.6Hz).

[Referential Example 253]

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



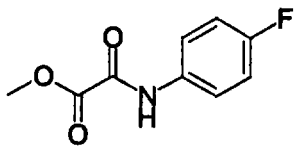
10% Palladium on carbon (6.0 g) was added to a solution of the compound (9.0 g) obtained in Referential

Example 252 in methanol (300 ml), and the mixture was vigorously stirred at room temperature for 11 hours under a hydrogen pressure of 4 atm. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain the title compound (7.67 g).

^{1}H-NMR ($CDCl_3$) δ: 1.42-1.54(1H,m), 1.66-1.89(5H,m), 2.30-2.40(1H,m), 2.51(3H,s), 2.68-3.05(6H,m), 2.92(3H,s), 3.00(3H,s),3.10-3.18(1H,m), 3.65-3.77(2H,m), 4.21-4.28(1H,m), 7.52(1H,d,J=6.1Hz).

[Referential Example 254]

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



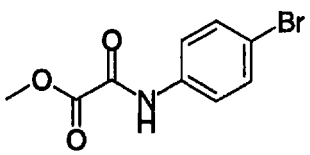
The title compound was obtained from 4-fluoroaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.00-7.14(2H,m), 7.55-7.68(2H,m), 8.85(1H,br.s).

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

[Referential Example 255]

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



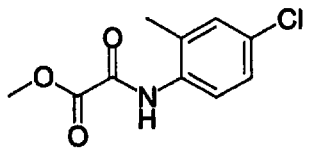
The title compound was obtained from 4-bromoaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.49(2H,d,J=9.0Hz), 7.55(2H,d,J=9.0Hz), 8.85(1H,br.s).

MS (FAB)m/z: 258 M^+.

[Referential Example 256]

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



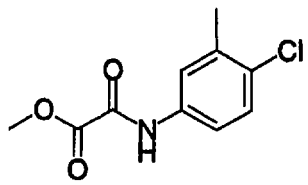
The title compound was obtained from 4-chloro-2-methylaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 2.31(3H,s), 3.99(3H,s), 7.15-7.30(2H,m), 7.98(1H,d,J=8.8Hz), 8.77(1H,br).

MS (FAB) m/z: 228$(M+H)^+$.

[Referential Example 257]

Methyl 2-[(4-chloro-3-methylanilino)-2-oxoacetate:

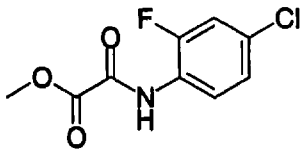


The title compound was obtained from 4-chloro-3-methylaniline and methyl chlorooxoacetate in a similar manner to Reference Example 242.

^{1}H-NMR($CDCl_3$)δ:2.39(3H,s),3.98(3H,s),7.33(1H,d,J=12.5Hz),
7.44(1H,dd,J=12.5,2.5Hz),7.53(1H,d,J=2.5Hz),8.81(1H,br.s).
MS(ESI)m/z:228$(M+H)^+$.

[Referential Example 258]

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

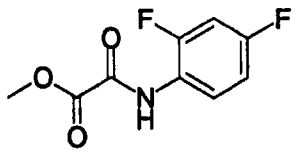


The title compound was obtained from 4-chloro-2-fluoroaniline and methyl chlorooxoacetate in a similar manner to Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.15-7.24(2H,m),
8.33(1H,t,J=8.4Hz), 9.05(1H,br.s).
MS (ESI) m/z: 232$(M+H)^+$.

[Referential Example 259]

Methyl 2-(2,4-difluoroanilino)-2-oxoacetate:

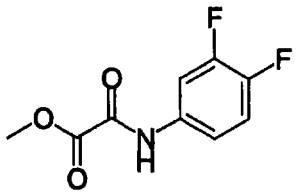


The title compound was obtained from 2,4-difluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 6.87-7.00(2H,m)、8.29-
8.38(1H,m), 8.99(1H,br.s).
MS (ESI) m/z: 215 M^+.

[Referential Example 260]

Methyl 2-(3,4-difluoroanilino)-2-oxoacetate:



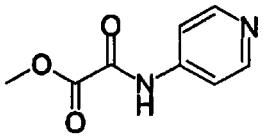
The title compound was obtained from 3,4-difluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.98(3H,s), 7.10-7.28(2H,m), 7.67-7.78(1H,m), 8.83(1H,br.s).

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

[Referential Example 261]

Methyl 2-oxo-2-(pyridin-4-ylamino)acetate:



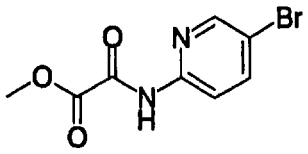
The title compound was obtained from 4-aminopyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.58(2H,dd,J=4.8,1.6Hz), 8.60(2H,dd,J=4.8,1.6Hz), 9.04(1H,br.s).

MS (ESI) m/z: 181$(M+H)^+$.

[Referential Example 262]

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



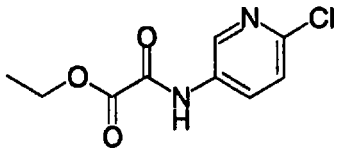
The title compound was obtained from 2-amino-5-bromopyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 3.99(3H,s), 7.87(1H,dd,J=8.8,2.4Hz), 8.19(1H,d,J=8.8Hz), 8.41(1H,d,J=2.4Hz), 9.38(1H,br.s).

MS (FAB) m/z: 259 M^+.

[Referential Example 263]

Ethyl 2-[(6-chloropyridin-3-yl)amino]-2-oxoacetate:



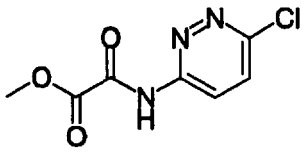
5-Amino-2-chloropyridine (386 mg) was dissolved in N,N-dimethylformamide (8 ml), and potassium 2-ethoxy-2-oxoacetate (469 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (863 mg) and 1-hydroxybenzotriazole monohydrate (203 mg) were added to stir the mixture at room temperature for 2 days. After the solvent was distilled off under reduced pressure, methylene chloride and 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. After the solvent was concentrated under reduced pressure, the residue was

purified by flash column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain residue (200 mg) containing the title compound.

^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.2Hz), 4.44(2H,q,J=7.2Hz), 7.36(1H,d,J=8.7Hz), 8.24(1H,dd,J=8.7,2.7Hz), 8.55(1H,d,J=2.7Hz), 9.03(1H,br.s).

[Referential Example 264]

Methyl 2-[(6-chloropyridazin-3-yl)amino]-2-oxoacetate:



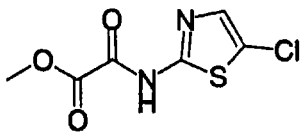
3-Amino-6-chloropyridazine (516 mg) was dissolved in pyridine (26 ml), and triethylamine (665 µl) and methyl chlorooxoacetate (441 µl) were successively added under ice cooling to stir the mixture at room temperature for 14 hours. After water was added to the reaction mixture to conduct liquid separation, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (748 mg).

^{1}H-NMR ($CDCl_3$) δ: 4.03(3H,s), 7.59(1H,d,J=9.3Hz), 8.52(1H,d,J=9.3Hz), 9.88(1H,br.s).

MS (FAB) m/z: 215M^+.

[Referential Example 265]

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



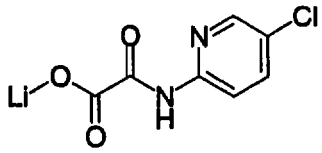
The title compound was obtained from 2-amino-5-chlorothiazole and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{1}H-NMR ($CDCl_3$) δ: 4.02(3H,s), 7.48(1H,s), 11.03(1H,br.s).

MS (ESI) m/z: 221$(M+H)^+$.

[Referential Example 266]

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

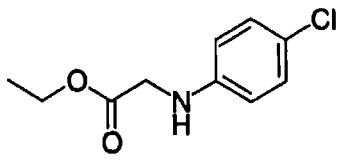


Water (5.0 ml) and lithium hydroxide (128 mg) were added to a solution of the compound (1.12 g) obtained in Referential Example 243 in tetrahydrofuran (20 ml) at room temperature, and the mixture was stirred for 5 hours. The solvent was distilled off under reduced pressure, hexane (30 ml) was added to the resultant white solids, and the mixture was stirred for 30 minutes. The solides were collected by filtration and then dried to obtain the title compound (1.02 g).

^{1}H-NMR (DMSO-d_6) δ: 7.90(1H,dd,J=8.9,2.6Hz), 8.12(1H,d,J=8.9Hz), 8.34(1H,d,J=2.6Hz), 10.18(1H,s).

[Referential Example 267]

Ethyl 2-(4-chloroanilino)acetate:

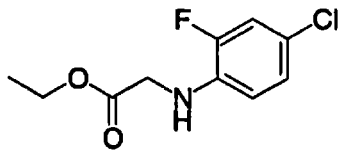


4-Chloroaniline (2.0 g) was dissolved in acetonitrile (20 ml), and ethyl bromoacetate (2.1 g) and potassium carbonate (2.2 g) were added to stir the mixture at 60°C for 2 days. The reaction mixture was filtered through Celite pad, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (hexane:chloroform = 2:1) to obtain the title compound (2.3 g).

^{1}H-NMR ($CDCl_3$) δ: 1.30(3H,t,J=7.3Hz), 3.86(2H,s), 4.24(2H,q,J=7.3Hz), 4.26-4.35(1H,m), 6.53(2H,dd,J=6.6,2.2Hz), 7.14(2H,dd,J=6.6,2.2Hz).

[Referential Example 268]

Ethyl 2-(4-chloro-2-fluoroanilino)acetate:



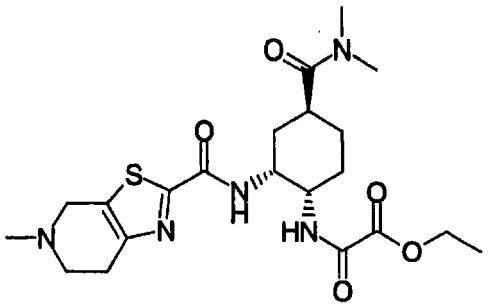
The title compound was obtained from 4-chloro-2-fluoroaniline and ethyl bromoacetate in a similar manner to the process described in Referential Example 267.

^{1}H-NMR ($CDCl_3$) δ: 1.29(3H,t,J=7.3Hz), 3.91(2H,s), 4.22(2H,q,J=7.3Hz), 4.42-4.51(1H,m), 6.49(1H,t,J=8.8Hz), 6.98(1H,dt,J=8.8,2.5Hz), 7.01(1H,dd,J=11.3,2.5Hz).

[Referential Example 269]

Ethyl 2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-

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



The compound (1.5 g) obtained in Referential Example 253 was dissolved in N,N-dimethylformamide (15 ml), and potassium 2-ethoxy-2-oxoacetate (962 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g) and 1-hydroxybenzotriazole monohydrate (227 mg) were added to stir the mixture at room temperature for 14 hours. After the solvent was distilled off under reduced pressure, a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 47:3) to obtain the title compound (1.13 g).

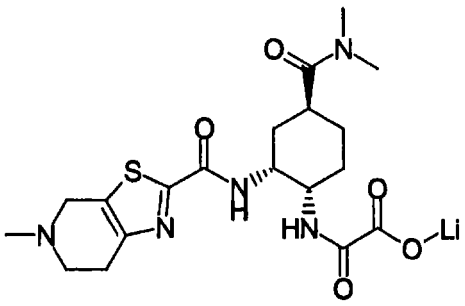
^{1}H-NMR ($CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 1.55-2.15(6H,m), 2.52(3H,s), 2.77-2.89(3H,m), 2.94(5H,br.s), 3.06(3H,s), 3.71(1H,d,J=15.5Hz), 3.73(1H,d,J=15.5Hz), 4.06-4.13(1H,m), 4.32(2H,q,J=7.1Hz), 4.60-4.63(1H,m), 7.39(1H,d,J=8.3Hz),

7.83(1H,d,J=7.6Hz).

MS (ESI) m/z: 466$(M+H)^+$.

[Referential Example 270]

Lithium 2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)-carbonyl]amino}cyclohexyl)amino]-2-oxoacetate:

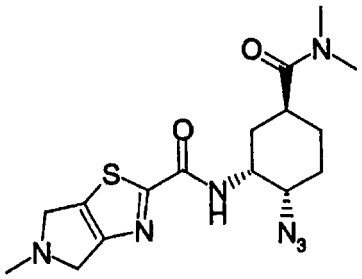


The compound (1.13 g) obtained in Referential Example 269 was dissolved in tetrahydrofuran (20 ml), methanol (10 ml) and water (10 ml), and lithium hydroxide (58 mg) was added to stir the mixture at room temperature for 30 minutes. The solvent was distilled off under reduced pressure to obtain the title compound (1.10 g).

^{1}H-NMR (DMSO-d_6) δ: 1.41-1.73(4H,m), 2.00-2.07(2H,m), 2.39(3H,s), 2.74-2.99(11H,m), 3.67(2H,s), 3.82-3.88(1H,m), 4.28-4.30(1H,m), 8.66-8.70(2H,m).

[Referential Example 271]

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



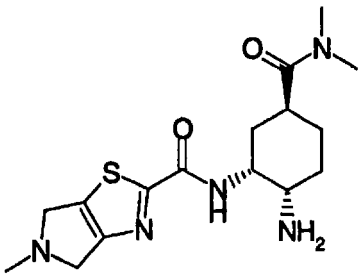
The title compound was obtained from the compound obtained in Referential Example 293 and the compound obtained in Referential Example 251 in a similar manner to the process described in Referential Example 252.

^{1}H-NMR ($CDCl_3$) δ: 1.73-1.87(4H,m), 2.11-2.20(2H,m), 2.67(3H,s), 2.85-2.90(1H,m), 2.93(3H,s), 3.00(3H,s), 3.90-4.10(5H,m), 4.57-4.62(1H,m), 7.20-7.22(1H,m).

MS (FAB) m/z: 378$(M+H)^+$.

[Referential Example 272]

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

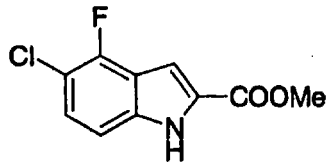


The title compound was obtained from the compound obtained in Referential Example 271 in a similar manner to the process described in Referential Example 253.

^{1}H-NMR ($CDCl_3$) δ: 1.67-1.97(6H,m), 2.36-2.40(1H,m), 2.67(3H,s), 2.92(3H,s), 3.00(3H,s), 3.07-3.18(1H,m), 3.92-3.95(2H,m), 4.02-4.06(2H,m), 4.23-4.26(1H,m), 7.50-7.52(1H,m).

[Referential Example 273]

Methyl 5-chloro-4-fluoroindole-2-carboxylate:



Ethanol (100 ml) was added to sodium hydride (content: 60%, 4.7 g) at 0°C under an argon atmosphere, and the mixture was stirred for 10 minutes. After 2-nitropropane (11 ml) was added to the reaction mixture to stir the mixture for 10 minutes, 1-(bromomethyl)-3-chloro-2-fluorobenzene (10 g) was added to stir the resultant mixture at room temperature for 3.5 hours. Precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was partitioned in diethyl ether and water, and an organic layer was successively washed with a 1N aqueous solution of sodium hydroxide, water and 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 chromatagraphy on silica gel (ethyl acetate:hexane = 3:7) to obtain crude 3-chloro-2-fluorobenzaldehyde (5.5 g) as a pale yellow oil. Methanol

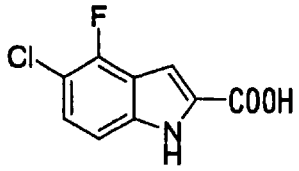
(20 ml) was added to sodium hydride (content: 60%, 1.6 g) at 0°C under an argon atmosphere, and the mixture was stirred for 10 minutes. The reaction mixture was cooled to -20°C, and the crude 3-chloro-2-fluorobenzaldehyde (5.5 g) and a solution of methyl 2-azidoacetate (5.0 g) in methanol (10 ml) were added within 20 minutes. The temperature of the reaction mixture was raised to 0°C , and after the mixture was stirred for 2.5 hours, water (40 ml) was added thereto. The reaction mixture was concentrated under reduced pressure, the residue was extracted with a mixed solvent of methylene chloride and ethyl acetate. The extract was washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatagraphy on silica gel (toluene:hexane = 3:17) to obtain crude methyl 2-azido-3-[(3-chloro-2-fluoro)phenyl]acrylate (2.6 g). This product was dissolved in xylene (50 ml), and the solution was stirred at 130°C to 140°C for 3 hours. The reaction mixture was concentrated, and the resultant residue was purified by column chromatagraphy on silica gel (methylene chloride) and then crystallized from diethyl ether-hexane to obtain the title compound (440 mg).

^{1}H-NMR (DMSO-d_6) δ: 4.08(3H,s), 7.20(1H,s), 7.31-7.38(2H,m).

MS (FAB) m/z: 228$(M+H)^+$.

[Referential Example 274]

5-Chloro-4-fluoroindole-2-carboxylic acid:



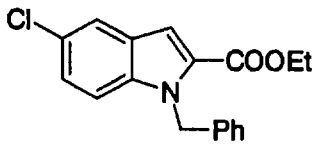
The compound (440 mg) obtained in Referential Example 273 was dissolved in tetrahydrofuran (10 ml), an aqueous solution (5 ml) of lithium hydroxide (160 mg) was added, and the mixture was stirred at room temperature for 3 hours. After an aqueous solution (5 ml) of lithium hydroxide (240 mg) was additionally added to the reaction mixture, and the mixture was stirred for additional 1 hour, the reaction mixture was concentrated under reduced pressure. The residue was neutralized with 1N hydrochloric acid and extracted 3 times with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (390 mg).

^{1}H-NMR (DMSO-d_6) δ: 6.79(1H,s), 7.16-7.26(2H,m).

MS (FAB) m/z: 214$(M+H)^+$.

[Referential Example 275]

Ethyl 1-benzyl-5-chloroindole-2-carboxylate:



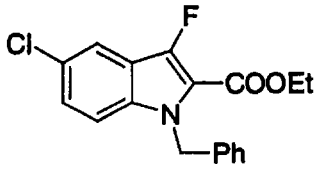
Ethyl 5-chloroindole-2-carboxylate (1.4 g) was

dissolved in N,N-dimethylformamide (30 ml), and potassium carbonate (2.9 g) and benzyl chloride (2.4 ml) were added. The mixture was heated and stirred for 1.5 hours on a hot bath controlled to 100°C. The reaction mixture was concentrated under reduced pressure, and the residue was poured into ice water and extracted 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, and the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:19) and crystallized from diethyl ether-hexane to obtain the title compound (1.6 g).

^{1}H-NMR ($CDCl_3$) δ: 1.36(3H,t,J=7.1Hz), 4.33(2H,q,J=7.1Hz), 5.83(2H,s), 7.00-7.02(2H,d), 7.20-7.38(6H,m), 7.67(1H,d,J=1.7Hz).

[Referential Example 276]

Ethyl 1-benzyl-5-chloro-3-fluoroindole-2-carboxylate:



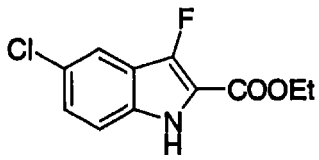
1-Fluoro-2,6-dichloropyridinium triflate (4.4 g) was added to a methylene chloride solution (30 ml) of the compound (2.2 g) obtained in Referential Example 275, and the mixtrue was heated under reflux for 3 days. The reaction mixture was partitioned in ethyl acetate and water,

and a water layer was extracted with ethyl acetate. The resultant organic layers were combined, successively washed with 1N hydrochloric acid, water and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:24) to obtain the crude title compound (2.8 g). A part of this product was purified by preparative thin-layer chromatography on silica gel to obtain the title compound.

^{1}H-NMR (DMSO-d_6) δ: 1.25(3H,t,J=7.1Hz), 4.29(2H,q,J=7.1Hz), 5.77(2H,s), 6.97-6.99(2H,m), 7.18-7.28(3H,m), 7.39(1H,dd,J=9.0,2.1Hz), 7.69(1H,dd,J=9.0,2.1Hz), 7.78(1H,d,J=2.1Hz).

[Referential Example 277]

Ethyl 5-chloro-3-fluoroindole-2-carboxylate:



The crude compound (1.4 g) obtained in Referential Example 276 was dissolved in anisole (30 ml), and aluminum chloride (2.9 g) was added portionwise to the solution under ice cooling. The reaction mixture was stirred at room temperature for 30 minutes, and aluminum chloride (2.9 g) was additionally added to stir the mixture for 18 hours. Aluminum chloride (8.0 g) was added to the reaction mixture, and the mixture was stirred for 5 hours, to which water was

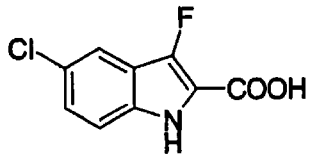
added. The reaction mixture was extracted with ethyl acetate, the resultant organic layers were combined, successively washed with saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride) to obtain the title compound (470 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.43(3H,t,J=7.2Hz), 4.45(2H,q,J=7.2Hz), 7.25-7.31(2H,m), 7.66(1H,d,J=0.73Hz), 8.53(1H,br.s).

MS (FAB) m/z: 242$(M+H)^+$.

[Referential Example 278]

5-Chloro-3-fluoroindole-2-carboxylic acid:



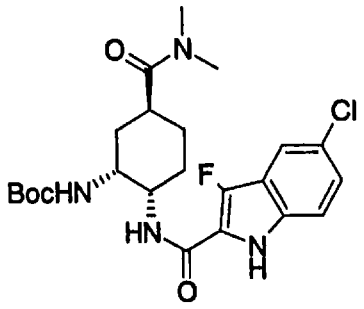
The title compound was obtained from the compound obtained in Referential Example 277 in a similar manner to Referential Example 274.

^{1}H-NMR (DMSO-d_6) δ: 7.31(1H,dd,J=8.8,1.9Hz), 7.42(1H,dd,J=8.8,1.9Hz), 7.70(1H,d,J=1.9Hz), 11.78(1H,s)

MS (FAB) m/z: 214$(M+H)^+$.

[Referential Example 279]

tert-Butyl (1R,2S,5S)-{[(5-chloro-3-fluoroindol-2-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



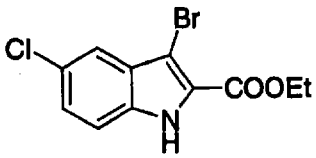
The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 278 in a similar manner to Referential Example 97.

^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.73-2.11(6H,m), 2.65(1H,br.s), 2.96(3H,s), 3.07(3H,s), 4.20(1H,br.s), 4.28(1H,br.s), 4.78(1H,br),7.23-7.30(3H,m), 7.58(1H,s), 9.03(1H,s).

MS (FAB) m/z: 481$(M+H)^+$.

[Referential Example 280]

Ethyl 3-bromo-5-chloroindole-2-carboxylate:



N-Bromosuccinimide (440 mg) was added to a solution of ethyl 5-chloroindole-2-carboxylate (500 mg) in N,N-dimethylformamide (10 ml). The reaction mixture was stirred at room temperature for 18 hours, and the solvent was distilled off under reduced pressure. The residue was partitioned in ethyl acetate and water, and a water layer

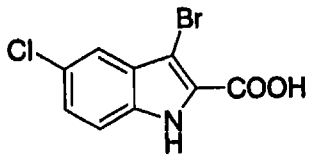
was extracted with ethyl acetate. The resultant organic layers were combined, washed with saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The solvent was distilled off, the residue was purified by column chromatagraphy on silica gel (ethyl acetate:hexane = 1:9), and white powder thus obtained was washed with hexane to obtain the title compound (680 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.42-1.48(3H,m), 4.43-4.49(2H,m), 7.30-7.32(2H,m), 7.65(1H,d,J=0.74Hz), 9.11(1H,s)

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

[Referential Example 281]

3-Bromo-5-chloroindole-2-carboxylic acid:



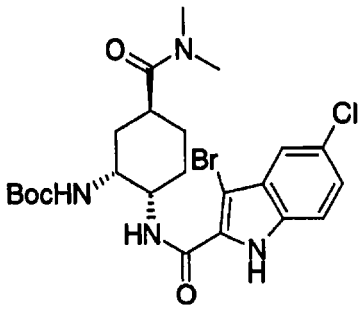
The title compound was obtained from the compound obtained in Referential Example 280 in a similar manner to Referential Example 274.

^{1}H-NMR (DMSO-d_6) δ: 7.35(1H,dd,J=8.8,2.0Hz), 7.48-7.53(2H,m), 12.33(1H,s)

MS (FAB) m/z: 275$(M+H)^+$.

[Referential Example 282]

tert-Butyl (1R,2S,5S)-2-{[(3-bromo-5-chloroindol-2-yl)-carbonyl]amino}-5-[(dimethylamino)carbonyl]cyclohexyl-carbamate:



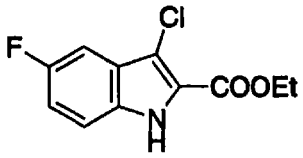
The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 281 in a similar manner to Referential Example 97.

^{1}H-NMR ($CDCl_3$) δ: 1.42(9H,s), 1.58-2.17(6H,m), 2.70(1H,br.s), 2.96(3H,s), 3.07(3H,s), 4.23-4.28(2H,m), 4.83(1H,br), 7.34-7.41(3H,m), 7.52(1H,s), 9.76(1H,s).

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

[Referential Example 283]

Ethyl 3-chloro-5-fluoroindole-2-carboxylate:



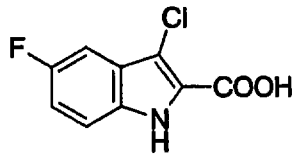
Ethyl 5-fluoroindole-2-carboxylate (2.0 g) was dissolved in N,N-dimethylformamide (20 ml), and a solution of N-chlorosuccinimide (1.4 g) in N,N-dimethylformamide (10 ml) was added dropwise to the solution under ice cooling. The mixture was stirred at room temperature for 18 hours, and the reaction mixture was diluted with ethyl acetate and successively washed with a saturated aqueous solution of

sodium hydrogencarbonate and saturated aqueous solution of sodium chloride. The resultant organic layer was then dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 5:1) to obtain the title compound (1.9 g).

^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.4Hz), 4.46(2H,q,J=7.4Hz), 7.14(1H,dt,J=8.0,2.7Hz), 7.32-7.36(2H,m), 8.91(1H,br).

[Referential Example 284]

3-Chloro-5-fluoroindole-2-carboxylic acid:

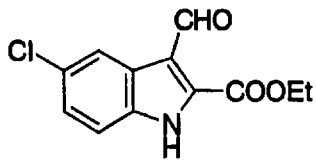


The title compound was obtained from the compound obtained in Referential Example 283 in a similar manner to Referential Example 274.

^{1}H-NMR (DMSO-d_6) δ: 7.20(1H,dt,J=8.8,2.4Hz), 7.31(1H,dd,J=8.8,2.4Hz), 7.46(1H,dd,J=8.8,4.4Hz), 12.12(1H,br).

[Referential Example 285]

Ethyl 5-chloro-3-formylindole-2-carboxylate:

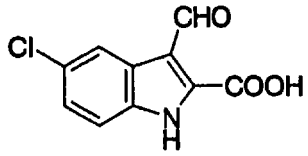


After phosphorus oxychloride (2.0 ml) was added to N-methylformanilide (2.9 g), and the mixture was stirred for 15 minutes, 1,2-dichloroethane (50 ml) and ethyl 5-chloroindole-2-carboxylate (4.0 g) were added, and the resultant mixture was heated under reflux for 1 hour. The reaction mixture was poured into an aqueous solution (28 ml) of sodium acetate (14 g) under ice cooling. After stirring for 18 hours, insoluble matter was collected by filtration. This product was successively washed with water and diethyl ether to obtain the title compound (3.56 g).

^{1}H-NMR (DMSO-d_6) δ: 1.38(3H,t,J=7.1Hz), 4.44(2H,q,J=7.1Hz), 7.38(1H,dd,J=8.0,1.4Hz), 7.56(1H,d,J=8.0Hz), 8.19(1H,d,J=1.4Hz), 10.53(1H,s).

[Referential Example 286]

5-Chloro-3-formylindole-2-carboxylic acid:

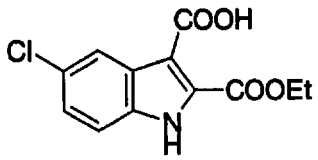


The compound (1.0 g) obtained in Referential Example 285 was dissolved in ethanol (10 ml), and a 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to stir the mixture at 50°C for 2 hours. 1N Hydrochloric acid (11 ml) was added to the reaction mixture, the resultant mixture was stirred, and insoluble matter was collected by filtration to obtain the title compound (0.86 g).

^{1}H-NMR (DMSO-d_6) δ: 7.39(1H,d,J=8.0Hz), 7.55(1H,d,J=8.0Hz), 8.20(1H,s), 10.58(1H,s), 12.90(1H,br).

[Referential Example 287]

5-Chloro-2-ethoxycarbonylindole-3-carboxylic acid:

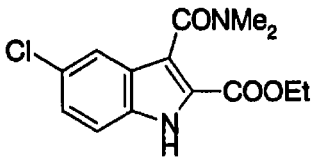


The compound (1.5 g) obtained in Referential Example 286 and sulfamic acid (1.7 g) were dissolved in tert-butanol (30 ml)-water (30 ml), and sodium chlorite (1.6 g) was added to stir the mixture for 8 hours. The reaction mixture was diluted with water and extracted with ethyl acetate, and the extract was successively washed with 1N hydrochloric acid and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was recrystallized from a mixed solvent of isopropyl ether and hexane to obtain the title compound (0.7 g).

^{1}H-NMR (DMSO-d_6) δ: 1.34(3H,t,J=7.1Hz), 4.38(2H,q,J=7.1Hz), 7.33(1H,dd,J=8.0,1.4Hz), 7.52(1H,d,J=8.0Hz), 7.97(1H,d,J=1.4Hz), 12.75(1H,br).

[Referential Example 288]

Ethyl 5-chloro-3-[(dimethylamino)carbonyl]indole-2-carboxylate:

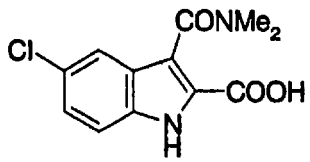


The compound (0.7 g) obtained in Referential Example 287 was dissolved in N,N-dimethylformamide (10 ml), and dimethylamine hydrochloride (0.26 g), 1-hydroxy-benzotriazole monohydrate (0.43 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.0 g) were added to stir the mixture at room temperature for 2 days. After the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride in that order, the resultant organic layer was dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure , and the residue was recrystallized from a mixed solvent of isopropyl ether and hexane to obtain the title compound (0.6 g).

^{1}H-NMR (DMSO-d_6) δ: 1.29(3H,t,J=7.1Hz), 2.78(3H,s), 3.04(3H,s), 4.30(2H,q,J=7.1Hz), 7.31(1H,dd,J=8.0,1.4Hz), 7.45(1H,d,J=1.4Hz), 7.48(1H,d,J=8.0Hz), 12.29(1H,s).

[Referential Example 289]

5-Chloro-3-[(dimethylamino)carbonyl]indole-2-carboxylic acid:

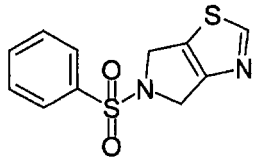


The title compound was obtained from the compound obtained in Referential Example 288 in a similar manner to Referential Example 286.

^{1}H-NMR (DMSO-d_6) δ: 2.91(6H,s), 7.29(1H,d,J=8.0Hz), 7.44(1H,d,J=8.0Hz), 7.47(1H,s), 12.16(1H,s).

[Referential Example 290]

5-(Phenylsulfonyl)-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole:



Benzenesulfonamide (638 mg) and 4,5-bis(bromomethyl)thiazole (M. Al. Hariri, O. Galley, F. Pautet, H. Fillion, Eur. J. Org. Chem., 1998, 593-594.) (1.10 g) were dissolved in N,N-dimethylformamide (10 ml), sodium hydride (60% in oil, 357 mg) was added at a time, and the mixture was stirred at room temperature for 3 hours. Water and methylene chloride were added to conduct liquid separation. After the resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was purified by column chromatography on silica gel (methylene chloride:ethyl acetate = 9:1) to obtain the title compound (137 mg).

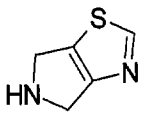
^{1}H-NMR ($CDCl_3$) δ: 4.60-4.63(2H,m), 4.70-4.73(2H,m), 7.52-

7.64(3H,m), 7.88-7.92(2H,m), 8.71(1H,s).

MS (FAB) m/z: 267$(M+H)^+$.

[Referential Example 291]

5,6-Dihydro-4H-pyrrolo[3,4-d]thiazole dihydrobromide:



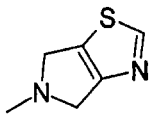
A mixture of the compound (800 mg) obtained in Referential Example 290, phenol (800 µl) and 47% hydrobromic acid (5.00 ml) was heated under reflux for 2 hours. After the reaction mixture was cooled to room temperature, ethyl acetate and water were added to conduct liquid separation. The resultant water layer was concentrated under reduced pressure. Ethyl acetate was added to the residue, precipitate was collected by filtration to obtain the title compound (521 mg).

^{1}H-NMR ($DMSO-d_6$) δ: 4.42(2H,br.s), 4.56(2H,br.s), 9.14(1H,s).

MS (FAB) m/z: 127$(M+H)^+$.

[Referential Example 292]

5-Methyl-5,6-dihydro-4H-pyrrolo[3,4-d]thiazole:



The title compound was obtained from the compound obtained in Referential Example 291 in a similar manner to Referential Example 9.

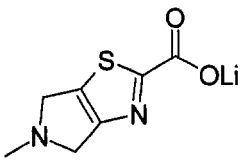
^{1}H-NMR ($CDCl_3$) δ: 2.67(3H,s), 3.95-3.99(2H,m),

4.01-4.05(2H,m), 8.69(1H,s).

MS (ESI) m/z: 141$(M+H)^+$.

[Referential Example 293]

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

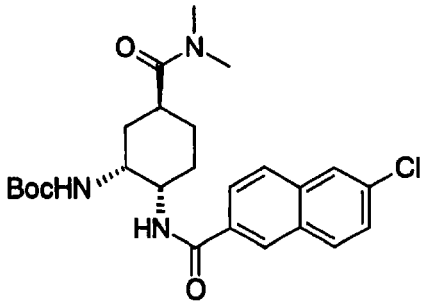


The title compound was obtained from the compound obtained in Referential Example 292 in a similar manner to Referential Example 5.

^{1}H-NMR (DMSO-d_6) δ: 2.52(3H,s), 3.73(2H,t,J=3.2Hz), 3.87(2H,t,J=3.2Hz).

[Referential Example 294]

tert-Butyl (1R,2S,5S)-2-[(6-chloro-2-naphthoyl)amino]-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



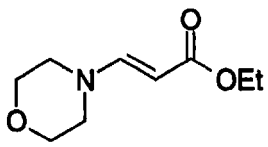
The title compound was obtained from the compound obtained in Referential Example 144 and 6-chloronaphthalene-2-carboxylic acid (Eur. J. Chem-Chim. Ther., 1984, Vol. 19, pp. 205-214) in a similar manner to Referential Example 97.

^{1}H-NMR ($CDCl_3$) δ: 1.30-2.00(15H,m), 2.60-2.80(1H,m), 2.96(3H,s), 3.09(3H,s), 4.00-4.20(1H,m), 4.20-4.30(1H,m), 4.75-4.95(1H,m), 7.44(1H,d,J=9.0Hz), 7.70-7.95(5H,m), 8.31(1H,s).

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

[Referential Example 295]

Ethyl (E)-3-(morpholin-4-yl)-2-acrylate:



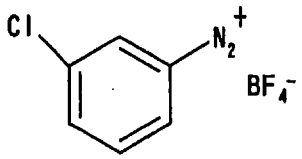
Ethyl propionate (2.0 ml) was dissolved in methylene chloride (20 ml), and morpholine (1.70 ml) was added dropwise under ice cooling. After stirring at room temperature for 1 hour, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 20:1) to obtain the title compound (3.72 g).

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 3.21(4H,t,J=5.1Hz), 3.71(4H,t,J=5.1Hz), 4.14(2H,q,J=7.1Hz), 4.70(1H,d,J=13.4Hz), 7.36(1H,d,J=13.4Hz).

MS (FAB) m/z: 186$(M+H)^+$.

[Referential Example 296]

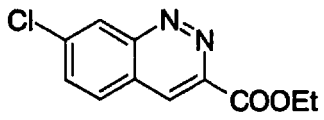
3-Chlorobenzenediazonium tetrafluoroborate:



3-Chloroaniline (2.0 g) was dissolved in a mixed solvent of water (30 ml) and concentrated hydrochloric acid (3.5 ml), and sodium nitrite (1.30 g) was added under ice cooling to stir the mixture for 10 minutes. After concentrated hydrochloric acid (5.3 ml) and sodium tetrafluoroborate (6.90 g) were added to the reaction mixture to stir the mixture for 30 minutes under ice cooling, precipitate was collected by filtration and washed with water, methanol and diethyl ether to obtain the title compound (2.63 g). This compound was used in the next reaction as it was.

[Referential Example 297]

Ethyl 7-chlorocinnoline-3-carboxylate:



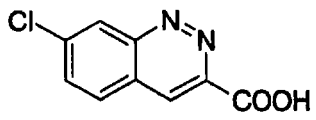
The compound (1.45 g) obtained in Referential Example 295 was dissolved in acetonitrile (100 ml), and the compound (1.73 g) obtained in Referential Example 296 was added. After stirred at room temperature for 1 hour, the mixture was heated under reflux for 7 days. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride → methylene chloride:ethyl acetate = 10:1, then, hexane:ethyl acetate = 4:1 → 1:1) to obtain the title compound (0.25 g).

^{1}H-NMR ($CDCl_3$) δ: 1.53(3H,t,J=7.1Hz), 4.62(2H,q,J=7.1Hz),

7.80(1H,dd,J=8.8,2.0Hz), 7.95(1H,d,J=8.8Hz), 8.64(1H,s), 8.68(1H,d,J=2.0Hz).

[Referential Example 298]

7-Chlorocinnoline-3-carboxylic acid:



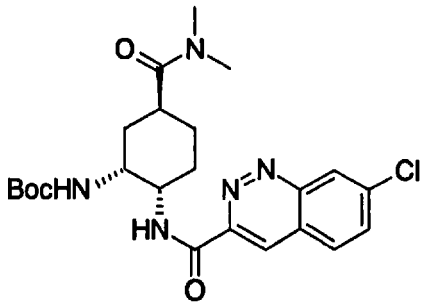
The title compound was obtained from the compound obtained in Referential Example 297 in a similar manner to Referential Example 286.

^{1}H-NMR (DMSO-d_6) δ: 8.02(1H,dd,J=8.8,2.0Hz), 8.34(1H,d,J=8.8Hz), 8.70(1H,s), 8.90(1H,s).

MS (FAB) m/z: 209$(M+H)^+$.

[Referential Example 299]

tert-Butyl (1R,2S,5S)-2-{[(7-chlorocinnolin-3-yl)carbonyl]-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 298 in a similar manner to Referential Example 97.

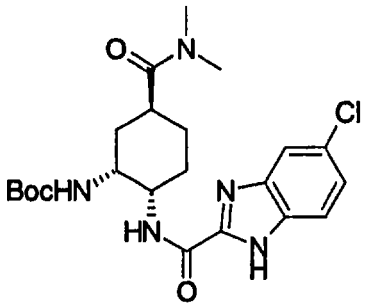
^{1}H-NMR ($CDCl_3$) δ: 1.36(9H,s), 1.80-2.20(5H,m), 2.72(1H,m),

2.96(3H,s), 3.07(3H,s), 3.49(1H,d,J=3.7Hz), 4.30-4.45(2H,m), 4.87(1H,br), 7.77(1H,dd,J=8.8,2.0Hz), 7.96(1H,d,J=8.8Hz), 8.59(2H,br), 8.72(1H,s).

MS (FAB) m/z: 476$(M+H)^+$.

[Referential Example 300]

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



10% Palladium on carbon (50 mg) was added to a solution of the compound (235 mg) obtained in Referential Example 143 in tetrahydrofuran (5.0 ml), and the mixture was stirred overnight at room temperature under a hydrogen atmosphere. To a solution of the product obtained by filtering the reaction mixture and concentrating the filtrate and 5-chlorobenzimidazole-2-carboxylic acid (Bull. Chem. Soc. Jpn., Vol. 62, p. 2668, 1989) (165 mg) in N,N-dimethylformamide (5.0 ml) were added 1-hydroxybenzotriazole monohydrate (100 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (171 mg) at room temperature, and the mixture was stirred for 4 days. After concentrating the reaction mixture, methylene

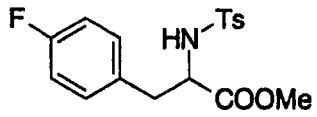
chloride, a saturated aqueous solution of sodium hydrogencarbonate and water were added to conduct liquid separation, and the resultant water layer was extracted with methylene chloride. After the resultant organic layers were combined and dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 10:1) to obtain the title compound (250 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.01-2.00(6H,m), 1.34(9H,s), 2.79(3H,s), 2.80-2.95(1H,m), 2.98(3H,s), 3.89-4.06(2H,m), 7.08(1H,d,J=6.6Hz), 7.31(1H,d,J=8.5Hz), 7.62(2H,br.s), 8.47(1H,d,J=8.5Hz), 13.46(1H,br.s).

MS(ESI) m/z: 466$(M+H)^+$.

[Referential Example 301]

Methyl 3-(4-fluorophenyl)-2-{[(4-methylphenyl)sulfonyl]-amino}propionate:



Methyl 2-amino-3-(4-fluorophenyl)propionate (2.01 g), p-toluenesulfonyl chloride (2.25 g) and 4-dimethylaminopyridine (309 mg) were dissolved in chloroform (30 ml), and pyridine (3.0 ml) was added to heat the mixture under reflux for 4.5 hours. P-Toluenesulfonyl chloride (2.20 g) was additionally added, and the mixture was heated under reflux for 3.5 hours. The reaction

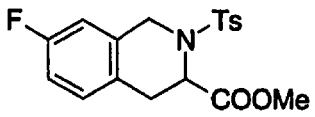
mixture was poured into ice and 1N hydrochloric acid (17 ml) to conduct liquid separation. The resultant organic layer was successively washed with a saturated aqueous solution of sodium hydrogencarbonate and saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 9:1 → 2:1) to obtain the title compound (2.89 g).

^{1}H-NMR ($CDCl_3$) δ: 2.41(3H,s), 2.90-3.10(2H,m), 3.51(3H,s), 4.10-4.20(1H,m), 5.04(1H,d,J=9.0Hz), 6.85-6.95(2H,m), 7.00-7.10(2H,m), 7.20-7.30(2H,m), 7.60-7.70(2H,m).

MS (ESI) m/z: 352$(M+H)^+$.

[Referential Example 302]

Methyl 7-fluoro-2-[(4-methylphenyl)sulfonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate:



The compound (1.50 g) obtained in Referential Example 301 and paraformaldehyde (207 mg) were dissolved in chloroform (40 ml), and the system was purged with argon. Trifluoroborane-diethyl ether complex (1.20 ml) was then added, and the mixture was stirred at room temperature for 7.5 hours. The reaction mixture was poured into ice and a saturated aqueous solution of sodium hydrogencarbonate to conduct liquid separation. The resultant organic layer was

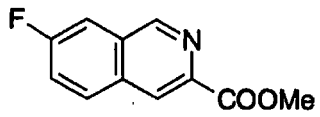
then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (1.45 g).

^{1}H-NMR ($CDCl_3$) δ: 2.42(3H,s), 3.15(2H,d,J=3.9Hz), 3.46(3H,s), 4.45(1H,d,J=15.9Hz), 4.69(1H,d,J=15.9Hz), 5.01(1H,t,J=4.4Hz), 6.70-6.80(1H,m), 6.80-6.90(1H,m), 7.00-7.10(1H,m), 7.29(2H,d,J=8.1Hz), 7.72(2H,d,J=8.3Hz).

MS (ESI) m/z: 364$(M+H)^+$.

[Referential Example 303]

Methyl 7-fluoroisoquinoline-3-carboxylate:



The compound (1.45 g) obtained in Referential Example 302 was dissolved in N,N-dimethylformamide (40 ml). Oxygen was introduced into this solution, and the solution was stirred at 100°C for 3.5 hours. After the reaction mixture was concentrated under reduced pressure, and a saturated aqueous solution of sodium hydrogencarbonate and methylene chloride were added to the residue to conduct liquid separation, the resultant organic layer was succesively washed with a 10% aqueous solution of citric acid and 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

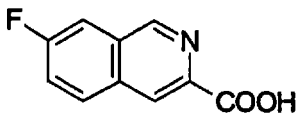
column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1) to obtain the title compound (0.59 g).

^{1}H-NMR ($CDCl_3$) δ: 4.07(3H,s), 7.55-7.65(1H,m), 7.65-7.75(1H,m), 8.00-8.05(1H,m), 8.61(1H,s), 9.30(1H,s).

MS (ESI) m/z: 206$(M+H)^+$.

[Referential Example 304]

7-Fluoroisoquinoline-3-carboxylic hydrochloride:



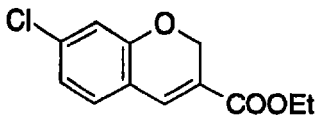
The compound (1.45 g) obtained in Referential Example 303 was dissolved in concentrated hydrochloric acid (18 ml), and the solution was heat under reflux for 2.5 hours. The reaction mixture was cooled, and crystals were collected by filtration, washed with water and then dried to obtain the title compound (0.46 g).

^{1}H-NMR (DMSO-d_6) δ: 7.90-8.00(1H,m), 8.15-8.25(1H,m), 8.40-8.50(1H,m), 8.82(1H,s), 9.55(1H,s).

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

[Referential Example 305]

Ethyl 7-chloro-2H-chromene-3-carboxylate:



4-Chloro-2-hydroxybenzaldehyde (Acta. Chem. Scand., Vol. 53, p. 258, 1999) (510 mg) was dissolved in tetrahydrofuran (40 ml), sodium hydride (60% in oil, 157

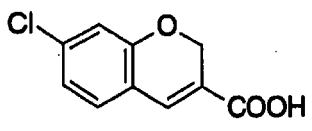
mg) was added, and the mixture was stirred at room temperature for 2 hours. A tetrahydrofuran solution (10 ml) of ethyl 2-diethylphosphonoacrylate (J. Org. Chem., Vol. 43, P. 1256, 1978) (769 mg) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for 2 hours and then heated overnight under reflux. After the reaction mixture was cooled to room temperature, water and diethyl ether were added 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 (hexane:ethyl acetate = 10:1) to obtain the title compound (247 mg).

^{1}H-NMR (DMSO-d_6) δ: 1.33(3H,t,J=7.1Hz), 4.27(2H,q,J=7.1Hz), 4.99(2H,d,J=1.2Hz), 6.85(1H,d,J=1.2Hz), 6.89(1H,dd,J=8.1,2.0Hz), 7.04(1H,d,J=8.1Hz), 7.38(1H,d,J=1.0Hz).

MS (EI) m/z: 238(M^+).

[Referential Example 306]

7-Chloro-2H-chromene-3-carboxylic acid:

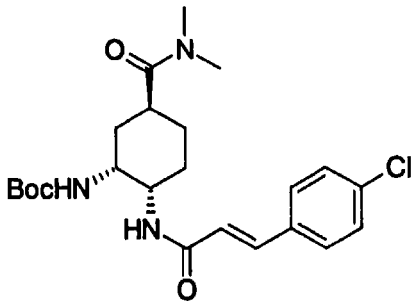


The title compound was obtained from the compound obtained in Referential Example 305 in a similar manner to Referential Example 274.

^{1}H-NMR (DMSO-d_6) δ: 4.92(1H,d,J=2.0Hz), 6.95(1H,d,J=2.0Hz), 7.01(1H,dd,J=8.1,2.2Hz), 7.35(1H,d,J=8.1Hz), 7.44(1H,s).
MS (EI) m/z: 210 M^+.

[Referential Example 307]

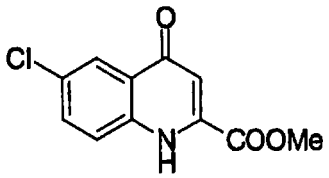
tert-Butyl (1R,2S,5S)-2-{[(E)-3-(4-chlorophenyl)-2-propenoyl]amino}-5-[(dimethylamino)carbonyl]cyclohexylcarbamate:



The title compound was obtained from the compound obtained in Referential Example 144 and 4-chlorocinnamic acid in a similar manner to Referential Example 97.
^{1}H-NMR ($CDCl_3$) δ: 1.30-1.55(3H,m), 1.48(9H,s), 1.60-2.30(4H,m), 2.57-2.70(1H,m), 2.95(3H,s), 3.06(3H,s), 4.01(1H,br s), 4.10-4.20(1H,m), 4.78(1H,br.s), 6.30(1H,d,J=15.6 Hz), 7.02(1H,s), 7.31(2H,d,J=8.5 Hz), 7.40(2H,d,J=8.5 Hz), 7.52(1H,d,J=15.6 Hz).
MS (ESI)m/z: 450$(M+H)^+$.

[Referential Example 308]

Methyl 6-chloro-4-oxo-1,4-dihydroquinoline-2-carboxylate:



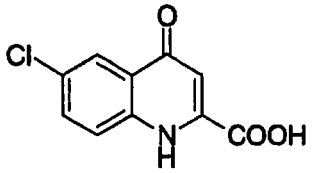
Dimethyl acetylenedicarboxylate (13.5 ml) was added to a solution of 4-chloroaniline (12.76 g) in methanol (150 ml), and the mixture was heated under reflux for 8 hours. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in diphenyl ether (70 ml), and the solution was heated under reflux at 240°C for 4 hours. After cooling the reaction mixture, a mixed solvent of hexane and diethyl ether was added, and crystals deposited were collected by filtration and washed to obtain the title compound (11.09 g).

^{1}H-NMR (DMSO-d_6) δ: 3.97(3H,s), 7.76(1H,dd,J=9.0,2.5Hz), 7.90-8.05(2H,m), 12.28(1H,br.s).

MS (ESI) m/z: 238$(M+H)^+$.

[Referential Example 309]

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



The title compound was obtained from the compound obtained in Referential Example 308 in a similar manner to Referential Example 286.

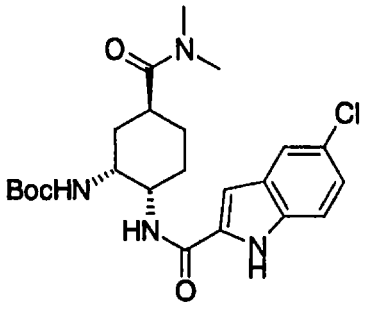
^{1}H-NMR (DMSO-d_6) δ: 6.90-7.05(1H,m), 7.90-8.05(2H,m),

10.10-10.30(1H,m), 12.13(1H,br.s).

MS (ESI) m/z: 224$(M+H)^+$.

[Referential Example 310]

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



Water (10 ml) and lithium hydroxide (263 mg) were added to a solution of the compound (5.00 g) obtained in Referential Example 97 in tetrahydrofuran (40 ml), and the mixture was stirred overnight at room temperature. The reaction mixture was filtered, the filtrate was concentrated, and 1-hydroxybenzotriazole monohydrate (1.75 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.32 g) and diisopropylethylamine (11.3 ml) were added to a solution of the resultant residue and dimethylamine hydrochloride (1.85 g) in N,N-dimethylformamide (100 ml) at room temperature. The resultant mixture was stirred for 2 days. After concentrating the reaction mixture, methylene chloride, a saturated aqueous solution of sodium hydrogencarbonate and water were added to conduct liquid separation. The resultant water layer was extracted with methylene chloride.

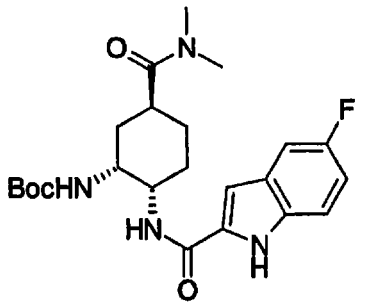
The organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure. The residue was purified by column chromatagraphy on silica gel (methylene chloride:acetone = 2:1 → 1:1) to obtain the title compound (4.59 g).

^{1}H-NMR ($CDCl_3$) δ: 1.60-1.76(2H,m), 1.73(9H,s), 1.76-1.87(1H,m), 1.93(1H,br.s), 2.14(1H,br.s), 2.28(1H,br.s), 2.65(1H,br.s), 2.95(3H,s), 3.05(3H,s), 4.01(1H,br.s), 4.21(1H,br.s),4.84(1H,br.s), 6.81(1H,br.s), 7.20(1H,dd,J=8.8,1.9Hz), 7.36(1H,d,J=8.8Hz), 7.59(1H,br.s), 8.02(1H,br.s), 10.06(1H,br.s).

MS (FAB) m/z: 465$(M+H)^+$.

[Referential Example 311]

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



1) Ethyl (1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-fluoroindol-2-yl)carbonyl]amino}-cyclohexane-carboxylate was obtained from the compound obtained in Referential Example 96 and 5-fluoroindole-2-carboxylic acid in a similar manner to Referential Example 91.

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.52(9H,s), 1.67-2.41(7H,m), 3.97(1H,br.s), 4.15(2H,q,J=7.1Hz), 4.08-4.22(1H,m), 6.83(1H,s), 7.00-7.05(1H,m), 7.32-7.36(1H,m), 8.02(1H,s), 9.51(1H,s).

MS (FAB) m/z: 448$(M+H)^+$.

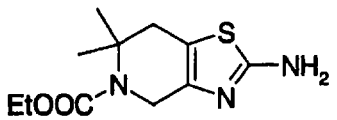
2) The title compound was obtained from the compound obtained above in a similar manner to Referential Example 310.

^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.57-1.79(2H,m), 1.79-2.00(2H,m), 2.14(1H,br.s), 2.31(1H,br.s), 2.65(1H,br.s), 2.95(3H,s), 3.07(3H,s), 4.02(1H,br.s), 4.17-4.25(1H,m), 4.80(1H,br.s), 6.82(1H,br.s), 7.02(1H,dt,J=2.3,9.0Hz), 7.24(1H,br.s), 7.35(1H,dd,J=9.0,4.3Hz), 7.91(1H,br.s), 9.49(1H,br.s).

MS (FAB) m/z: 447$(M+H)^+$.

[Referential Example 312]

Ethyl 2-amino-6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxylate:



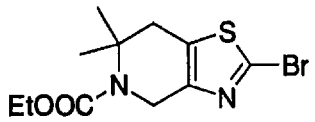
After copper(I) cyanide (918 mg) was suspended in tetrahydrofuran (50 ml) under an argon atmosphere, and the suspension was cooled to -20°C, n-butyllithium (1.56 N hexane solution, 6.41 ml) was added dropwise over 5 minutes, and the mixture was stirred at -20°C for 30 minutes. After the reaction mixture was cooled to -50°C,

diisobutylaluminum hydride (1.00 M hexane solution) was added dropwise over 20 minutes, and the mixture was stirred at -50°C for 1 hour. A solution of ethyl 2,2-dimethyl-5-oxo-5,6-dihydro-2H-pyridine-1-carboxylate (Helv. Chim. Acta, Vol. 81, p. 303, 1998) (986 mg) in tetrahydrofuran (5 ml) was added dropwise to the reaction mixture over 5 minutes, and the mixture was stirred at -50°C for 2 hours. After raising the temperature of the reaction mixture to -20°, bromine (4.90 ml) was added at a time, and the mixture was stirred at -20°C for 30 minutes. Water and ethyl acetate were added to the reaction mixture to conduct liquid separation. The resultant organic layer was washed with a saturated aqueous solution of sodium sulfite and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in N,N-dimethylformamide (10 ml), thiourea (760 mg) was added, and the mixture was stirred overnight at 50°C. After the solvent was distilled off, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatography on silica gel (ethyl acetate:hexane = 4:1) to obtain the title compound (412 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.1Hz), 1.54(6H,s), 2.65-2.67(2H,m), 4.09(2H,q,J=7.1Hz), 4.44-4.46(2H,m), 4.78(2H,br.s).

[Referential Example 313]

Ethyl 2-bromo-6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]-pyridine-5(4H)-carboxylate:



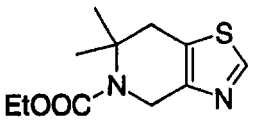
Copper(II) bromide (431 mg) was suspended in acetonitrile (8 ml), and tert-butyl nitrite (249 mg) was added dropwise at room temperature. After an acetonitrile solution (8 ml) of the compound (412 mg) obtained in Referential Example 312 was added to the reaction mixture under ice cooling, the mixture was heated to 50°C and stirred for 15 minutes. The solvent was distilled off under reduced pressure, and diethyl ether and 10% hydrochloric acid were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 6:1) to obtain the title compound (151 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.26(3H,t,J=7.1Hz), 1.55(6H,s), 2.79-2.81(2H,m), 4.10(2H,q,J=7.1Hz), 4.65-4.67(2H,m).

MS (ESI) m/z: 319$(M+H)^+$.

[Referential Example 314]

Ethyl 6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]-pyridine-5(4H)-carboxylate:

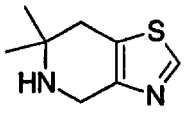


n-Butyllithium (1.56N hexane solution, 1.04 ml) was added to a solution with the compound (432 mg) obtained in Referential Example 313 in diethyl ether (5 ml) at -78°C, and the mixture was stirred at -78°C for 30 minutes. Water and diethyl ether were added to the reaction mixture to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off to obtain the title compound (307 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.28(3H,t,J=7.1Hz), 1.55(6H,s), 2.90(2H,s), 4.12(2H,q,J=7.1Hz), 4.75(2H,m), 8.63(1H,s).

[Referential Example 315]

6,6-Dimethyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine:



The compound (307 mg) obtained in Referential Example 314 was dissolved in a mixed solvent of water (5 ml), ethanol (5 ml) and dioxane (5 ml), and lithium hydroxide (598 mg) was added to this reaction mixture to heat the mixture under reflux for 7 days. After allowing the reaction mixture to cool to room temperature, water and methylene chloride were added to conduct liquid separation. The resultant water layer was extracted 6 times with methylene chloride. The resultant organic layers were

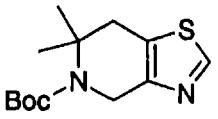
dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain the title compound (207 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.23(6H,s), 2.71-2.73(2H,m), 4.09-4.11(2H,m), 8.61(1H,s).

MS (ESI) m/z: 168(M^+).

[Referential Example 316]

tert-Butyl 6,6-dimethyl-6,7-dihydrothiazolo[4,5-c]pyridine-5(4H)-carboxylate:



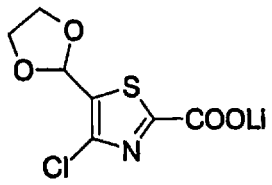
The compound (207 mg) obtained in Referential Example 315 was dissolved in methylene chloride (5 ml), and di-tert-butyl dicarbonate (404 mg) and 4-(N,N-dimethylamino)-pyridine (151 mg) were added to stir the mixture at room temperature for 2 hours. Di-tert-butyl dicarbonate (404 mg) was additionally added, and the mixture was stirred overnight at room temperature. Further, di-tert-butyl dicarbonate (1.00 g) was added, and the mixture was stirred for 1 hour. Methylene chloride and 10% hydrochloric acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 4:1) to obtain the title compound (95.4 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.52(6H,s), 2.87(2H,s), 4.69(2H,s), 8.62(1H,s).

MS (ESI) m/z: 269$(M+H)^+$.

[Referential Example 317]

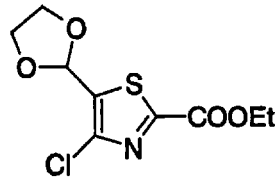
Lithium 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:



2,4-Dichlorothiazole-5-carbaldehyde ethyleneacetal (J. Chem. Soc. Perkin Trans. 1, 1992, p. 973) (2.26 g) was dissolved in tetrahydrofuran (15 ml), and n-butyllithium (1.5N hexane solution, 6.8 ml) was added under cooling with dry ice-acetone to stir the mixture for 20 minutes. At the same temperature, carbon dioxide was then introduced. The reaction mixture was gradually heated to room temperature over 1.5 hours and then concentrated. Hexane was added to the reaction mixture to powder the product. The product was collected by filtration and suspended in ethyl acetate, and formed powder was collected again by filtration to obtain the title compound (1.65 g).

[Referential Example 318]

Ethyl 4-chloro-5-(1,3-dioxolan-2-yl)thiazole-2-carboxylate:



The compound (242 mg) obtained in Referential Example

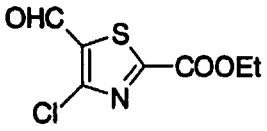
317 and ethanol (0.2 ml) were dissolved in N,N-dimethylformamide (2 ml), and 1-hydroxybenzotriazole monohydrate (136 mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (250 mg) were added to stir the mixture at room temperature for a night. The solvent was distilled off under reduced pressure, and diethyl ether and diluted hydrochloric acid were added to separate an organic layer. The organic layer was washed with water and a saturated aqueous solution of sodium hydrogencarbonate and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain the title compound (170 mg).

^{1}H-NMR ($CDCl_3$) δ : 1.43(3H,t,J=7.3Hz), 4.00-4.10(2H,m), 4.10-4.20(2H,m), 4.48(2H,q,J=7.3Hz), 6.15(1H,s).

MS (ESI) m/z: 264$(M+H)^+$.

[Referential Example 319]

Ethyl 4-chloro-5-formylthiazole-2-carboxylate:



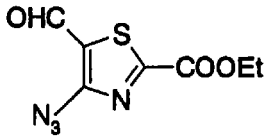
The compound (132 mg) obtained in Referential Example 318 was dissolved in diethyl ether (5 ml), and 20% hydrochloric acid (0.3 ml) was added to stir the mixture at room temperature for 7 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with diethyl ether. The extract was dried over anhydrous magnesium sulfate, and the

solvent was distilled off under reduced pressure to obtain the title compound (110 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.46(3H,t,J=7.1Hz), 4.52(2H,q,J=7.1Hz), 10.12(1H,s).

[Referential Example 320]

Ethyl 4-azido-5-formylthiazole-2-carboxylate:

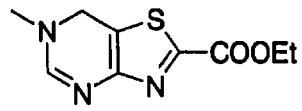


The compound (5.15 g) obtained in Referential Example 319 was dissolved in dimethyl sulfoxide (30 ml), and sodium azide (1.52 g) was added to stir the mixture at room temperature for 2.5 hours. Ice water was added to the reaction mixture to conduct extraction with diethyl ether. The extract was washed twice with water and then dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (1.78 g)

^{1}H-NMR ($CDCl_3$) δ: 1.45(3H,t,J=7.1Hz), 4.50(2H,q,J=7.1Hz), 9.95(1H,s).

[Referential Example 321]

Ethyl 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-carboxylate:



The compound (1.56 g) obtained in Referential Example 320 was dissolved in methylene chloride (20 ml), and acetic acid (2 ml), methylamine (2N tetrahydrofuran solution, 21 ml) and sodium triacetoxyborohydride (2.98 g) were added to stir the mixture. After 1 hour, sodium triacetoxyborohydride (2.98 g) was additionally added, and the stirring was continued for additional 4.5 hours. A 0.5N aqueous solution (100 ml) of sodium hydroxide was added to the reaction mixture to alkalify it. After the reaction mixture was extracted with methylene chloride, the extract was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure to obtain a brown oil (1.43 g). This oil was dissolved in ethanol (50 ml), 10% palladium on carbon (2.0 g) was added to conduct hydrogenation at normal temperature and pressure. After 2.5 hours, the catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in methylene chloride (30 ml), and trimethyl orthoformate (0.7 ml) and boron trifluoride-diethyl ether complex (0.3 ml) were added to stir the mixture at room temperature for 15 hours. A saturated aqueous solution of sodium hydrogencarbonate was added to the reaction mixture to conduct extraction with methylene chloride. The extract was dried over anhydrous sodium sulfate. The solvent was

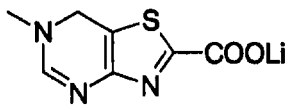
distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 97:3) to obtain the title compound (100 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.41(3H,t,J=7.1Hz), 2.95(3H,s), 4.44(2H,q,J=7.1Hz), 4.87(2H,s), 7.06(1H,s).

MS (ESI) m/z: 226$(M+H)^+$.

[Referential Example 322]

Lithium 6-methyl-6,7-dihydrothiazolo[4,5-d]pyrimidine-2-carboxylate:

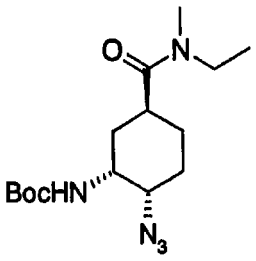


The compound (463 mg) was dissolved in tetrahydrofuran (20 ml), and lithium hydroxide (54.1 mg) and water (4 ml) were added to stir the mixture at room temperature for 4.5 hours. The solvent was distilled off under reduced pressure, and the residue was dried by means of a vacuum pump to obtain the title compound (460 mg).

^{1}H-NMR (DMSO-d_6) δ: 2.86(3H,s), 4.71(2H,s), 7.03(1H,s).

[Referential Example 323]

tert-Butyl (1R,2S,5S)-2-azido-5-{[ethyl(methyl)amino]-carbonyl}cyclohexylcarbamate:



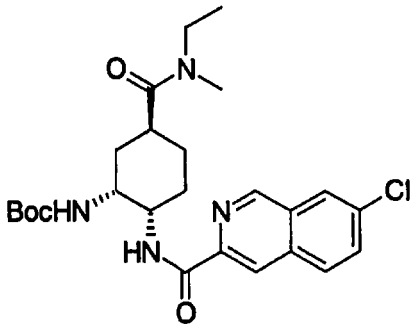
The title compound was obtained by condensing the compound obtained in Referential Example 250 with ethylmethylamine.

^{1}H-NMR ($CDCl_3$) δ: 1.08,1.18(total 3H,each t,J=7.1Hz), 1.46(9H,s), 1.52-1.80(4H,m), 2.04-2.08(2H,m), 2.71-2.77(1H,m), 2.89,2.98(total 3H,each s), 3.32,3.39(total 2H,each q,J=7.1Hz), 3.74-3.76(1H,m), 4.09-4.11(1H,m), 4.60(1H,br.s).

MS (EI) m/z: 326$(M+H)^+$.

[Referential Example 324]

tert-Butyl (1R,2S,5S)-2-{[(7-chloroisoquinolin-3-yl)-carbonyl]amino}-5-{[ethyl(methyl)amino]carbonyl}-cyclohexylcarbamate:



The compound (1.44 g) obtained in Referential Example 323 was dissolved in methanol (20 ml), 10% palladium on carbon (150 mg) was added, and the mixture was stirred

under a hydrogen atmosphere. After 24 hours, the catalyst was removed by filtration, and the solvent was then concentrated under reduced pressure to obtain a colorless oil. This oil was used in the next reaction as it is.

The above-obtained oil was dissolved in methylene chloride (30 ml), and the compound (850 mg) obtained in Referential Example 57, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.27 g), 1-hydroxybenzotriazole monohydrate (900 mg) and N-methylmorpholine (1.34 g) were added to stir the mixture at room temperature. After 17 hours, methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation, and the resultant organic layer was dried over anhydrous magnesium sulfate. The solvent was disilled off under reduced pressure, and the residue was subjected to column chromatagraphy on silica gel (methanol:methylene chloride = 1:50) to obtain the title compound (1.61 g).

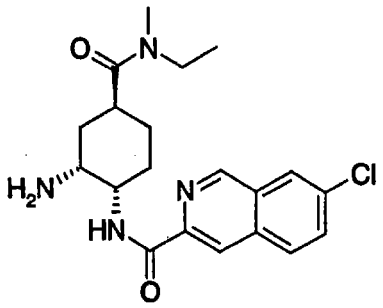
^{1}H-NMR ($CDCl_3$) δ: 1.10,1.22(total 3H,each t,J=7.1Hz), 1.43(9H,s), 1.84-2.17(6H,m), 2.66(1H,br.s), 2.92, 3.03(total 3H,each s), 3.35-3.44(2H,m), 4.20-4.30(2H,m), 5.30(1H,br.s), 7.70(1H,d,J=8.6Hz), 7.92(1H,d,J=8.6Hz), 8.00(1H,s), 8.40(1H,br.s), 8.56(1H,s), 9.03(1H,s).

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

[Referential Example 325]

N-((1S,2R,4S)-2-Amino-4-[(7-chloroisoquinolin-3-yl)-carbonyl]-4-{[ethyl(methyl)amino]carbonyl}cyclohexyl)-7-

chloroisoquinoline-3-carboxamide:



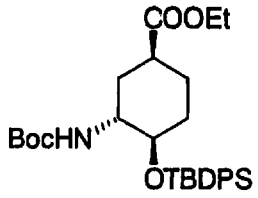
The compound (1.60 g) obtained in Referential Example 324 was dissolved in an ethanol solution (25 ml) of hydrochloric acid, and the solution was stirred at room temperature for 30 minutes. The solvent was distilled off under reduced pressure, and methylene chloride and a 1N aqueous solution of sodium hydroxide were added to the residue to conduct liquid separation. The resultant water layer was extracted with methylene chloride, and organic layers were combined and dried over potassium carbonate. The solvent was distilled off under reduced pressure, hexane was added to the residue, and precipitate was collected by filtration to obtain the title compound (1.22 g).

^{1}H-NMR (DMSO-d_6) δ: 1.10,1.23(total 3H,each t,J=7.1Hz), 1.26(2H,br.s), 1.69-2.11(6H,m), 2.89(1H,br.s), 2.93,3.05(total 3H,each s), 3.38-3.45(2H,m), 3.52(1H,s), 4.18(1H,br.s), 7.70(1H,dd,J=8.8,2.0Hz), 7.94(1H,d,J=8.8Hz), 8.02(1H,d,J=2.0Hz), 8.50(1H,br.s), 8.59(1H,s), 9.11(1H,s).

MS (FAB) m/z: 389$(M+H)^+$.

[Referential Example 326]

Ethyl (1R*,3S*,4S*)-3-[(tert-butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexanecarboxylate:

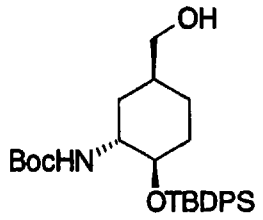


The compound (28.0 g) obtained in Referential Example 88 was dissolved in N,N-dimethylformamide (500 ml), and tert-butyldiphenylsilyl chloride (63.5 ml) and imidazole (19.9 g) were added. After the mixture was stirred at room temperature for 10 hours, ethyl acetate and water were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed twice with water and dried over anhydrous sodium sulfate. After the solvent was distilled off under reduced pressure, the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 1:0 → 47:3) to obtain the title compound (52.5 g) containing 0.4 molecules of N,N-dimethylformamide.

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.27(3H,t,J=7.1Hz), 1.38(9H,s), 1.43-1.59(3H,m), 1.63-1.67(1H,m), 1.92-1.98(1H,m), 2.25-2.32(1H,m), 2.37-2.42(1H,m), 3.66(1H,br.s), 3.80(1H,br.s), 4.16(2H,q,J=7.1Hz), 4.32(1H,d,J=8.1Hz), 7.34-7.46(6H,m), 7.65-7.73(4H,m).

[Referential Example 327]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(hydroxymethyl)cyclohexanecarbmate:

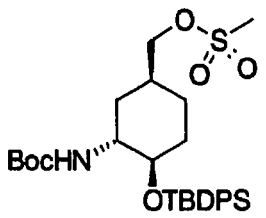


Lithium aluminum hydride (7.11 g) was suspended in absolute diethyl ether (100 ml) at 0°C while purging with argon, and a diethyl ether solution (500 ml) of the compound (52.5 g) obtained in Referential Example 326 was added dropwise over 30 minutes. After stirring at 0°C for 30 minutes, methanol (100 ml) was added dropwise to the reaction mixture. The resultant slurry was removed by filtration through Celite, and the filtrate was concentrated. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 3:1) to obtain the title compound (29.6 g).

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.32-1.74(16H,m), 1.87(1H,t,J=10.4Hz), 3.35-3.55(2H,m), 3.71(1H,br.s), 3.79(1H,br.s), 4.36(1H,br.s), 7.34-7.44(6H,m), 7.65-7.72(4H,m).

[Referential Example 328]

((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)methyl methane-sulfonate:



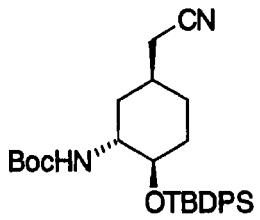
The compound (29.5 g) obtained in Referential Example 327 was dissolved in methylene chloride (200 ml) and pyridine (20 ml), and methanesulfonyl chloride (9.5 ml) was added to stir the mixture at room temperature for 6 hours. The solvent was distilled off under reduced pressure, and ethyl acetate and water were added to the residue to conduct liquid separation. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed twice with water and then dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound (29.8 g).

^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,s), 1.43-1.61(5H,m), 1.86-1.89(2H,m), 3.02(3H,s), 3.77(1H,br.s), 3.81(1H,br.s), 4.10(2H,d,J=5.4Hz), 4.32(1H,br.s), 7.35-7.45(6H,m), 7.64-7.68(4H,m).

MS (ESI) m/z: 562$(M+H)^+$.

[Referential Example 329]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(cyanomethyl)cyclohexanecarbamate:

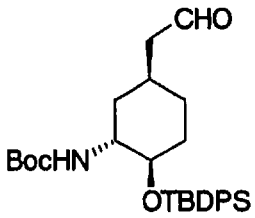


The compound (29.8 g) obtained in Referential Example 328 was dissolved in N,N-dimethylformamide (400 ml), and sodium cyanide (3.64 g) was added to stir the mixture at 80°C for 11 hours. Ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction mixture to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, 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 chromatagraphy on silica gel (hexane:ethyl acetate = 5:1) to obtain the title compound (20.6 g).

^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,s), 1.43-1.68(5H,m), 1.79-1.85(1H,m), 1.88-1.95(1H,m), 2.32(2H,d,J=7.1Hz), 3.77(1H,br.s), 3.82(1H,br.s), 4.32(1H,br.d,J=6.8Hz), 7.35-7.45(6H,m), 7.65-7.71(4H,m).

[Referential Example 330]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-oxy}-5-(2-oxoethyl)cyclohexanecarbamate:



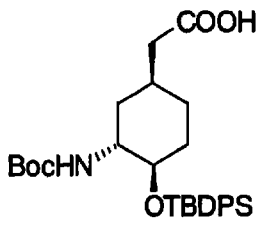
The compound (2.00 g) obtained in Referential Example 329 was dissolved in absolute methylene chloride (20 ml), and the system was purged with argon and then cooled to -78°C. To the solution, was added dropwise diisobutylaluminum hydride (0.95 M hexane solution, 8.55 ml). The temperature of the mixture was then allowed to raise to room temperature and stirred for 3 hours. The reaction mixture was cooled to 0°C, and methanol (10 ml) was added dropwise. The resultant slurry was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 1:0 → 49:1) to obtain the title compound (1.45 g).

^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.38(9H,s), 1.43-1.54(5H,m), 1.82-1.88(1H,m), 2.06(1H,br.s), 2.42-2.43(2H,m), 3.72(1H,br.s), 3.77(1H,br.s), 4.38(1H,br.s), 7.34-7.44(6H,m), 7.65-7.68(4H,m), 9.77(1H,t,J=1.7Hz).

MS (FAB) m/z: 496$(M+H)^+$.

[Referential Example 331]

2-((1R*,3S*,4S*)-3-[(tert-Butoxycarbonyl)amino]-4-{[tert-butyl(diphenyl)silyl]oxy}cyclohexyl)acetic acid:



The compound (8.40 g) obtained in Referential Example 330 was dissolved in a mixed solvent of water (33 ml) and tert-butanol (120 ml), and 2-methyl-2-butene (8.08 ml), sodium dihydrogenphosphate dihydrate (2.64 g) and sodium chlorite (3.45 g) were added to stir the mixture at room temperature for 1.5 hours. Methylene chloride and water were added to the reaction mixture to dilute it. The resultant water layer was adjusted to pH of about 4 with 1N hydrochloric acid. Liquid separation was conducted, and the resultant water layer was extracted twice with methylene chloride. Organic layers were combined and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 2:1 → 1:1) to obtain the title compound (7.62 g).

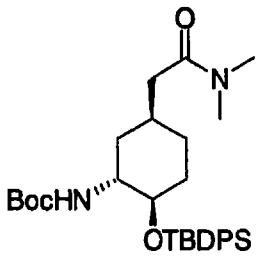
^{1}H-NMR ($CDCl_3$) δ: 1.07(9H,s), 1.22-1.63(15H,m), 1.82(1H,br.s), 2.17(1H,br.s), 2.27-2.33(1H,m), 3.69(1H,br.s), 3.84(1H,br.s), 7.00(1H,br.s), 7.33-7.42(6H,m), 7.63-7.65(4H,m).

MS (ESI) m/z: 512$(M+H)^+$.

[Referential Example 332]

tert-Butyl (1R*,2R*,5S*)-2-{[tert-butyl(diphenyl)silyl]-

oxy}-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:



The compound (7.62 g) obtained in Referential Example 331 was dissolved in N,N-dimethylformamide (150 ml), and dimethylamine hydrochloride (6.07 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.56 g), 1-hydroxybenzotriazole monohydrate (1.01 g) and triethylamine (10.3 ml) were added to stir the mixture at room temperature for 4 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 extracted with methylene chloride, and organic layers were combined and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1). The solvent was distilled off, hexane was added to the residue, and formed white precipitate was collected by filtration to obtain the title compound (6.42 g).

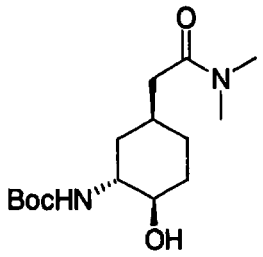
^{1}H-NMR ($CDCl_3$) δ: 1.08(9H,s), 1.38(9H,br.s), 1.43-1.55(5H,m), 1.79-1.86(1H,m), 2.03(1H,br.s), 2.21-2.32(2H,s), 2.94(3H,s), 3.03(3H,s), 3.74(1H,br.s), 3.80(1H,br.s),

4.49(1H,br.s), 7.33-7.44(6H,m), 7.64-7.69(4H,m).

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

[Referential Example 333]

tert-Butyl (1R*,2R*,5S*)-5-[2-(dimethylamino)-2-oxoethyl]-2-hydroxycyclohexanecarbamate:



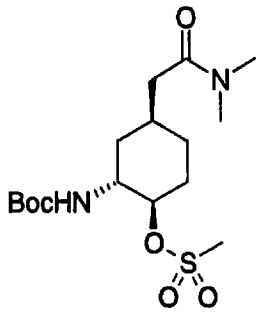
The compound (6.36 g) obtained in Referential Example 332 was dissolved in tetrahydrofuran (50 ml), and tetrabutylammonium fluoride (1N tetrahydrofuran solution, 17.85 ml) was added to stir the mixture at room temperature for 13 hours. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (3.49 g).

^{1}H-NMR ($CDCl_3$) δ: 1.44(9H,s), 1.46-1.60(4H,m), 1.79-1.84(2H,m), 2.28-2.35(3H,s), 2.82(1H,br.s), 2.95(3H,s), 3.01(3H,s),3.56(2H,br.s), 4.67(1H,br.s).

MS (ESI) m/z: 301$(M+H)^+$.

[Referential Example 334]

((1R*,2R*,4S*)-2-[(tert-Butoxycarbonyl)amino]-4-[2-(dimethylamino)-2-oxoethyl]cyclohexyl methanesulfonate:



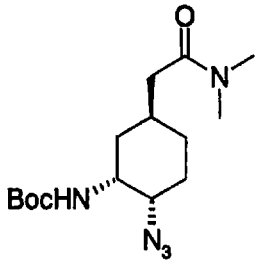
The compound (8.05 mg) obtained in Referential Example 333 was dissolved in methylene chloride (50 ml), and the solution was cooled to -78°C under an argon atmosphere to add dropwise methanesulfonyl chloride (2.70 ml). After the temperature of the mixture was allowed to raise to 0°C and stirred for 30 minutes, it was stirred at room temperature for 2 hours. Water was added to the reaction mixture to conduct liquid separation, and the resultant water layer was extracted with methylene chloride. Organic layers were combined, washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1 → 0:1) to obtain the title compound (3.63 g).

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.59-1.74(4H,m), 1.85-2.30(5H,m), 2.95(3H,s), 3.00(3H,s), 3.10(3H,s), 3.79-3.83(1H,m), 4.72(1H,br.s), 4.91(1H,br.s).

MS (ESI) m/z: 379$(M+H)^+$.

[Referential Example 335]

tert-Butyl (1R*,2S*,5S*)-2-azido-5-[2-(dimethylamino)-2-oxoethyl]cyclohexanecarbamate:



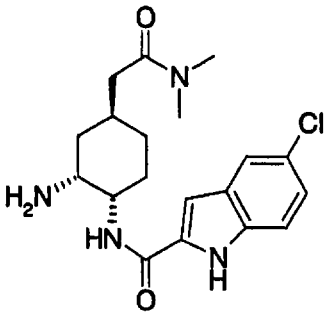
The compound (3.62 g) obtained in Referential Example 334 was dissolved in N,N-dimethylformamide (20 ml), and sodium azide (3.11 g) was added to stir the mixture at 75°C for 17 hours. The reaction mixture was poured into a mixed solvent of water and ethyl acetate to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate, and organic layers were combined, washed with water, a saturated aqueous solution of sodium hydrogencarbonate and 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 flash column chromatagraphy on silica gel (ethyl acetate) to obtain the title compound (1.30 g).

^{1}H-NMR ($CDCl_3$) δ: 1.14-1.21(1H,m), 1.33-1.40(1H,m), 1.45(9H,s), 1.61-1.71(1H,m), 1.78-1.91(3H,m), 2.22-2.27(3H,m), 2.94(3H,s), 3.00(3H,s), 3.60-3.62(1H,m), 3.97(1H,br.s), 4.76(1H,br.s).

MS (ESI) m/z: 326$(M+H)^+$.

[Referential Example 336]

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



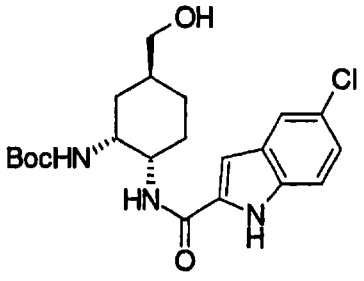
The title compound was obtained by treating, in a similar manner to Referential Example 69, a product obtained by catalytically reducing the compound obtained in Referential Example 335 in a similar manner to Referential Example 324 and then condensing it with 5-chloroindole-2-carboxylic acid.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.19(1H,m), 1.51-1.56(1H,m), 1.70-1.73(1H,m), 1.81-1.91(2H,m), 1.99-2.03(1H,m), 2.19-2.30(3H,m), 2.83(3H,s), 2.99(3H,s), 3.63(1H,br.s), 4.08(1H,br.s), 7.19(1H,dd,J=8.7,1.7Hz), 7.35(1H,s), 7.44(1H,d,J=8.7Hz), 7.69(1H,d,J=1.7Hz), 8.22(3H,br.s), 8.62(1H,d,J=7.1Hz), 11.91(1H,s).

MS (ESI) m/z: 377$(M+H)^+$.

[Referential Example 337]

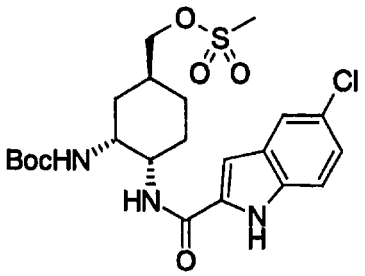
tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-(hydroxymethyl)cyclohexanecarbamate:



The title compound was obtained from the compound obtained in Referential Example 97 in a similar manner to step 2) of Referential Example 129.

[Referential Example 338]

((1S,3R,4S)-3-[(tert-butoxycarbonyl)amino]-4-{[(5-chloroindol-2-yl)carbonyl]amino}cyclohexyl)methyl methanesulfonate:



The compound (500 mg) obtained in Referential Example 337 and triethylamine (329 ml) were suspended in tetrahydrofuran (8ml)-methylene chloride (8 ml), and the suspension was cooled to -78°C. After methanesulfonyl chloride (138 ml) was added dropwise to the suspension, the temperature of the suspension was gradually raised to -5°C, and the suspension was stirred for 15 hours at the same temperature. After the reaction mixture was concentrated, water was added to the residue to conduct extraction 3 times with methylene chloride. The resultant organic layers were washed with saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate, and the solvent was then distilled off under reduced pressure to obtain the title compound (654 mg).

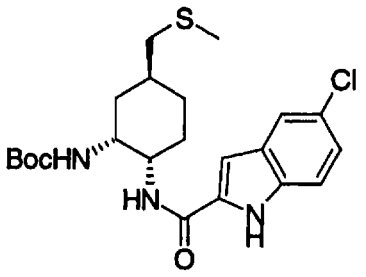
^{1}H-NMR ($CDCl_3$) δ: 1.57(9H,s), 1.84-2.01(4H,m), 2.28-

2.31(1H,m), 3.04(3H,s), 3.68(1H,s), 3.74-3.75(1H, m), 3.91-3.93(1H,m), 4.02-4.12(2H,m), 4.18-4.20(1H,m), 4.85(1H,br.s), 6.81(1H,s), 7.21(1H,dd,J=2.0,8.8Hz), 7.34(1H,d,J=8.8Hz), 7.60(1H,s), 8.02(1H,br.s), 9.27(1H,br.s).

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

[Referential Example 339]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(methylsulfanyl)methyl]cyclohexanecarbamate:



The compound (654 mg) obtained in Referential Example 338 was dissolved in N,N-dimethylformamide (8 ml), and a 15% aqueous solution (1.8 ml) of sodium thiomethoxide was added to stir the mixture at room temperature for 4 hours. The reaction mixture was poured into water and extracted 3 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. The residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1) to obtain the title compound (492 mg).

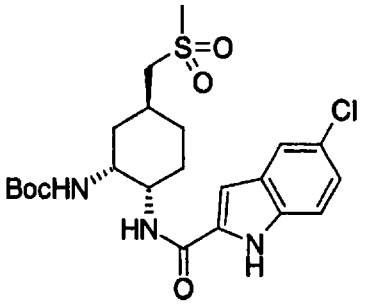
^{1}H-NMR ($CDCl_3$) δ: 1.52(9H,s), 1.87-3.04(13H,m), 3.91-3.94(1H,m), 4.12-4.15(1H,m), 4.95(1H,br.s), 6.81(1H,s), 7.19(1H,dd,J=8.8,1.2Hz), 7.35(1H,d,J=8.8Hz), 7.57(1H,s),

9.82(1H,br.s).

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

[Referential Example 340]

tert-Butyl (1R,2S,5S)-2-{[(5-chloroindol-2-yl)carbonyl]-amino}-5-[(methylsulfonyl)methyl]cyclohexanecarbamate:

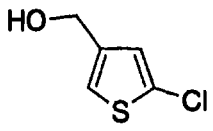


The compound (300 mg) obtained in Referential Example 339 was dissolved in methylene chloride (10 ml), and m-chloroperbenzoic acid (70%, 400 mg) was added at 0°C under stirring. After stirring was continued for 1 hour as it is, the reaction mixture was poured into water and extracted 3 times with ethyl acetate. The resultant organic layers were washed with saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated. After the residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 24:1), liquid separation was conducted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate, and the resultant organic layer was concentrated to obtain the title compound (254 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.44-2.19(13H,m), 2.22-2.30(2H,m), 2.89-3.25(7H,m), 3.93-4.15(2H,m), 4.98(1H,br.s), 6.82(1H,s),

7.21(1H,dd,J=8.8,2.0Hz), 7.34(1H,d,J=8.8Hz), 7.60(1H,br.s), 9.54(1H,br.s).

[Referential Example 341] (5-Chlorothien-3-yl)methanol:

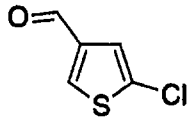


5-Chlorothiophene-3-carboxylic acid (Monatsh. Chem., Vol. 120, p. 53, 1989) (6.93 g) was dissolved in tetrahydrofuran (750 ml), and triethylamine (27.3 ml) and ethyl chloroformate (18.7 ml) were added to stir the mixture at room temperature for 2.5 hours. An aqueous solution (41 ml) of sodium borohydride (19.3 g) was added dropwise over 10 minutes, and the mixture was stirred at room temperature for 18.5 hours. After acetic acid was added to the reaction mixture to acidify it, the solvent was distilled off under reduced pressure. Water and methylene chloride were added to the residue to conduct liquid separation. The resultant organic layer was washed with water and a saturated aqueous solution of sodium hydrogencarbonate. After drying the organic layer, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatagraphy on silica gel (ethyl acetate:hexane = 1:4) to obtain the title compound (5.17 g).

^{1}H-NMR ($CDCl_3$) δ: 1.63(1H,t,J=5.8Hz), 4.59(2H,d,J=5.3Hz), 6.91(1H,d,J=1.7Hz), 6.98-6.99(1H,m).

[Referential Example 342]

5-Chlorothiophene-3-carbaldehyde:

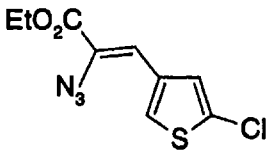


The compound (5.17 g) obtained in Referential Example 341 was dissolved in methylene chloride (400 ml), and manganese dioxide (51.3 g) was added to stir the mixture at room temperature for 15 hours. After the reaction mixture was filtered, the solvent was distilled off under reduced pressure to obtain the title compound (2.84 g).

^{1}H-NMR ($CDCl_3$) δ: 7.35(1H,d,J=1.7Hz), 7.88(1H,d,J=1.7Hz), 9.75(1H,s).

[Referential Example 343]

Ethyl 2-azido-3-(5-chlorothien-3-yl)acrylate:



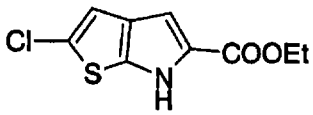
After ethanol (15 ml) was added to a 20% ethanol solution (10.7 ml) of sodium ethoxide, and the mixture was cooled to 0°C, a mixture of the compound (1.01 g) obtained in Referential Example 342 and ethyl azidoacetate (3.55 g) was added dropwise over 30 minutes, and the resultant mixture was stirred at 0°C for 3 hours. A cooled aqueous solution of ammonium chloride was added to the reaction mixture to conduct extraction 3 times with diethyl ether. Organic layers were combined, and the solvent was distilled

off under reduced pressure. The residue was purified by flach column chromatagraphy on silica gel (ethyl acetate:hexane = 1:49) to obtain the title compound (1.04 g).

^{1}H-NMR ($CDCl_3$) δ: 1.38(3H,t,J=7.1Hz), 4.34(2H,q,J=7.1Hz), 6.75(1H,s), 7.39(1H,d,J=1.7Hz), 7.54(1H,d,J=1.7Hz).

[Referential Example 344]

Ethyl 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylate:

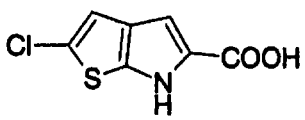


The compound (0.97 g) obtained in Referential Example 343 was dissolved in xylene (20 ml), and the solution was heated under reflux for 30 minutes. After allowing the reaction mixture to cool, the solvent was distilled off under reduced pressure. Hexane was added to the residue, solids formed were collected by filtration to obtain the title compound (0.608 g).

^{1}H-NMR ($CDCl_3$) δ: 1.38(3H,t,J=7.0Hz), 4.35(2H,q,J=7.0Hz), 6.90(1H,s), 7.00(1H,d,J=1.9Hz), 9.32(1H,br).

[Referential Example 345]

2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid:



The title compound was obtained from the compound obtained in Referential Example 344 in a similar manner to

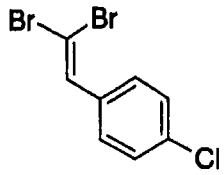
Referential Example 274.

^{1}H-NMR (CD_3OD) δ: 3.35(1H,s), 6.94(1H,s), 6.96(1H,s).

MS (ESI) m/z: 200$(M-H)^-$.

[Referential Example 346]

1-Chloro-4-(2,2-dibromovinyl)benzene:



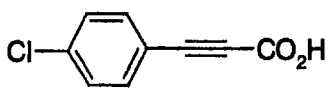
4-Chlorobenzaldehyde (2.81 g) was dissolved in methylene chloride (300 ml), and carbon tetrabromide (13.3 g) and triphenylphosphine (21.0 g) were added to stir the mixture at room temperature for 90 minutes. After insoluble matter deposited was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatagraphy on silica gel (hexane:ethyl acetate = 20:1) to obtain the title compound (5.54 g).

^{1}H-NMR ($CDCl_3$) δ: 7.33(2H,d,J=8.5Hz), 7.43(1H,s), 7.47(2H,d,J=8.5Hz).

MS (EI) m/z: 296(M^+).

[Referential Example 347]

3-(4-Chlorophenyl)-2-propiolic acid:



The compound (1.0 g) obtained in Referential Example

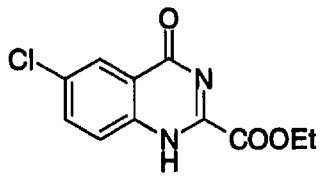
346 was dissolved in tetrahydrofuran (30 ml), and n-butyllithium (1.59 N hexane solution, 4.46 ml) was added dropwise at -78°C under an argon atmosphere. The temperature of the reaction mixture was allowed to raise to room temperature and stirred for 1 hour. The reaction mixture was cooled again to -78°C, 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

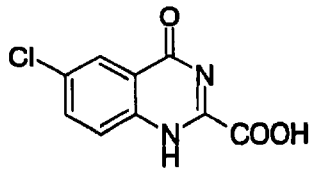
(15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure, and the resultant residue was dissolved in acetic acid (50 ml). Acetic anhydride (5.0 ml) was added to the solution, and the mixture was heated under reflux for 16 hours. 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:



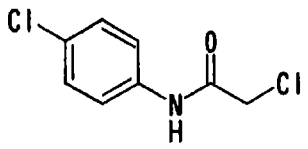
Lithium hydroxide (263 mg) was added to a solution of the compound (1.26 g) obtained in Referential Example 348 in a mixed solvent of water (5 ml) and tetrahydrofuran (15 ml), and the mixture was stirred at room temperature for 18 hours. The reaction mixture was neutralized with 1N hydrochloric acid (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:

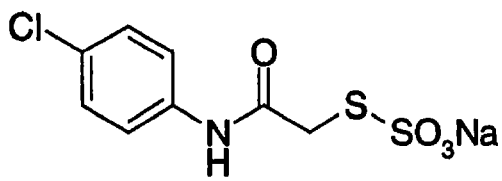


p-Chloroaniline (3.82 g) was dissolved in ethyl acetate (30 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 3.5 hours, crystals deposited were collected by filtration to obtain the title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



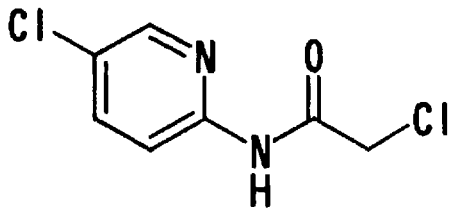
The compound (5.79 g) obtained in Referential Example

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:

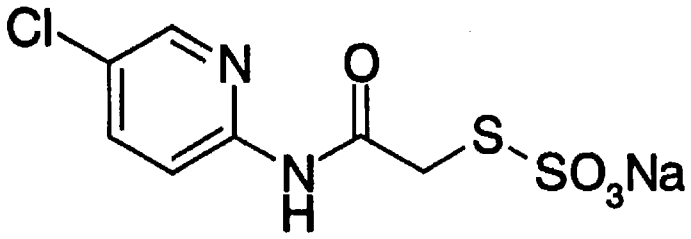


2-Amino-5-chloropyridine (3.85 g) was dissolved in ethyl acetate (60 ml), and chloroacetyl chloride (2.39 ml) was added at room temperature to stir the mixture for 1 hour. After the reaction mixture was heated and stirred at 60°C for 30 minutes, chloroacetyl chloride (0.5 ml) was additionally added, 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:



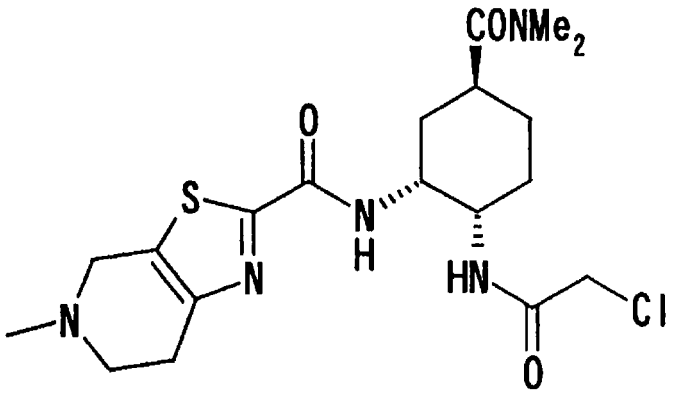
An aqueous solution (130 ml) with sodium thiosulfate pentahydrate (6.35 g) and sodium hydrogencarbonate (2.15 g) dissolved therein was added to a solution with the compound (6.18 g) obtained in Referential Example 352 dissolved in

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

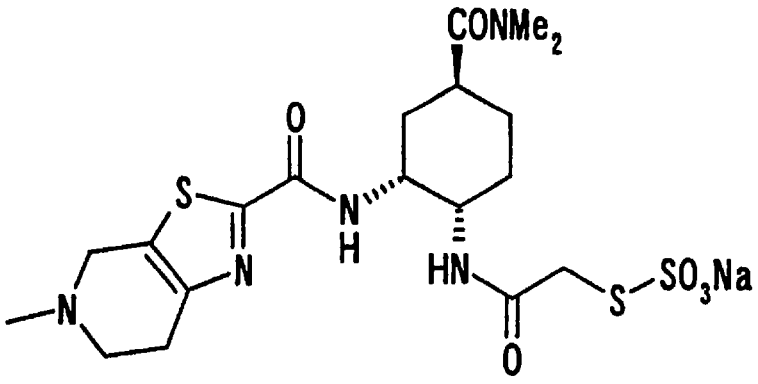
by filtration and dissolved in methylene chloride-methanol, and the solvent was distilled off under reduced pressure to obtain the crude title compound (112 mg).

^{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:



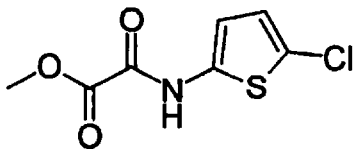
The compound (106 mg) obtained in Referential Example 354 was dissolved in ethanol (1.5 ml), and an aqueous solution (1.5 ml) of sodium thiosulfate pentahydrate (55 mg) and sodium hydrogencarbonate (18.6 mg) dissolved therein was added at a time at 90°C under stirring. The resultant mixture was heated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

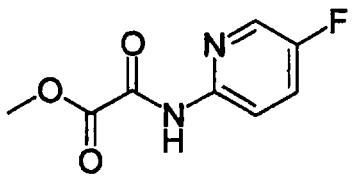
(hexane:ethyl acetate = 3:1), and the solvent was distilled off to obtain the title compound (1.44 g).

^{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:



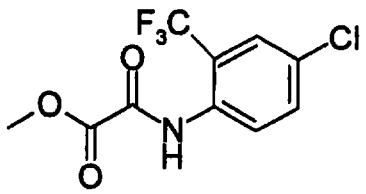
The title compound was obtained from 2-amino-5-fluoropyridine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



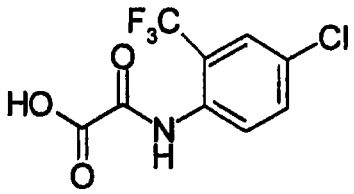
The title compound was obtained from 4-chloro-2-trifluoroaniline and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



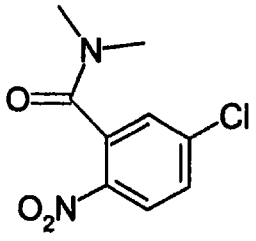
Lithium hydroxide (28 mg) was added to a solution of the compound (297 mg) obtained in Referential Example 358 in a mixed solvent of tetrahydrofuran (7ml) and water (3 ml), and the mixture was stirred at room temperature for 2 hours. 1N Hydrochloric acid (8 ml) and methylene chloride (20 ml) were added 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:

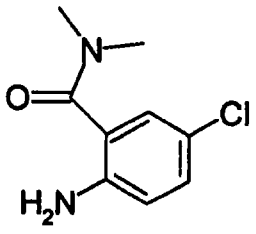


The title compound was obtained by condensing 5-chloro-2-nitrobenzoic acid with dimethylamine in a similar manner to the process described in Referential Example 143.

^{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

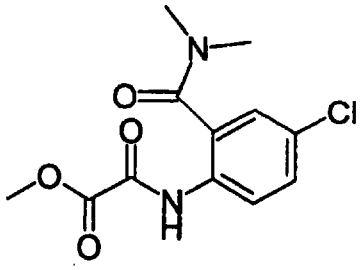
were combined, washed with distilled water and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resultant residue was subjected to column chromatography on silica gel (methylene chloride:hexane = 1:1 → 1:0 → methanol:methylene chloride = 1:100) to obtain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

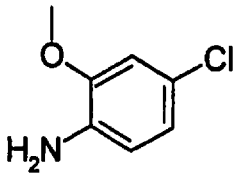


The title compound was obtained from the compound obtained in Referential Example 361 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



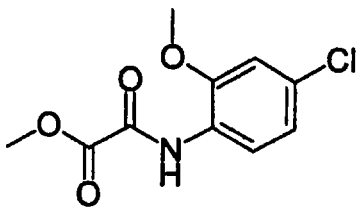
The title compound was obtained from 5-chloro-2-nitroanisole in a similar manner to the process described in Referential Example 361.

^{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:



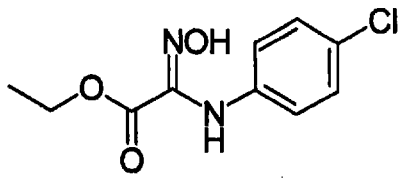
The title compound was obtained from the compound obtained in Referential Example 363 and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



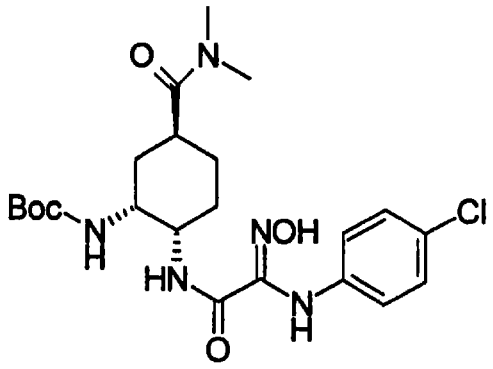
The title compound was obtained from 4-chloroaniline (3.03 g) and ethyl 2-chloro-2-hydroxyiminoacetate in a similar manner to the process described in literature (Gilchrist, T. L.; Peek, M. E.; Rees, C. W.; J. Chem. Soc. Chem. Commun., 1975, 913).

^{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),

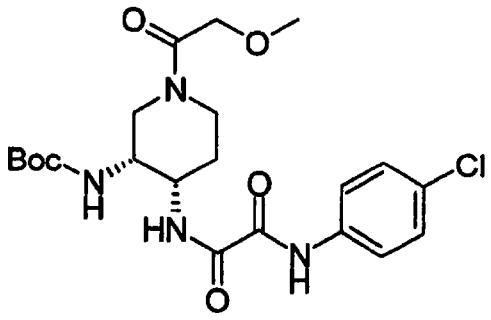
and the mixture was stirred at 70°C for 3 days. After the reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 30:1) to obtain the title compound (180 mg).

^{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.

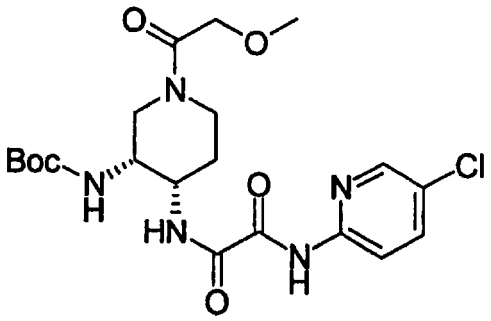
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.94-2.07(1H,br), 2.70-3.00(1H,m), 3.10-3.37(1H,m), 3.44(3H,s), 3.88-4.22(4H,m), 4.55-4.69(1H,br), 4.80-4.90(0.5H,br), 5.36-5.48(0.5H,br), 7.20-7.30(1H,br), 7.32(2H,d,J=8.8Hz),

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:



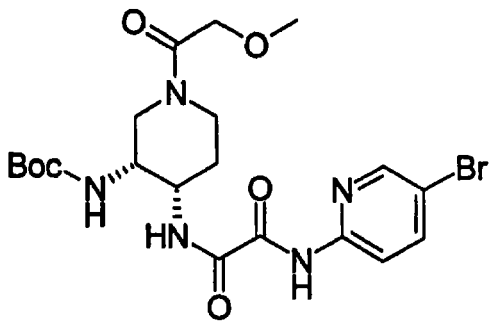
The title compound was obtained from the compound obtained in Referential Example 266 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{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:

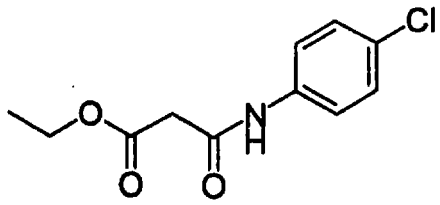


The title compound was obtained from the compound obtained in Referential Example 375 and the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{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:



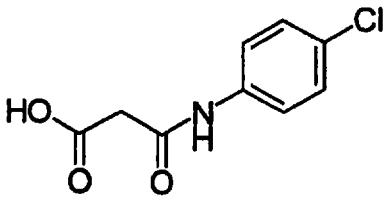
Potassium ethyl malonate (3.2 g), 1-hydroxybenzotriazole (2.1 g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.5 g) were successively added to a solution of 4-chloroaniline (2.0 g) in N,N-

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:



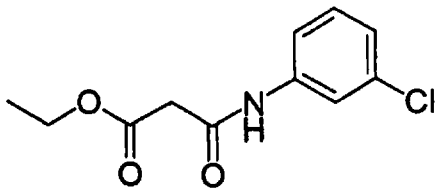
A 1N aqueous solution (10 ml) of sodium hydroxide was added dropwise to a solution of the compound (1.0 g) obtained in Referential Example 370 in ethanol (10 ml) at room temperature, and the mixture was stirred for 2 hours. 1N Hydrochloric acid (10 ml) was added to the reaction mixture, the mixture was 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:

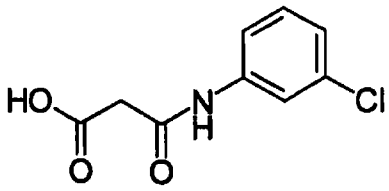


The title compound was obtained by condensing 3-chloroaniline with potassium ethyl malonate in a similar manner to the process described in Referential Example 370.

^{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:

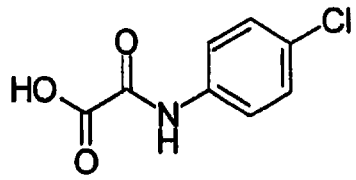


The title compound was obtained from the compound obtained in Referential Example 372 in a similar manner to the process described in Referential Example 371.

^{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:

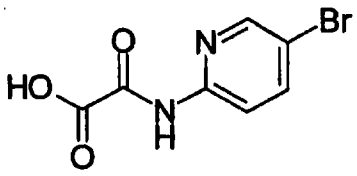


The title compound was obtained from the compound obtained in Referential Example 242 in a similar manner to the process described in Referential Example 359.

^{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]

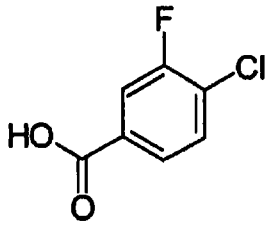
2-[(5-Bromopyridin-2-yl)amino]-2-oxoacetic acid:



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:



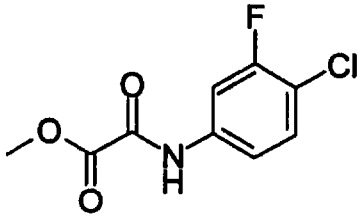
Sodium chlorite (17 g) was added portionwise to a mixture solution composed of 4-chloro-3-fluorobenzaldehyde

(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:



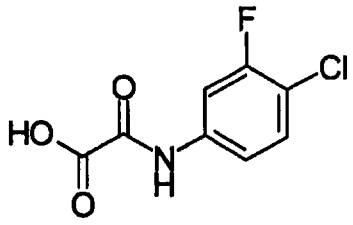
The title compound was obtained by subjecting the compound obtained in Referential Example 376 to Curtius rearrangement reaction and then condensing this product with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 356.

^{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:

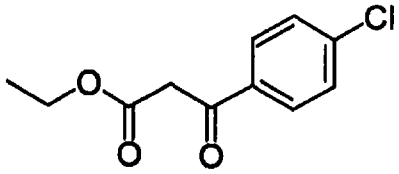


The title compound was obtained from the compound obtained in Referential Example 377 in a similar manner to the process described in Referential Example 359.

^{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:



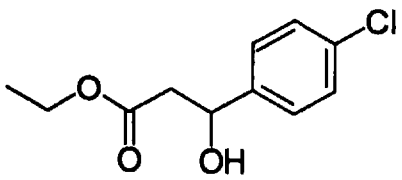
Triethylamine (17 ml) and magnesium chloride (5.5 g) were added to a suspension of potassium ethyl malonate (8.2 g) in ethyl acetate (100 ml) under ice cooling, and the mixture was stirred for 18 hours while the temperature of the system was gradually raised to room temperature. On the other hand, a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



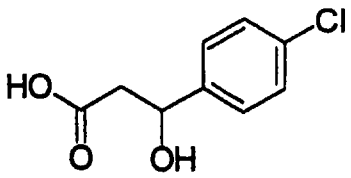
Sodium borohydride (0.2 g) was added portionwise under ice cooling to a solution of the compound (1.0 g) obtained in Referential Example 379 in tetrahydrofuran (10

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:



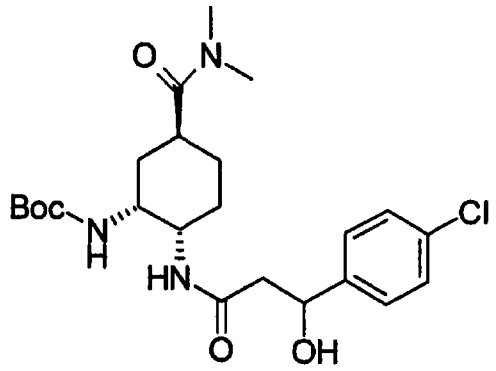
The title compound was obtained from the compound obtained in Referential Example 380 in a similar manner to the process described in Referential Example 359.

^{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:



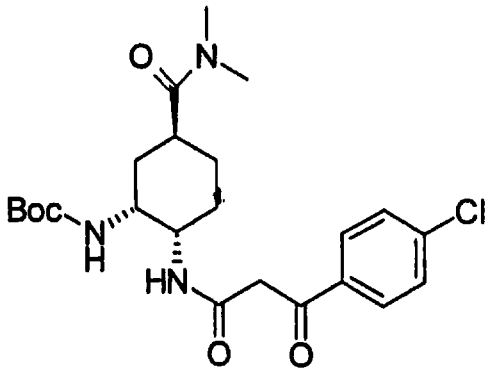
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 381 in a similar manner to the process described in Referential Example 91.

^{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:



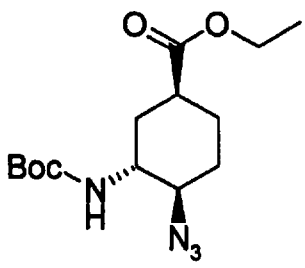
Manganese dioxide (0.47 g) was added to a solution of the compound (0.5 g) obtained in Referential Example 382 in 1,4-dioxane (20 ml) at room temperature, and the mixture was stirred for 4 days. Insoluble matter was removed by filtration through Celite pad, and the resultant filtrate was concentrated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



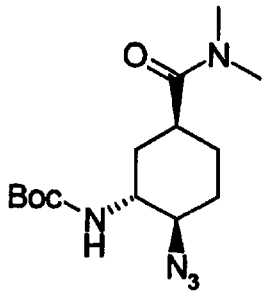
The title compound was obtained from the compound obtained in Referential Example 248 in a similar manner to the process described in Referential Example 249.

$[\alpha]_D^{25}$ +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:



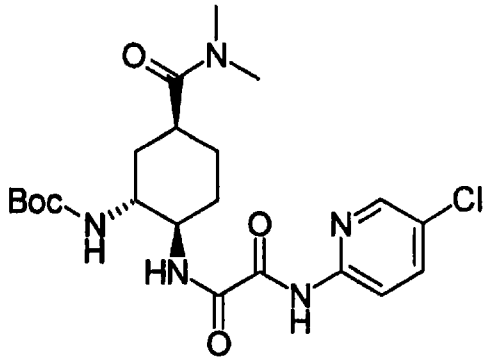
The title compound was obtained from the compound obtained in Referential Example 384 in similar manners to Referential Examples 250 and 251.

^{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:



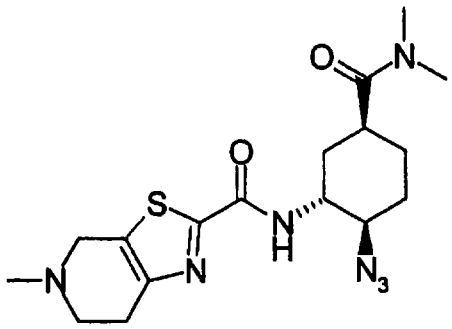
The title compound was obtained by converting the azide group of the compound obtained in Referential Example 385 into an amino group in a similar manner to the process described in Referential Example 90 and then condensing this product with the compound obtained in Referential Example 266 in a similar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



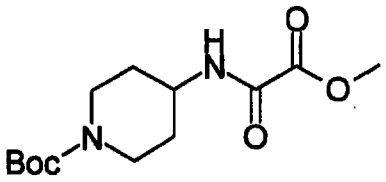
The title compound was obtained from the compound obtained in Referential Example 385 and the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.

^{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.

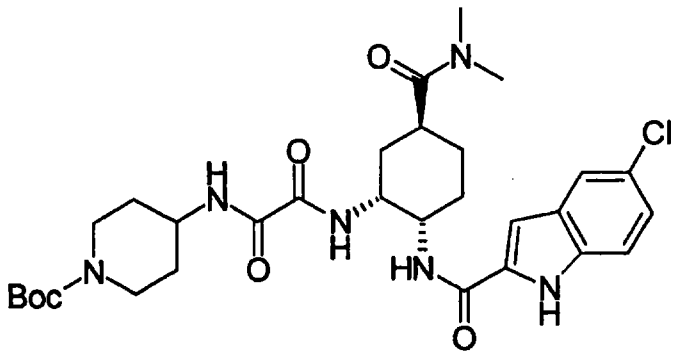
^{1}H-NMR (DMSO-d_6) δ: 1.46(9H,s), 1.34-1.51(2H,m), 1.89-

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:



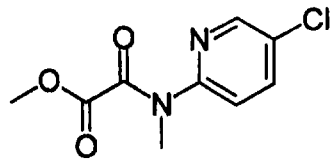
The title compound was obtained from the compound obtained in Referential Example 310 and the compound obtained in Referential Example 388 in a similar manner to the process described in Referential Example 191.

^{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:



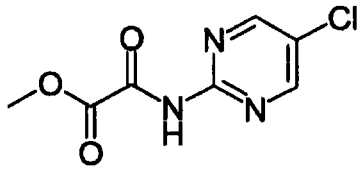
The title compound was obtained from 5-chloro-N-methyl-2-pyridineamine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



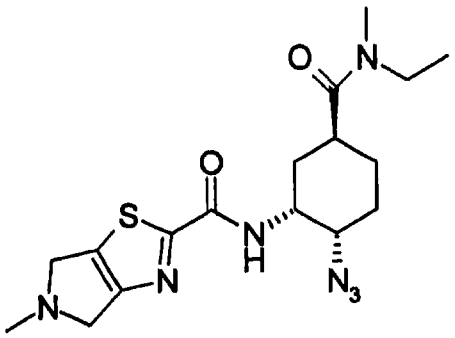
The title compound was obtained from 2-amino-5-chloropyrimidine and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



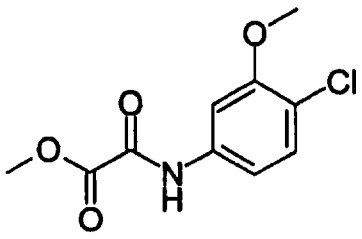
The title compound was obtained from the compound obtained in Referential Example 323 and the compound obtained in Referential Example 293 in a similar manner to the process described in Referential Example 252.

^{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:



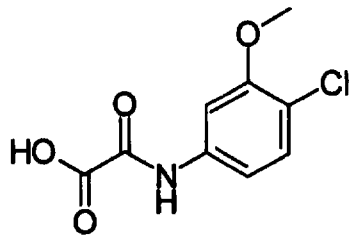
The title compound was obtained by reducing 2-chloro-5-nitroanisole in a similar manner to the process described in Referential Example 361 into an amino derivative and then condensing the amino derivative with

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:



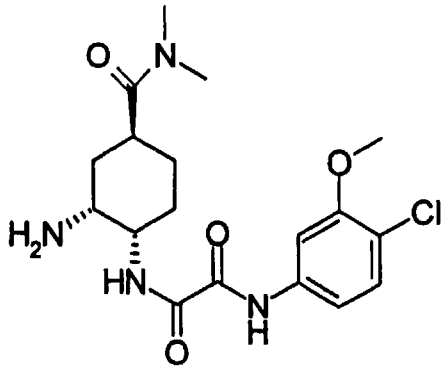
The title compound was obtained by hydrolyzing the compound obtained in Referential Example 393 in a similar manner to the process described in Referential Example 359.

^{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:



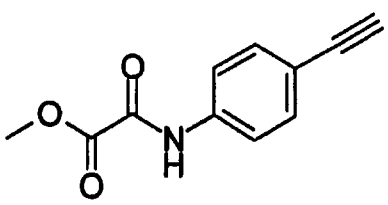
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 394 in a similar manner to the process described in Referential Example 97, treating this product with hydrochloric acid in a similar manner to the process 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:



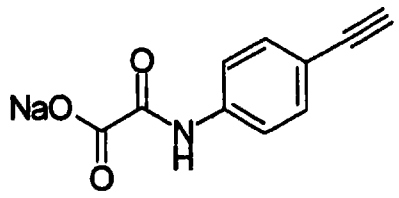
The title compound was obtained from 4-ethynylaniline

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:

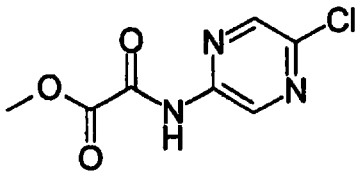


The title compound was obtained by hydrolyzing the compound obtained in Referential Example 396 with sodium hydroxide in a similar manner to the process described in Referential Example 266.

^{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:



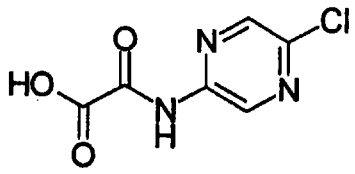
The title compound was obtained from 2-amino-5-chloropyrazine synthesized in accordance with literature (Sato, Nobuhiro et al., J. Heterocycl. Chem., 1982, 19(3), 673-4) and methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242.

^{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:



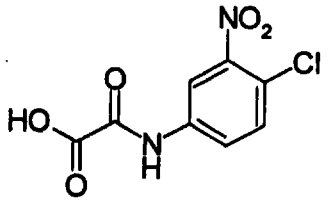
The title compound was obtained from the compound obtained in Referential Example 398 in a similar manner to the process described in Referential Example 359.

^{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.

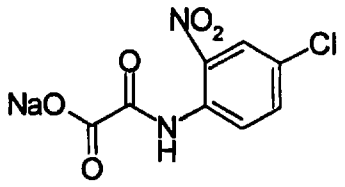
^{1}H-NMR (DMSO-d_6) δ: 7.76(1H,dd,J=8.8Hz), 8.04(1H,dd,J=8.8,2.4Hz), 8.55(1H,d,J=2.4Hz), 11.24(1H,s).

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:

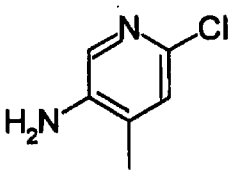


The title compound was obtained by condensing 4-chloro-2-nitroaniline with methyl chlorooxoacetate in a similar manner to the process described in Referential Example 242, hydrolyzing this product in a similar manner to the process described in Referential Example 266, dissolvig the resultant residue 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

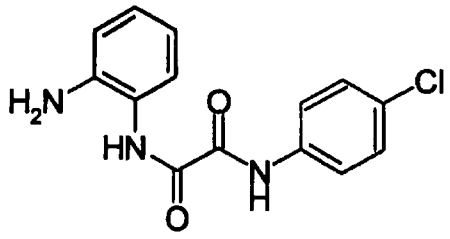
room temperature for 9 hours under a hydrogen atmosphere. The catalyst was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 3:2) to obtain the title compound (113 mg).

^{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.

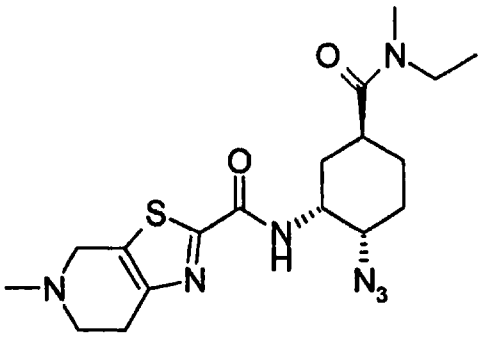
^{1}H-NMR (DMSO-d_6) δ: 5.00(2H,s), 6.59-6.63(1H,m), 6.78(1H,dd,J=8.1,1.2Hz), 6.96-7.01(1H,m), 7.25(1H,dd,J=7.8,1.2Hz), 7.44(2H,d,J=8.8Hz), 7.91(2H,d,J=8.8Hz), 10.04(1H,s),10.91(1H,s).

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:

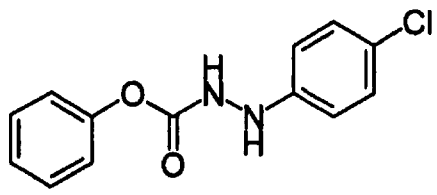


The title compound was obtained by treating the compound obtained in Referential Example 323 with hydrochloric acid, performing deprotection and then condensing this product with the compound obtained in Referential Example 10 in a similar manner to the process described in Referential Example 252.

^{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

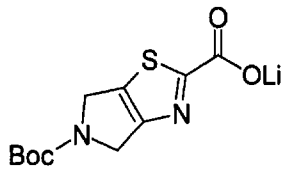
ml) and a saturated aqueous solution of sodium hydrogencarbonate. An organic layer was separated, dried over anhydrous sodium sulfate and then concentrated, giving (4-chlorophenyl)hydrazine as a brown solid. This product was dissolved in benzene (15 ml), and the solution was heated under reflux, to which 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:

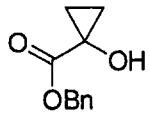


The title compound was obtained from the compound obtained in Referential Example 33 in a similar manner to the process described in Referential Example 10.

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

[Referential Example 407]

Benzyl 1-hydroxycyclopropanecarboxylate:



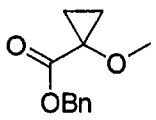
Triethylamine (1.0 ml) and benzyl bromide (650 µl) were added to a solution of 1-hydroxycyclopropanecarboxylic acid (409 mg) in tetrahydrofuran (3.0 ml), and the mixture was stirred at room temperature for 23 hours. Methylene chloride and 1N hydrochloric acid were added to the reaction mixture to separate 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:



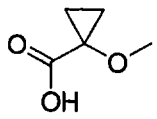
60% Sodium hydride in oil (345 mg) and methyl iodide (900 μl) were added to a solution of the compound (600 mg) obtained in Referential Example 407 in tetrahydrofuran (5.0 ml), and the mixture was heated under reflux for 28 hours. Ethyl acetate and a saturated aqueous solution of ammonium chloride were 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:

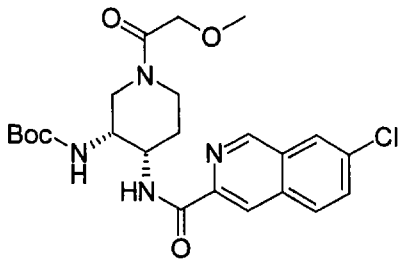


The title compound was obtained from the compound obtained in Referential Example 408 in a similar manner to the process described in Referential Example 152.

^{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:



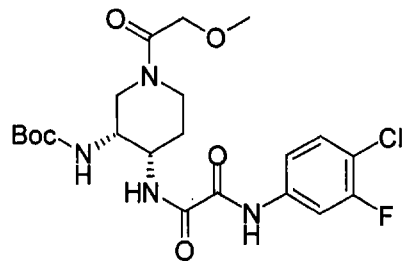
The title compound was obtained from the compound obtained in Referential Example 220 in a similar manner to the process described in Referential Example 214.

^{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

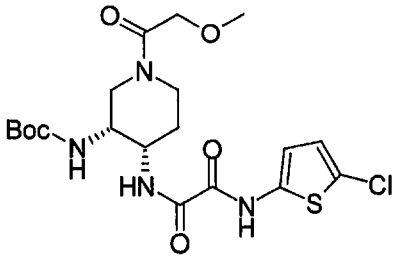
compound obtained in Referential Example 220 with the compound obtained in Referential Example 337 in a similar manner to the process described in Referential Example 214.

^{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.

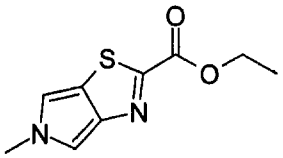
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.55-1.75(1H,br), 1.90-2.10(1H,br), 2.68-2.80(0.7H,m), 2.90-3.03(0.3H,br), 3.07-

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-

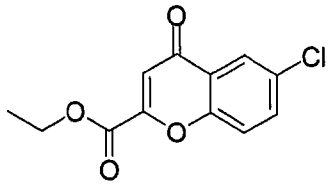
isobutyronitrile (227 mg) were added to a solution of the above-described product (19.53 g) in 1,2-dichloroethane (500 ml), and the mixture was refluxed for 42 hours. After cooling the reaction mixture, water and methylene chloride were added to separate the mixture into two layers. An organic layer 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).

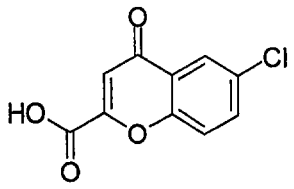
^{1}H-NMR ($CDCl_3$) δ: 1.44(3H,t,J=7.1Hz), 4.47(2H,q,J=7.1Hz), 7.12(1H,s), 7.58(1H,d,J=9.0Hz), 7.69(1H,dd,J=9.0,2.7Hz),

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:



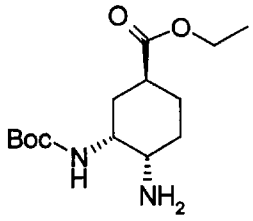
The title compound was obtained from the compound obtained in Referential Example 414 in a similar manner to the process described in Referential Example 359.

^{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:

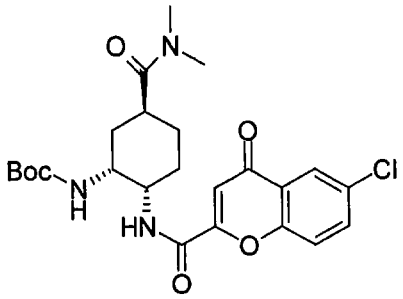


The title compound was obtained from the compound obtained in Referential Example 249 in a similar manner to the process described in Referential Example 90.

^{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:



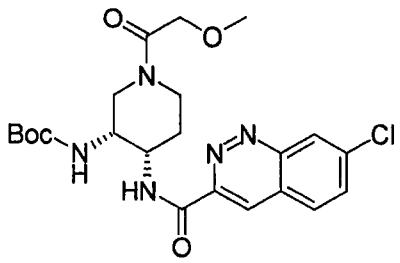
N,N-Dimethylformamide (0.02 ml) was added to a solution of the compound (213 mg) obtained in Referential Example 415 in thionyl chloride (2.0 ml), and the mixture was refluxed for 15 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in tetrahydrofuran (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:



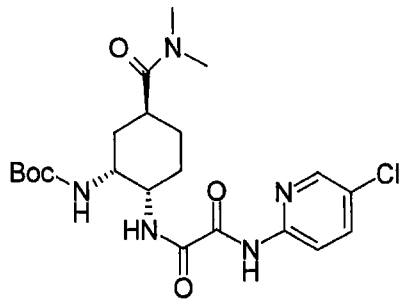
The title compound was obtained from the compound obtained in Referential Example 220 and the lithium salt of a carboxylic acid obtained by hydrolyzing the ester described in Referential Example 297 in a similar manner to the process described in Referential Example 214.

^{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:



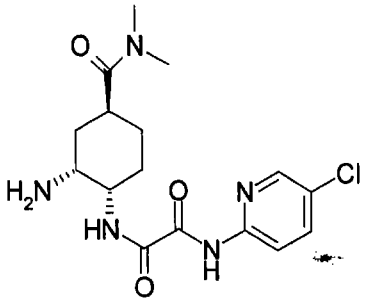
The title compound was obtained by condensing the compound obtained in Referential Example 144 with the compound obtained in Referential Example 266 in a similar manner to the process described in Referential Example 68.

^{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:



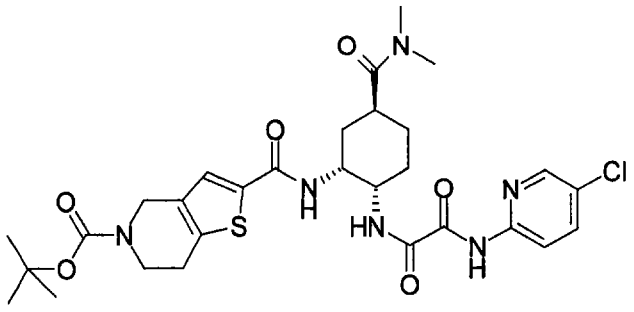
The title compound was obtained from the compound obtained in Referential Example 419 in a similar manner to the process described in Referential Example 69.

^{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-

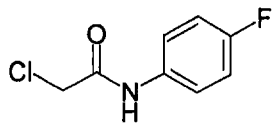
butoxycarbonyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid (WO94/21599).

^{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:

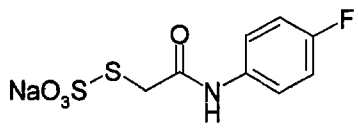


The title compound was obtained from p-fluoroaniline in a similar manner to the process described in Referential Example 350.

^{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:

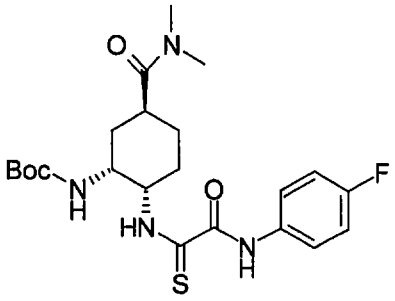


The title compound was obtained from the compound obtained in Referential Example 422 in a similar manner to the process described in Referential Example 351.

^{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:



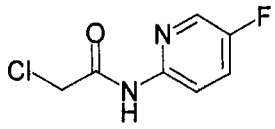
The compound (1.1 g) obtained in Referential Example 144 and the compound (1.2 g) obtained in Referential Example 423 were dissolved in N-methylmorpholine (20 ml), and the temperature of a bath was raised from room temperature to 140°C over 15 minutes to heat and stir the mixture for 15 minutes at the 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:



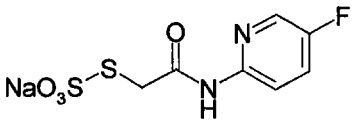
The title compound was obtained from 2-amino-5-fluoropyridine in a similar manner to the process described in Referential Example 352.

^{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:

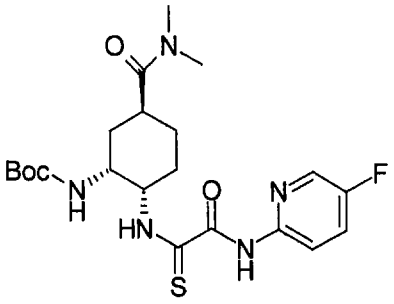


The title compound was obtained from the compound obtained in Referential Example 425 in a similar manner to the process described in Referential Example 353.

^{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:



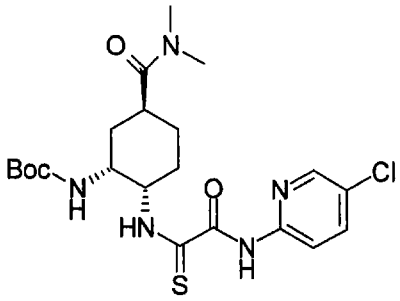
A solution of the compound (1.20 g) obtained in Referential Example 144 in pyridine (70 ml) was heated to 120°C, and the compound (2.42 g) obtained in Referential Example 426 was added. After stirring the mixture for 30 minutes, the reaction mixture was allowed to cool to room temperature, and the solvent 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:

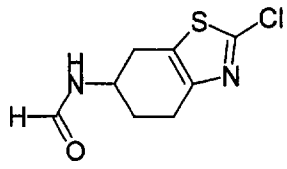


The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 353 in a similar manner to the process described in Referential Example 427.

^{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.

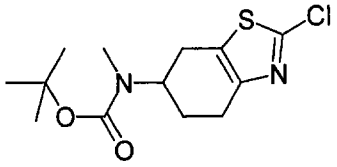
Acta., 1994, Vol. 77, p. 1256) (4.53 g) in methanol (200 ml), and the mixture was heated under reflux. After 19 hours, hydrochloric acid was added to decompose excessive reagents before the reaction mixture was concentrated under reduced pressure. After the residue was alkalified with a 1N aqueous solution 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

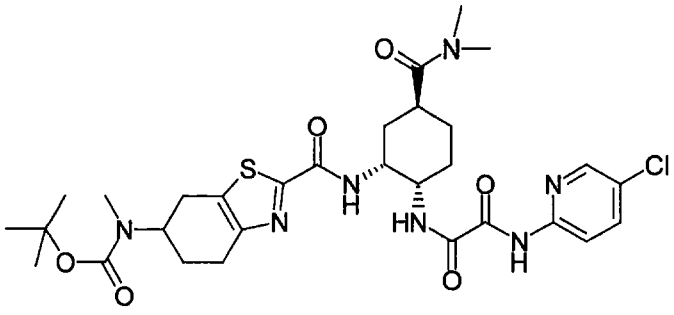
acid were added to conduct liquid separation. The resultant organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 2:1) to obtain the title compound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

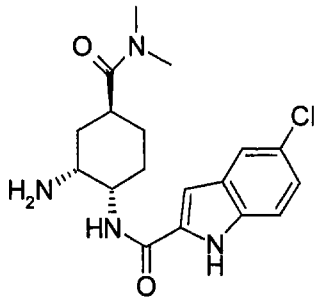
The lithium salt (350.2 mg) of the carboxylic acid obtained by the above-described reaction, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (287.6 mg), 1-hydroxybenzotriazole (202.7 mg) and N-methylmorpholine (0.319 ml) were added to a solution of the compound (490.5 mg) obtained in Referential 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:

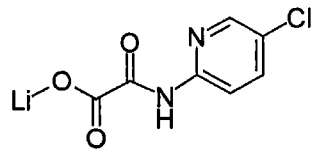


The title compound was obtained by deprotecting the compound obtained in Referential Example 310 in a similar manner to the process described in Referential Example 69.

^{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:



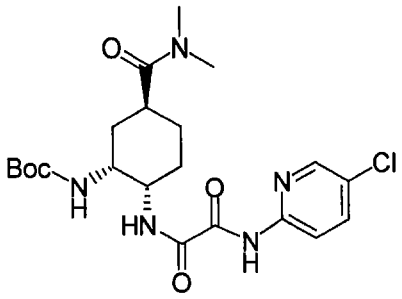
Methyl chlorooxoacetate (78.7 ml) was added dropwise to a suspension of 2-amino-5-chloropyridine (100 g) and sodium hydrogencarbonate (78.4 g) in tetrahydrofuran (2000 ml) at 0°C, and the mixture was stirred at room temperature for 2 hours. After the reaction mixture was added to a mixture of diethyl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



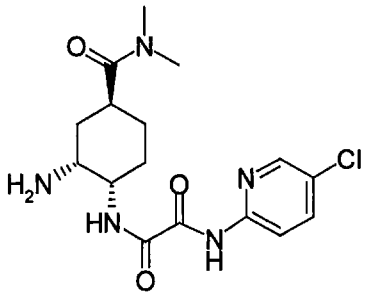
The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 433 in a similar manner to Referential Example 91.

^{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:



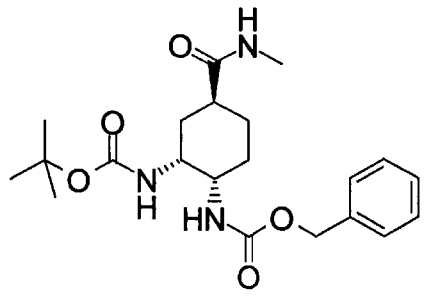
The title compound was obtained from the compound obtained in Referential Example 434 in a similar manner to

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).

[Referential Example 436]

Benzyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)amino]-4-[(methylamino)carbonyl]cyclohexylcarbamate:



The title compound was obtained from the compound obtained in Referential Example 142 and methylamine hydrochloride in a similar manner to Referential Example 143.

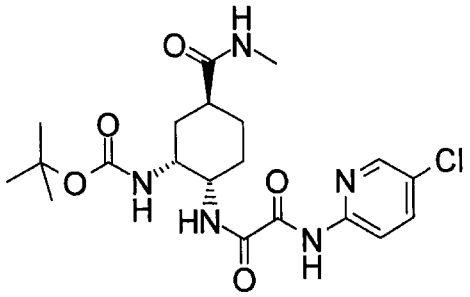
^{1}H-NMR (DMSO-d_6) δ: 1.39(9H,s), 1.40-1.61(4H,m), 1.63-1.73(1H,m), 1.75-1.85(1H,m), 2.23-2.48(1H,m), 2.53(3H,d,J=4.6Hz), 3.48(1H,br.s), 3.80-3.91(1H,m), 5.01(1H,1/2ABq,J=12.1Hz), 5.03(1H,1/2ABq,J=12.1Hz), 6.28-6.40(1H,m), 6.82-6.98(1H,m), 7.25-7.40(5H,m), 7.50-7.60(1H,m).

MS (FAB) m/z: 406$(M+H)^+$.

[Referential Example 437]

tert-Butyl (1R,2S,5S)-2-({2-[(5-chloropyridin-2-yl)amino]-

2-oxoacetyl}amino)-5-[(methylamino)carbonyl]cyclohexyl-carbamate:



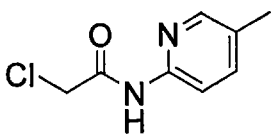
The title compound was obtained by deprotecting the compound obtained in Referential Example 436 in a similar manner to the process described in Referential Example 144 and condensing the resultant amine with the compound obtained in Referential Example 433 in a similar manner to the process described in Referential Example 91.

^{1}H-NMR (DMSO-d_6) δ: 1.35-1.75(3H,m), 1.39(9H,s), 1.75-1.86(2H,m), 1.87-1.95(1H,m), 2.30-2.40(1H,m), 2.55(3H,d,J=4.6Hz), 3.79-3.90(2H,m), 6.73-6.90(1H,m), 7.58-7.70(1H,m), 8.00-8.13(2H,m), 8.46(1H,dd,J=2.2,1.0Hz), 8.67(1H,d,J=7.6Hz), 10.26(1H,s).

MS (ESI: negative) m/z: 452[$(M-H)^-$, Cl^{35}], 454[$(M-H)^-$,Cl^{37}].

[Referential Example 438]

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

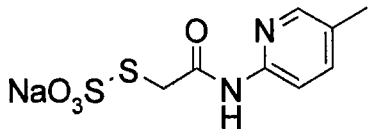


The title compound was obtained from 2-amino-5-picoline in a similar manner to the process described in Referential Example 425.

^{1}H-NMR (DMSO-d_6) δ: 2.30(3H,s), 4.40(2H,s), 7.83(1H,d,J=8.8Hz), 7.91(1H,d,J=8.5Hz), 8.21(1H,s), 11.40(1H,s).

[Referential Example 439]

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

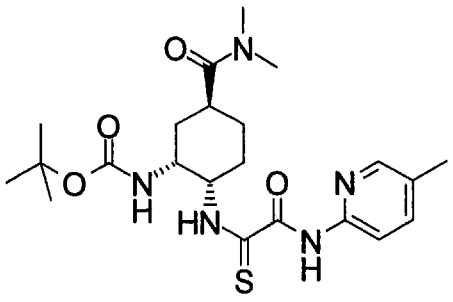


The title compound was obtained from the compound obtained in Referential Example 438 in a similar manner to the process described in Referential Example 353.

^{1}H-NMR (DMSO-d_6) δ: 2.24(3H,s), 3.74(2H,s), 7.59(1H,d,J=8.5Hz), 7.94(1H,d,J=8.3Hz), 8.12(1H,s), 10.26(1H,s).

[Referential Example 440]

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



The title compound was obtained from the compound obtained in Referential Example 144 and the compound obtained in Referential Example 439 in a similar manner to

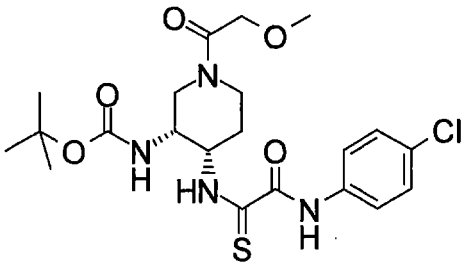
the process described in Referential Example 427.

^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.60-2.10(5H,m), 2.15-2.35(1H,m), 2.31(3H,s), 2.60-2.80(1H,m), 2.95(3H,s), 3.07(3H,s), 4.30-4.45(2H,m), 4.65-4.85(1H,m), 7.54(1H,dd,J=8.5,2.0Hz), 8.06(1H,br.d), 8.18(1H,s), 9.70-9.90(1H,m), 10.48(1H,s).

MS (ESI) m/z: 464$(M+H)^+$.

[Referential Example 441]

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



The title compound was obtained by deprotecting the compound obtained in Referential Example 220 by catalytic reduction in a similar manner to the process described in Referential Example 214 and condensing the resultant amine with the compound obtained in Referential Example 351 in a similar manner to the process described in Referential Example 427.

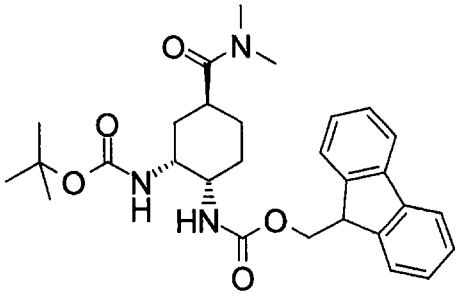
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.59-1.84(1H,m), 2.10-2.33(1H,m), 2.68-2.81(0.7H,m), 2.94-2.04(0.3H,m), 3.15-3.40(1H,m), 3.44(3H,s), 3.91-4.32(4H,m), 4.45-4.58(1H,m), 4.60-4.77(1H,m), 5.15-5.30(0.3H,br), 5.84-5.94(0.7H,m),

7.32(2H,d,J=8.6Hz), 7.61(2H,d,J=8.6Hz), 10.12(1H,s), 10.19-10.33(1H,br).

MS (FAB) m/z: 485[$(M+H)^+$,Cl^{35}], 487[$(M+H)^+$,Cl^{37}].

[Referential Example 442]

9H-Fluoren-9-ylmethyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)-amino]-4-[(dimethylamino)carbonyl]cyclohexylcarbamate:



The compound (856 mg) obtained in Referential Example 144 was dissolved in acetone (10 ml), to the solution were added 9-fluorenylmethyl pentafluorophenylcarbamate (1.34 g) and sodium hydrogencarbonate (302 mg), and the mixture was stirred at room temperature for 2.5 hours. 9-Fluorenylmethyl pentafluorophenylcarbamate (609 mg) and sodium hydrogencarbonate (151 mg) were additionally added, and the resultant mixture was heated under reflux for 30 minutes. The solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (SI-40B, methylene chloride:methanol = 93:7) to obtain the title compound (1.47 g).

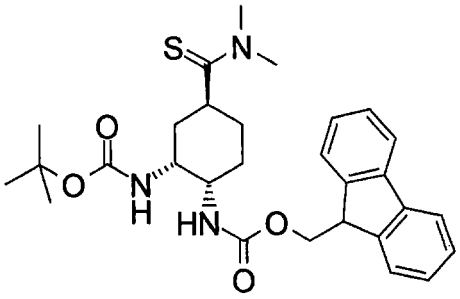
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.30-2.05(6H,m), 2.63(1H,br.s), 2.94(3H,s), 3.04(3H,s), 3.69(1H,br.s), 4.15(1H,br.s), 4.21(1H,br.s), 4.37(2H,br.s), 4.73(1H,br.s),

5.41(1H,br.s), 7.29(2H,t,J=7.3Hz), 7.39(2H,t,J=7.3Hz), 7.57(2H,d,J=7.3Hz), 7.75(2H,d,J=7.3Hz).

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

[Referential Example 443]

9H-Fluoren-9-ylmethyl (1S,2R,4S)-2-[(tert-butoxycarbonyl)-amino]-4-[(dimethylamino)carbothioyl]cyclohexylcarbamate:



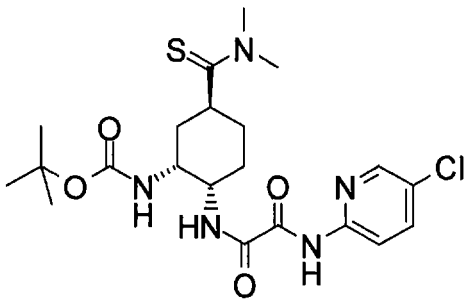
The compound (1.26 g) obtained in Referential Example 442 was dissolved in toluene (50 ml), to the solution was added a Lawesson's Reagent (1.00 g), and the mixture was stirred at 60°C for 1 hour. Insoluble matter was removed by filtration, and the solvent was distilled off under reduced pressure. The residue was dissolved in ethanol (50 ml), and di-tert-butyl dicarbonate (541 mg) and sodium hydrogencarbonate (208 mg) were added to the solution. The resultant mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure, and the residue was purified by flash column chromatagraphy on silica gel (hexane:ethyl acetate = 1:1 → methylene chloride:methanol = 9:1) to obtain the title compound (609 mg) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.43(9H,s), 1.43-2.10(6H,m), 2.92(1H,br.s), 3.31(3H,s), 3.47(3H,s), 3.74(1H,br.s),

4.09-4.19(2H,m), 4.38(2H,br.s), 4.75(1H,br), 5.29(1H,br.s), 7.29(2H,t,J=7.3Hz), 7.38(2H,t,J=7.3Hz), 7.55(2H,br.s), 7.75(2H,d,J=7.3Hz).

[Referential Example 444]

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



The compound (1.11 g) obtained in Referential Example 443 was dissolved in N,N-dimethylformamide (30 ml), to the solution was added piperazine (3.0 ml), and the mixture was stirred at room temperature for 15 minutes. The solvent was distilled off under reduced pressure, and ethyl acetate and water were added to the residue to conduct liquid separation. The resultant water layer was extracted twice with ethyl acetate. Organic layers were combined and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was was condensed with the compound obtained in Referential Example 433 in a similar manner to the process described in Referential Example 91 to obtain the title compound (629 mg).

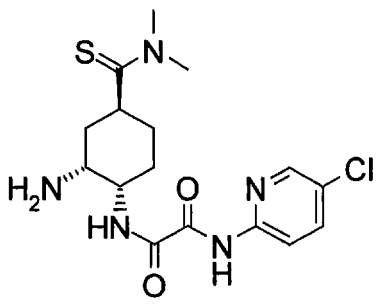
^{1}H-NMR ($CDCl_3$) δ: 1.45(9H,s), 1.48-2.23(6H,m),

2.98(1H,br.s), 3.36(3H,s), 3.49(3H,s), 3.98-4.04(1H,m), 4.22-4.25(1H,m), 4.75(1H,br.s), 7.70(1H,dd,J=8.8,2.7Hz), 7.85(1H,br.s), 8.16(1H,d,J=8.8Hz), 8.30(1H,d,J=2.7Hz), 9.73(1H,s).

MS (FAB) m/z: 484[$(M+H)^+$,Cl^{35}], 486[$(M+H)^+$,Cl^{37}].

[Referential Example 445]

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



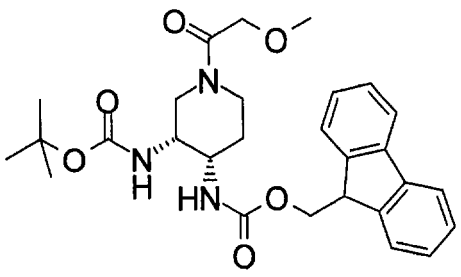
The title compound was obtained from the compound obtained in Referential Example 444 in a similar manner to the process described in Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.66-2.11(6H,m), 3.38(3H,s), 3.42(3H,s),3.52(1H,br.s), 3.75(1H,br.s), 3.88(1H,br.s), 8.03-8.09(2H,m), 8.21(3H,br.s), 8.48(1H,d,J=2.2Hz), 9.06(1H,d,J=6.8Hz), 10.34(1H,s).

MS (FAB) m/z: 384[$(M+H)^+$,Cl^{35}], 386[$(M+H)^+$,Cl^{37}].

[Referential Example 446]

9H-Fluoren-9-ylmethyl (3R,4S)-3-[(tert-butoxycarbonyl)-amino]-1-(2-methoxyacetyl)piperidin-4-ylcarbamate:



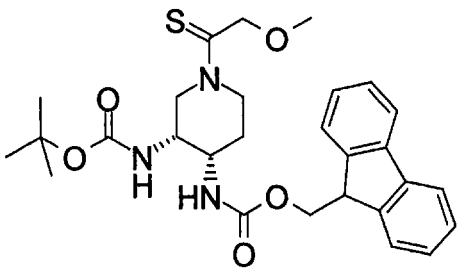
The title compound was obtained by deprotecting the compound obtained in Referential Example 220 by catalytic reduction in a similar manner to the process described in Referential Example 214 and treating the resultant amine in a similar manner to the process described in Referential Example 442.

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 1.55-1.80(1H,m), 1.92-2.20(1H,m), 2.70-3.35(2H,m), 3.44(3H,s), 3.77-4.90(10H,m), 5.29-5.45(0.6H,br), 5.75-5.90(0.4H,br), 7.26-7.34(2H,m), 7.39(2H,t,J=7.6Hz), 7.55-7.65(2H,m), 7.76(2H,d,J=7.6Hz).

MS (FAB) m/z: 510$(M+H)^+$.

[Referential Example 447]

9H-Fluoren-9-ylmethyl (3R,4S)-3-[(tert-butoxycarbonyl)-amino]-1-(2-methoxyethanethioyl)piperidin-4-ylcarbamate:



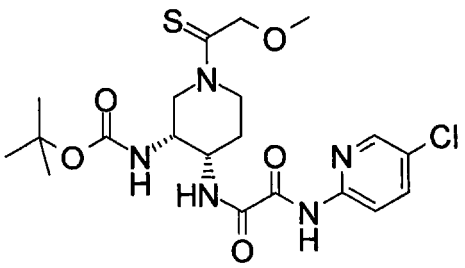
The title compound was obtained from the compound obtained in Referential Example 446 in a similar manner to the process described in Referential Example 443.

^{1}H-NMR ($CDCl_3$) δ: 1.48(9H,s), 1.50-1.80(1H,m), 2.07-2.23(1H,m), 3.04-3.18(0.5H,m), 3.25-3.37(0.5H,m), 3.44(1.5H,s), 3.47(1.5H,s), 3.88-4.75(9H,m), 5.00-5.70(2H,br), 5.98-6.23(1H,br), 7.26-7.29(2H,m), 7.39(2H,t,J=7.3Hz), 7.55-7.68(2H,m), 7.77(2H,d,J=7.3Hz).

MS (FAB) m/z: 526$(M+H)^+$.

[Referential Example 448]

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



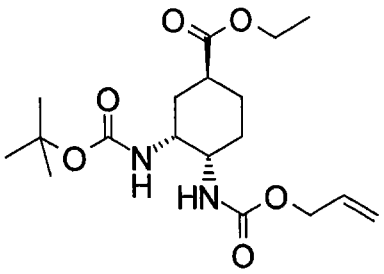
The title compound was obtained by treating the compound obtained in Referential Example 447 with diethylamine in a similar manner to the process described in Referential Example 444 to conduct deprotection and then condensing the resultant compound with the compound obtained in Referential Example 433.

^{1}H-NMR ($CDCl_3$) δ: 1.47(9H,s), 1.73-1.88(1H,m), 2.07-2.22(1H,m), 3.05-3.15(1H,m), 3.27-3.42(1H,m), 3.45(1H,s), 3.48(2H,s), 4.10-4.54(5H,m), 5.12-5.21(0.3H,br), 5.48-5.56(0.7H,br), 5.61-5.74(1H,br), 7.70(1H,dd,J=8.5,2.0Hz), 8.21(1H,d,J=8.5Hz), 8.31(1H,d,J=2.0Hz), 8.42-8.60(1H,br), 9.72(1H,br.s).

MS (ESI) m/z: 486[$(M+H)^+$,Cl^{35}], 488[$(M+H)^+$,Cl^{37}].

[Referential Example 449]

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



A 10% palladium on carbon catalyst (10.2 g) was added to a solution of the compound (10.0 g) obtained in Referential Example 141 in a mixed solvent of tetrahydrofuran (40 ml) and ethanol (40 ml), and the mixture was stirred at room temperature for 63 hours under a hydrogen atmosphere. After the catalyst was removed by filtration, the resultant filtrate was concentrated under reduced pressure. After the resultant colorless oil was dissolved in tetrahydrofuran (25 ml), and pyridine (2.3 ml) was added to the solution at room temperature, allylchloroformate (2.70 ml) was added dropwise at 0°C, and the mixture was stirred for 20 minutes. After ice and ethyl acetate were added to the reaction mixture, and the resultant mixture was stirred for 5 minutes, A 10% aqueous solution of citric acid was added to acidify the mixture. The resultant organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over

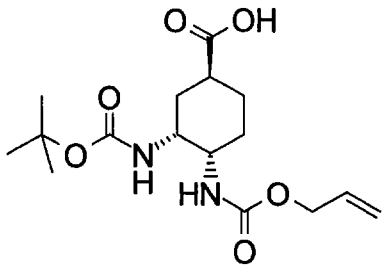
anhydrous sodium sulfate and then concentrated under reduced pressure. The resultant residue was purified by column chromatagraphy on silica gel (methylene chloride:methanol = 40:1) to obtain the title compound (6.03 g).

^{1}H-NMR ($CDCl_3$) δ: 1.25(3H,t,J=7.1Hz), 1.31-1.40(1H,m), 1.45(9H,s), 1.51-1.65(1H,m), 1.72-1.86(1H,m), 1.89-2.10(3H,m), 2.25-2.50(1H,br), 3.63-3.72(1H,m), 4.03-4.15(1H,br), 4.13(2H,q,J=7.1Hz), 4.49-4.59(2H,m), 4.60-4.75(1H,m), 5.20(1H,d,J=10.5Hz), 5.22-5.32(1H,br), 5.29(1H,dd,J=17.1,1.7Hz), 5.85-5.97(1H,m).

MS (ESI) m/z: 371$(M+H)^+$.

[Referential Example 450]

(1S,3R,4S)-4-{[(Allyloxy)carbonyl]amino}-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid:



The title compound was obtained from the compound obtained in Referential Example 449 in a similar manner to the process described in Referential Example 142.

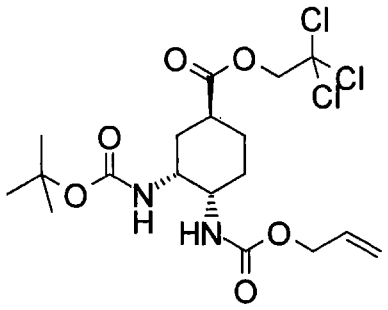
^{1}H-NMR ($CDCl_3$) δ: 1.35-2.15(6H,br), 1.45(9H,s), 2.35-2.65(1H,br), 3.65-3.75(1H,m), 4.00-4.15(1H,br), 4.48-4.63(2H,m), 4.63-4.80(1H,br), 5.03-5.33(1H,br), 5.21(1H,d,J=10.3Hz), 5.29(1H,dd,J=17.1,1.5Hz), 5.86-

5.97(1H,m).

MS (ESI) m/z: 343$(M+H)^+$.

[Referential Example 451]

2,2,2-Trichloroethyl (1S,3R,4S)-4-{[(allyloxy)carbonyl]-amino}-3-[(tert-butoxycarbonyl)amino]cyclohexane-carboxylate:



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.99 g), 1-hydroxybenzotriazole (2.81 g), 2,2,2-trichloroethanol (4.15 ml) and 4-dimethylaminopyridine (4.15 g) were added to a solution of the compound (5.93 g) obtained in Referential Example 450 in N,N-dimethylformamide (40 ml), and the mixture was stirred at room temperature for 1.5 hours. After the reaction mixture was concentrated under reduced pressure, ethyl acetate and water were added to the residue. The resultant water layer was extracted with ethyl acetate, and organic layers were combined, washed with a 10% aqueous solution of citric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was purified by column

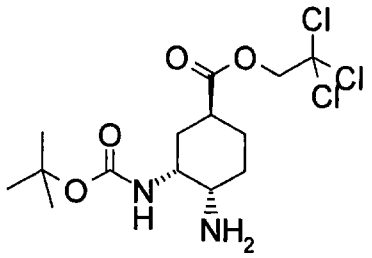
chromatography on silica gel (methylene chloride:methanol = 40:1) to obtain the title compound (8.88 g).

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.50(1H,m), 1.46(9H,s), 1.55-1.73(1H,m), 1.77-2.22(4H,m), 2.50-2.65(1H,br), 3.66-3.75(1H,m), 4.05-4.20(1H,m), 4.50-4.60(2H,m), 4.60-4.80(1H,br), 4.71(1H,d,J=11.8Hz), 4.77(1H,d,J=11.8Hz), 5.18-5.34(1H,br), 5.20(1H,d,J=10.5Hz), 5.30(1H,dd,J=17.4,1.0Hz), 5.86-5.97(1H,m).

MS (ESI) m/z: 473[$(M+H)^+$,3xCl^{35}], 475[$(M+H)^+$,2xCl^{35},Cl^{37}], 477[$(M+H)^+$,Cl^{35},2xCl^{37}].

[Referential Example 452]

2,2,2-Trichloroethyl (1S,3R,4S)-4-amino-3-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate:



Diethylamine (20 ml) and tetrakis(triphenylphosphine)palladium (719 mg) were added to a solution of the compound (8.83 g) obtained in Referential Example 451 in tetrahydrofuran (35 ml), and the mixture was stirred at room temperature for 2.5 hours under argon. A 10% aqueous solution (250 ml) of citric acid was added to the reaction mixture to acidify it, and diethyl ether was added thereto. After the resultant water layer was washed with diethyl ether, sodium carbonate was added to the water layer to

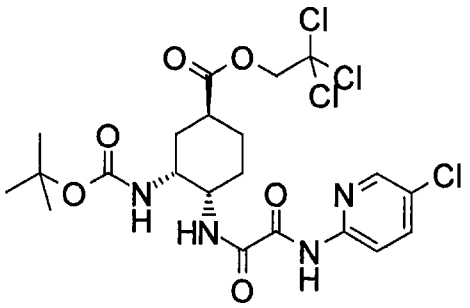
alkalify it, and the water layer was extracted with methylene chloride. The resultane methylene chloride layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure to obtain the title compound (4.35 g).

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50(3H,m), 1.46(9H,s), 1.58-1.69(1H,m), 1.70-1.81(2H,m), 1.98-2.07(1H,m), 2.22-2.31(1H,m), 2.55-2.66(1H,m), 2.97-3.04(1H,m), 3.79-3.93(1H,br), 4.70(1H,d,J=12.0Hz), 4.75-4.85(1H,br), 4.78(1H,d,J=12.0Hz).

MS (ESI) m/z: 389[$(M+H)^+$,3xCl^{35}], 391[$(M+H)^+$,2xCl^{35},Cl^{37}], 393[$(M+H)^+$,Cl^{35},2xCl^{37}].

[Referential Example 453]

2,2,2-Trichloroethyl (1S,3R,4S)-3-[(tert-butoxycarbonyl)-amino]-4-({2-[(5-chloropyridin-2-yl)amino]-2-oxoacetyl}-amino)cyclohexanecarboxylate:



The title compound was obtained by condensing the compound obtained in Referential Example 452 with the compound obtained in Referential Example 433 in a similar manner to the process described in Referential Example 91.

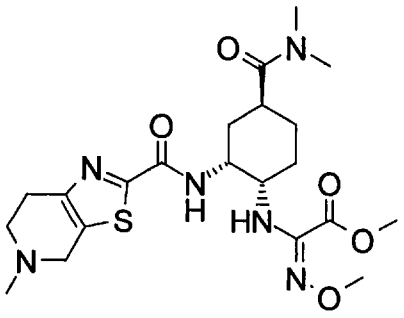
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,s), 1.50-1.63(1H,m), 1.65-

1.79(2H,m), 1.87-2.08(2H,m), 2.10-2.22(2H,m), 2.50-2.70(1H,br), 3.94-4.02(1H,m), 4.17-4.30(1H,br), 4.73(1H,d,J=12.0Hz), 4.78(1H,d,J=12.0Hz), 7.70(1H,dd,J=8.8,2.4Hz), 7.90-8.07(1H,br), 8.18(1H,d,J=8.8Hz), 8.31(1H,d,J=2.4Hz), 9.72(1H,br.s).

MS (ESI) m/z: 571[$(M+H)^+$,3xCl^{35}], 573[$(M+H)^+$,2xCl^{35},Cl^{37}], 575[$(M+H)^+$,Cl^{35},2xCl^{37}].

[Referential Example 454]

Methyl 2-[((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)amino]-2-(methoxyimino)-acetate:



The compound (435 mg) obtained in Referential Example 144 and methyl 2-(methoxyimino)-2-(methylsulfonyl)acetate (WO99/67209) (233 mg) were dissolved in tetrahydrofuran (5 ml), triethylamine (332 μl) was added to this solution, and the mixture was stirred overnight at 70°C. The reaction mixture was concentrated 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 oil layer was

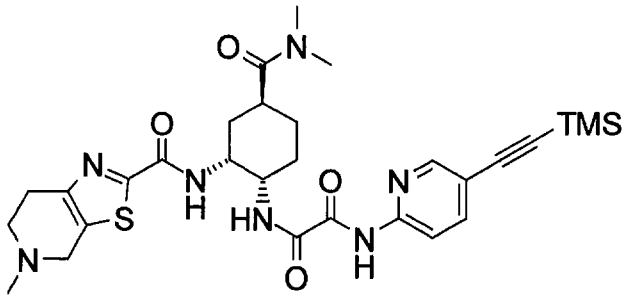
dried over anhydrous sodium sulfate. After concentrating the oil layer, the resultant residue was purified by column chromatography on silica gel (methylene chloride:methanol = 91:9) to obtain the title compound (111 mg).

^{1}H-NMR ($CDCl_3$) δ: 1.42-2.10(6H,m), 2.52(3H,s), 2.70-3.10(11H,m), 3.71(2H,br.s), 3.83(3H,s), 3.84(3H,s), 4.22-4.35(1H,m), 4.55-4.65(1H,m), 5.16(1H,d,J=8.8Hz), 7.25-7.30(1H,m).

MS (ESI) m/z: 481$(M+H)^+$.

[Referential Example 455]

N^1-((1S,2R,4S)-4-[(Dimethylamino)carbothioyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazol[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)-N^2-{5-[2-(trimethylsilyl)ethynyl]pyridin-2-yl}ethanediamide:



The compound (658 mg) obtained in Referential Example 204 was dissolved in tetrahydrofuran (10 ml), N,N-dimethylformamide (10 ml) and triethylamine (20 ml), and triphenylphosphine (87 mg), trimethylsilylacetylene (471 μl), palladium acetate (50 mg) were added to the solution. The resultant mixture was stirred at 80°C for 14 hours

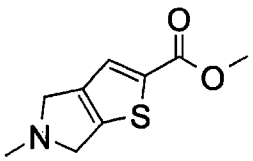
under an argon atmosphere. The reaction mixture was filtered through Celite, and the filtrate was fully washed with methylene chloride. Water was added to the filtrate to conduct liquid separation, and the resultant organic layer was decolored with activated carbon (about 3 g) and dried over anhydrous sodium sulfate. After filtration, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 93:7) to obtain the title compound (360 mg).

^{1}H-NMR ($CDCl_3$) δ: 0.25(9H,s), 1.66-2.13(6H,m), 2.52(3H,s), 2.78-2.96(8H,m), 3.05(3H,s), 3.70(1H,d,J=15.4Hz), 3.73(1H,d,J=15.4Hz), 4.08-4.15(1H,m), 4.66-4.69(1H,m), 7.42(1H,d,J=8.4Hz), 7.77(1H,dd,J=8.4,2.1Hz), 8.03(1H,d,J=8.1Hz), 8.13(1H,d,J=8.8Hz), 8.43(1H,d,J=2.1Hz), 9.74(1H,s).

MS (ESI) m/z: 610$(M+H)^+$.

[Referential Example 456]

Methyl 5-methyl-5,6-dihydro-4H-thieno[2,3-c]pyrrole-2-carboxylate:



Methyl 4,5-bis(chloromethyl)-2-thiophenecarboxylic acid (D. J. Zwanenburg and Hans Wynberg, J. Org. Chem., 34, 333-340, (1969)) (520 mg) was dissolved in acetonitrile (600 ml), methylamine (40% methanol solution, 722 μl) was

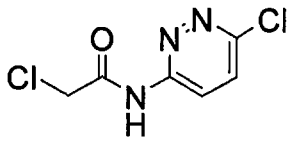
added to the solution, and the mixture was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 1:0 → 19:1) to obtain the title compound (176 mg).

^{1}H-NMR ($CDCl_3$) δ: 2.63(3H,s), 3.82-3.83(2H,m), 3.86(3H,s), 3.97-3.99(2H,m), 7.51(1H,s).

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

[Referential Example 457]

2-Chloro-N-(6-chloropyridazin-3-yl)acetamide:

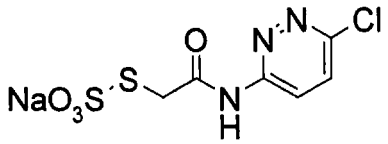


3-Amino-6-chloropyridazine (10.4 g) was dissolved in N,N-dimethylformamide (200 ml), chloroacetyl chloride (7.48 ml) was added to the solution, and the mixture was stirred at room temperature for 1 hour. The solvent was distilled off under reduced pressure, and ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate were added to the residue. Solids deposited were collected by filtration and washed with ethyl acetate and water to obtain the title compound (9.39 g).

^{1}H-NMR ($CDCl_3$) δ: 4.30(2H,s), 7.56(1H,d,J=9.3Hz), 8.51(1H,d,J=9.3Hz), 9.68(1H,br.s).

[Referential Example 458]

Sodium S-{2-[(6-chloropyridazin-3-yl)amino]-2-oxoethyl}thiosulfate:

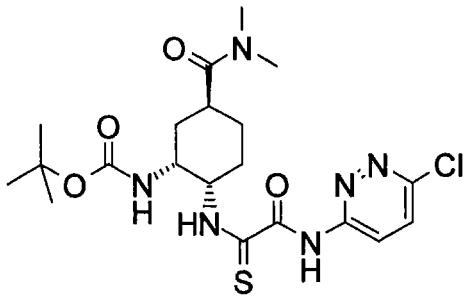


The title compound was obtained from the compound obtained in Referential Example 457 in a similar manner to the process described in Referential Example 353.

^{1}H-NMR (DMSO-d_6) δ: 3.84(2H,s), 7.87(1H,d,J=9.4Hz), 8.36(1H,d,J=9.4Hz), 11.21(1H,br.s).

[Referential Example 459]

tert-Butyl (1R,2S,5S)-2-({2-[(6-chloropyridazin-3-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)-carbothioyl]cyclohexylcarbamate:



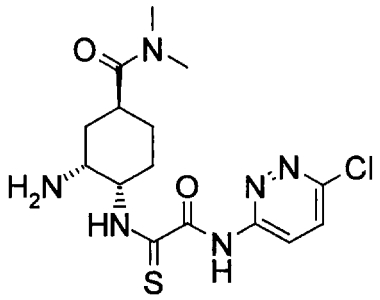
The title compound was obtained from the compound obtained in Referential Example 458 and the compound obtained in Referential Example 144 in a similar manner to the process described in Referential Example 427.

^{1}H-NMR ($CDCl_3$) δ: 1.35-1.58(10H,m), 1.71-1.80(1H,m), 1.86-1.94(2H,m), 2.09(1H,br.s), 2.30(1H,br.s), 2.96(3H,s), 3.08(3H,s), 4.36(2H,br.s), 4.79(1H,br.s), 5.30(1H,br.s), 7.54(1H,d,J=9.0Hz), 8.47(1H,d,J=9.0Hz), 10.03(1H,br.s),

11.03(1H,s).

[Referential Example 460]

(1S,3R,4S)-3-Amino-4-({2-[(6-chloropyridazin-3-yl)amino]-2-oxoethanethioyl}amino)-N,N-dimethylcyclohexane-carboxamide hydrochloride:



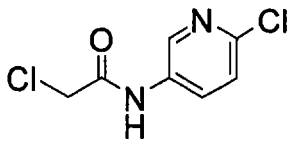
The title compound was obtained from the compound obtained in Referential Example 459 in a similar manner to the process described in Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.53(1H,m), 1.73-1.85(3H,m), 2.03-2.07(1H,m), 2.15-2.24(1H,m), 2.82(3H,s), 3.08(3H,s), 3.32-3.37(1H,m), 4.06(1H,br.s), 4.39(1H,br.s), 8.01(1H,d,J=9.3Hz), 8.37(1H,d,J=9.3Hz), 8.43(3H,br.s), 11.11(1H,d,J=6.6Hz), 11.37(1H,s).

MS (FAB) m/z: 385[$(M+H)^+$,Cl^{35}], 387[$(M+H)^+$,Cl^{37}].

[Referential Example 461]

2-Chloro-N-(6-chloropyridin-3-yl)acetamide:

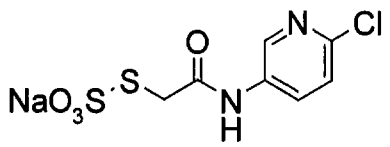


The title compound was obtained from 5-amino-2-chloropyridine in a similar manner to the process described in Referential Example 457.

^{1}H-NMR ($CDCl_3$) δ: 4.22(2H,s), 7.34(1H,d,J=8.5Hz), 8.14(1H,dd,J=8.5,2.7Hz), 8.30(1H,br.s), 8.45(1H,d,J=2.7Hz).

[Referential Example 462]

Sodium S-{2-[(6-chloropyridin-3-yl)amino]-2-oxoethyl}-thiosulfate:

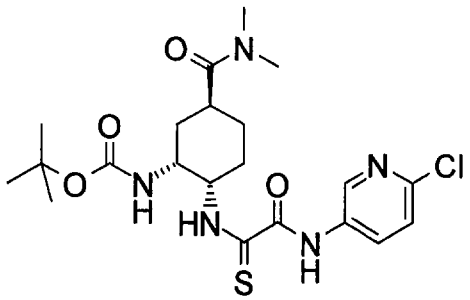


The title compound was obtained from the compound obtained in Referential Example 461 in a similar manner to the process described in Referential Example 353.

^{1}H-NMR (DMSO-d_6) δ: 3.77(2H,s), 7.47(1H,d,J=8.8Hz), 8.04(1H,dd,J=8.8,2.7Hz), 8.57(1H,d,J=2.7Hz), 10.51(1H,s).

[Referential Example 463]

tert-Butyl (1R,2S,5S)-2-({2-[(6-chloropyridin-3-yl)amino]-2-oxoethanethioyl}amino)-5-[(dimethylamino)carbonyl]-cyclohexylcarbamate:



The title compound was obtained from the compound obtained in Referential Example 462 and the compound obtained in Referential Example 144 in a similar manner to the process described in Referential Example 427.

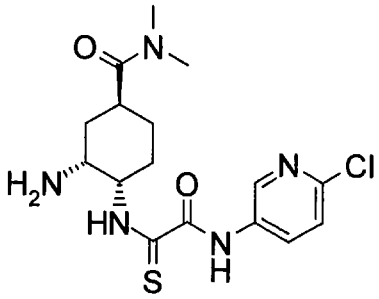
^{1}H-NMR ($CDCl_3$) δ: 1.46(9H,br.s), 1.60-2.23(6H,m),

2.68(1H,br.s), 2.96(3H,s), 3.08(3H,s), 4.34-4.38(2H,m), 4.78(1H,m), 7.33(1H,d,J=8.5Hz), 8.09(1H,br.s), 8.63(1H,s), 9.91(1H,br.s), 10.24(1H,s).

MS (ESI) m/z: 506[$(M+Na)^+$,Cl^{35}], 508[$(M+Na)^+$,Cl^{37}].

[Referential Example 464]

(1S,3R,4S)-3-Amino-4-({2-[(6-chloropyridin-3-yl)amino]-2-oxoethanethioyl}amino)-N,N-dimethylcyclohexane-carboxamide hydrochloride:



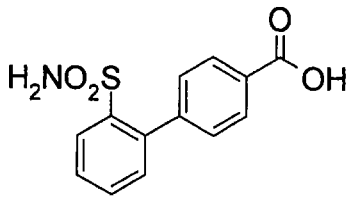
The title compound was obtained from the compound obtained in Referential Example 463 in a similar manner to the process described in Referential Example 69.

^{1}H-NMR (DMSO-d_6) δ: 1.46-1.49(1H,m), 1.79-1.81(3H,m), 1.99-2.03(1H,m), 2.14-2.16(1H,m), 2.82(3H,s),3.06(3H,s), 3.25-3.28(1H,m), 3.99(1H,br.s), 4.30-4.60(1H,br), 7.55(1H,d,J=8.7Hz), 8.26(1H,dd,J=8.7,2.4Hz), 8.38(3H,br.s), 8.85(1H,d,J=2.4Hz), 10.90(1H,d,J=6.8Hz), 11.07(1H,s).

MS (FAB) m/z: 384[$(M+H)^+$,Cl^{35}], 386[$(M+H)^+$,Cl^{37}].

[Referential Example 465]

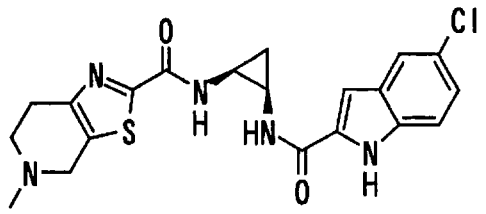
2'-Aminosulfonyl-1,1'-biphenyl-4-carboxylic acid:



2-Bromobenzenesulfonamide (800 mg) and 4-carboxyphenylboronic acid (563 mg) were suspended in a mixed solvent of toluene (5 ml) and water (5 ml). Tetrakis(triphenylphosphine)palladium (392 mg) and anhydrous sodium carbonate (1.08 g) were successively added to the suspension, and the mixture was heated under reflux overnight. After the reaction mixture was cooled to room temperature, diethyl ether and water were added to conduct liquid separation. The resultant organic layer was extracted twice with water. The resultant water layers were all combined, and 12N hydrochloric acid was added to this solution to acidify it. The solution was concentrated to about 20 ml under reduced pressure. Colorless powder deposited was collected by filtration and dried under reduced pressure to obtain the title compound (539 mg).
MS (EI) m/z: 277M^+.

[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).

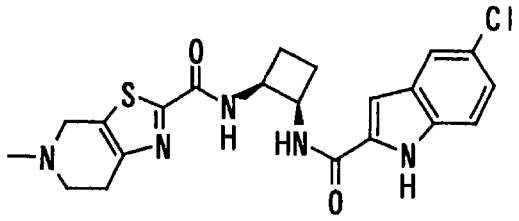
^{1}H-NMR (DMSO-d_6) δ: 1.15-1.35(2H,m), 2.88(3H,s), 2.95-3.25(4H,m), 3.35-3.75(2H,m), 4.32-4.45(1H,m),

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

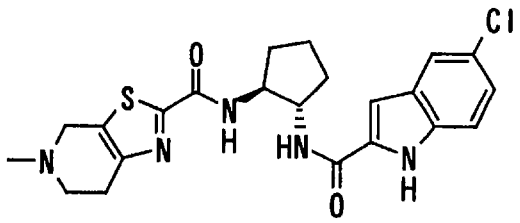
the residue was purified by column chromatography on silica gel (methanol:methylene chloride = 7:93). After ethyl acetate and a 1N ethanol solution of hydrochloric acid were added to the thus-obtained compound to acidify it, and the solvent was distilled off under reduced pressure. Ethyl acetate was 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

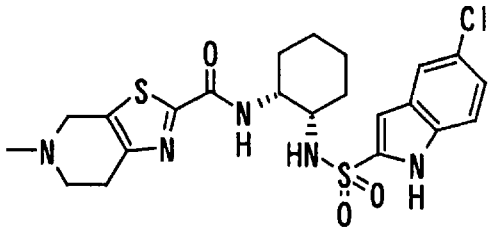
compound (120 mg) obtained in Referential Example 62 dissolved in N,N-dimethylformamide (5 ml), and the mixture was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and methylene chloride and a saturated aqueous solution of sodium hydrogencarbonate were added 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

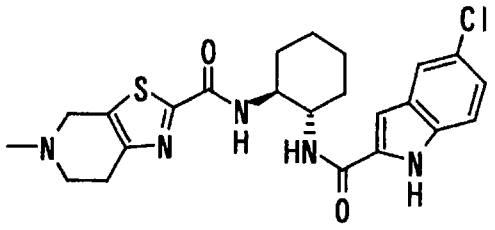
gel (methylene chloride:methanol = 100:3). 1N Hydrochloric acid (1 ml) was added to the resultant product, and the mixture was concentrated under reduced pressure to obtain the title compound (108 mg).

^{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

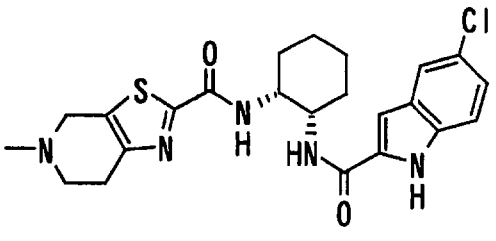
chloride and water were added to the residue to conduct liquid separation. The resultant organic layer was dried over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (methylene chloride:methanol = 25:1) 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:



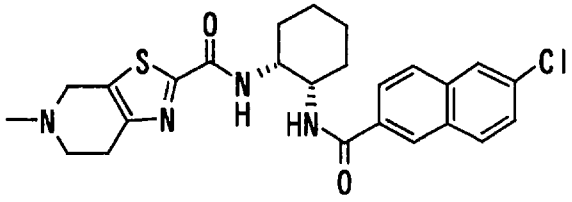
The title compound was obtained from the compound obtained in Referential Example 67 and 5-chloroindole-2-carboxylic acid in a similar manner to Example 5.

^{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-Chloronaphthoyl)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.

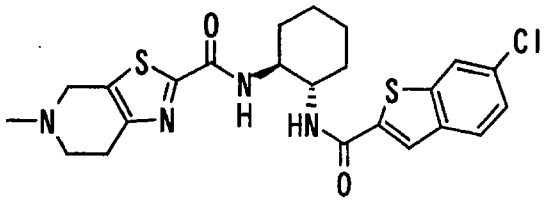
^{1}H-NMR (DMSO-d_6) δ: 1.40-1.56(2H,m), 1.57-1.77(4H,m), 1.90-2.10(2H,m), 2.90(3H,s), 3.13(2H,br.s), 3.28-3.74(2H,m),

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:



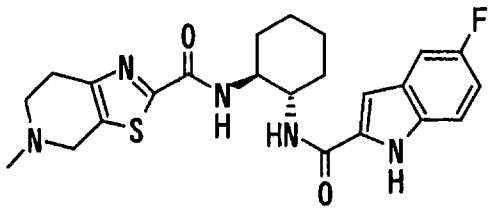
The title compound (239 mg) was obtained by dissolving the compound (255 mg) obtained in Referential Example 65, 6-chlorobenzo[b]thiophene-2-carboxylic acid (Japanese Patent Application Laid-Open No. 2000-119253) (141 mg), triethylamine (0.276 ml) and 1-hydroxybenzotriazole monohydrate (10 mg) in N,N-dimethylformamide (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:



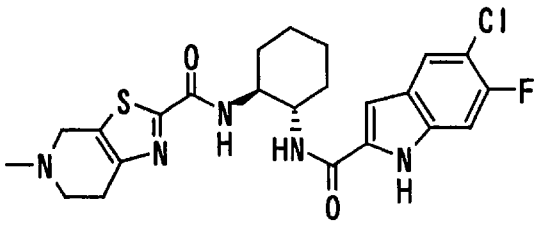
The title compound was obtained from the compound obtained in Referential Example 65 and 5-fluoroindole-2-carboxylic acid in a similar manner to Example 5.

^{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



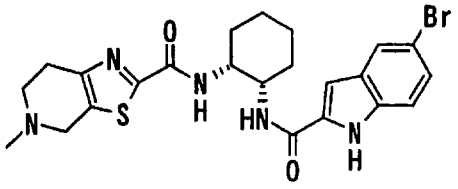
The title compound was obtained from the compound obtained in Referential Example 65 and the compound obtained in Referential Example 23 in a similar manner to Example 5.

^{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.

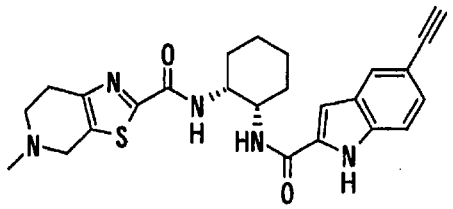
^{1}H-NMR (DMSO-d_6) δ: 1.43(2H,br.s), 1.61(4H,br.s),

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

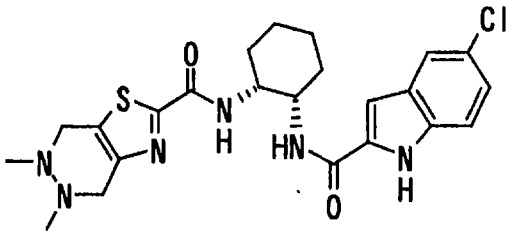
solvent was distilled off under reduced pressure to obtain residue. The resultant residue was purified by preparative thin-layer chromatography on silica gel (methylene chloride:acetone:methanol = 10:10:1) to obtain colorless solids. This product was dissolved in methanol (6 ml), potassium carbonate (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:



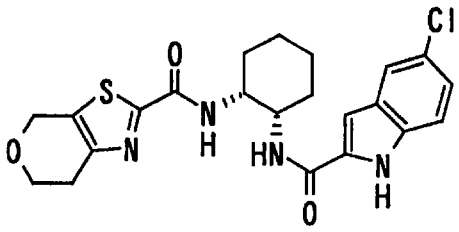
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 51 in a similar manner to Example 2.

^{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

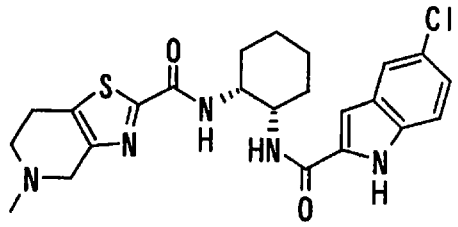
Example 2.

^{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:



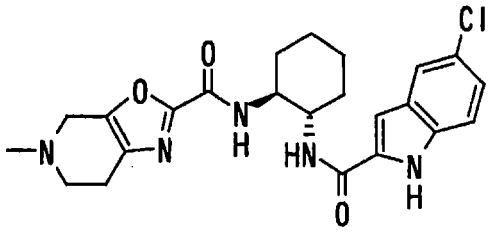
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 29 in a similar manner to Example 2.

^{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:



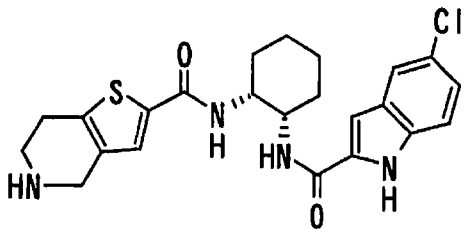
The title compound was obtained from the compound obtained in Referential Example 69 and the compound obtained in Referential Example 21 in a similar manner to Example 2.

^{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:



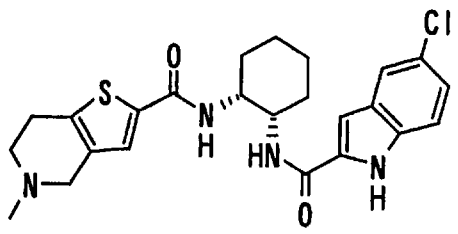
The title compound was obtained by condensing the compound obtained in Referential Example 71 with 5-tert-butoxycarbonyl-4,5,6,7-tetrahydrothieno[3,2-c]-pyridine-2-carboxylic acid (WO94/21599) and treating the formed product with hydrochloric acid to deprotect in a similar manner to Example 2.

^{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).

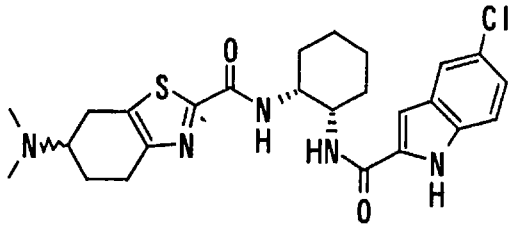
^{1}H-NMR (DMSO-d_6) δ: 1.40(2H,br.s), 1.50-1.71(4H,m), 1.97-2.05(2H,m), 2.87(3H,s), 2.98-3.20(1H,m), 3.30-3.38(2H,m), 3.54-3.70(1H,m), 4.05-4.42(4H,m), 7.14(1H,d,J=8.6Hz), 7.23(1H,s), 7.40(1H,d,J=8.6Hz), 7.63(1H,s), 7.77(1H,s), 8.17-8.27(2H,m), 10.83(1H,br.s), 11.92(1H,s).

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:



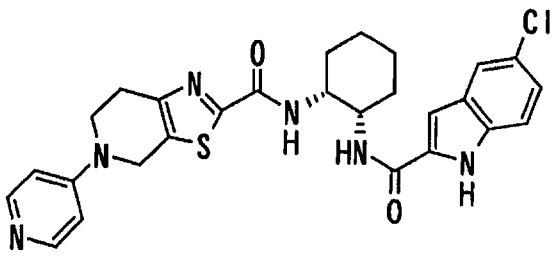
The title compound was obtained from the compound obtained in Referential Example 71 and the compound obtained in Referential Example 31 in a similar manner to Example 2.

^{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

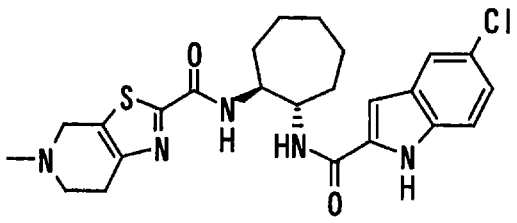
ml) was added dropwise to a solution of the compound (204 mg) obtained in Referential Example 24 in tetrahydrofuran (3 ml) at -78°C, the mixture was stirred at 0°C for 30 minutes. After the reaction mixture was cooled to -78°C again, it was warmed to room temperature in 20 minutes while blowing carbon 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:

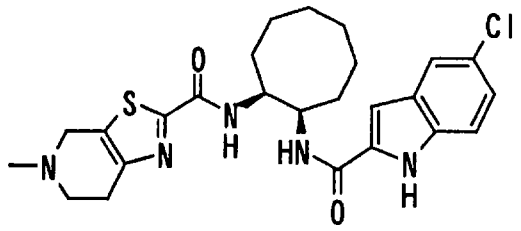


The title compound was obtained from the compound obtained in Referential Example 74 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{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}-cyclooctyl)-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine-2-carboxamide hydrochloride:



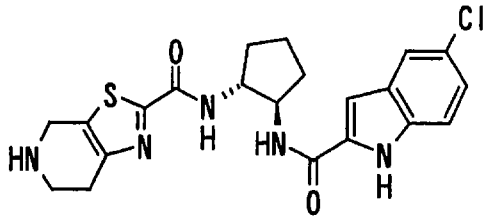
The title compound was obtained from the compound obtained in Referential Example 78 and the compound obtained in Referential Example 10 in a similar manner to Example 2.

^{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:



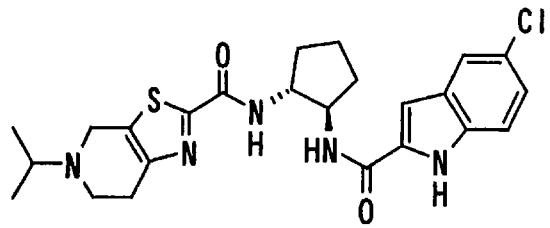
The title compound was obtained by treating a product obtained by the reaction of the compound obtained in Referential Example 63 with the compound obtained in Referential Example 34 with hydrochloric acid in a similar manner to Example 2.

^{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).

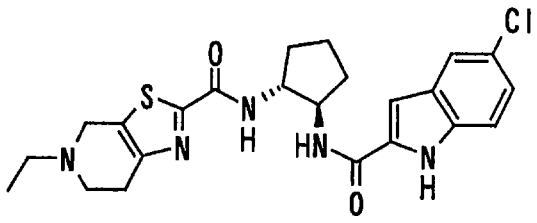
^{1}H-NMR (DMSO-d_6) δ: 1.27-1.39(6H,m), 1.58-1.80(4H,m), 1.95-2.10(2H,m), 3.00-3.12(1H,m), 3.25-3.45(2H,m), 3.59-3.77(2H,m), 4.25-4.39(1H,m), 4.40-4.55(2H,m), 4.57-4.65(1H,m), 7.10(1H,s), 7.14(1H,d,J=8.8Hz), 7.38(1H,d,J=8.8Hz), 7.68(1H,s), 8.56(1H,d,J=8.8Hz), 8.90(1H,d,J=8.8Hz), 11.39(1H,br.s), 11.76(0.5H,s),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



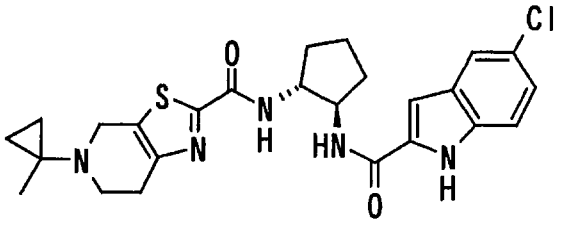
The compound (500 mg) obtained in Example 23 was dissolved in N,N-dimethylformamide (10 ml), and triethylamine (576 µl) and ethyl iodide (329 µl) were added to stir the mixture overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and water was added to the residue 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:



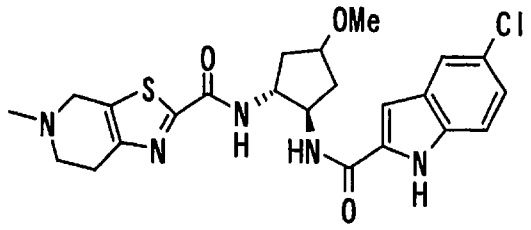
The title compound was obtained from the compound obtained in Referential Example 63 and the compound obtained in Referential Example 39 in a similar manner to Example 2.

^{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$(M+H)^+$.

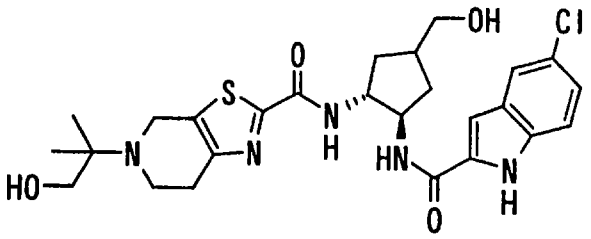
Stereoisomer B:

^{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),