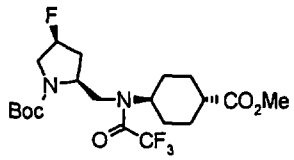
including 3H, s at δ 3.64), 5.17 (1H, d, J=54.0Hz).

(Step 3) Synthesis of methyl trans-4-(N-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate

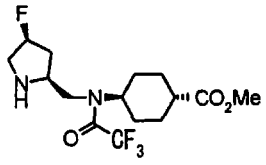


Methyl trans-4-(N-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethyl)amino)cyclohexanecarboxylate (776.1 mg, 2.165 mmol) was dissolved in methylene chloride (15 ml). Under stirring at 0°C, triethylamine (0.91 ml, 6.496 mmol) and trifluoroacetic acid (0.46 ml, 3.248 mmol) were added to the resulting solution, followed by stirring for 3 hours at the same temperature. Water was added to the reaction and the mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1, v/v) eluate fractions, methyl trans-4-(N-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate (864.0 mg, 88%) was obtained as a light brown oil.

^{1}H-NMR ($CDCl_3$) δ: 0.12-2.29 (total 20H, m, including 9H, s at δ 1.42), 3.20-3.79 (total 8H, series of m, including 3H,

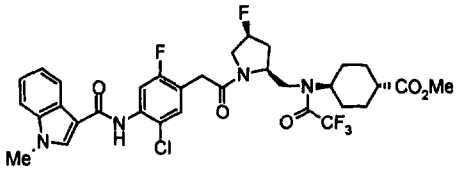
s at δ: 3.66), 4.62 and 4.70 (total 1H, m), 5.24 (1H, br d, J=46.8Hz).

(Step 4) Synthesis of methyl trans-4-(N-((4S)-fluoro-(2S)-pyrrolidinylmethyl)trifluoroacetylamino)cyclohexanecarboxylate



Methyl trans-4-(N-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethyl)trifluoroacetylamino)cyclohexanecarboxylate (864.0 mg, 1.901 mmol) was dissolved in dioxane (5 ml). To the resulting solution was added 4N HCl/dioxane (20 ml) under stirring at 0°C. After stirring at room temperature for 18 hours, the reaction mixture was distilled under reduced pressure to remove the solvent to give methyl trans-4-(N-((4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate as a pale yellow oil. The resulting compound was provided for the subsequent reaction without further purification.

(Step 5) Synthesis of methyl trans-4-(N-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate

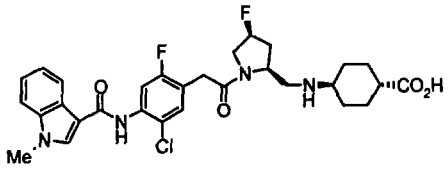


In DMF (18 ml), triethylamine (0.26 ml, 1.865 mmol) and EDC HCl (357.6 mg, 1.865 mmol) were added to methyl trans-4-(N-((4S)-fluoro-(2S)-pyrrolidinylmethyl)trifluoroacetylamino)cyclohexanecarboxylate (486.0 mg, 1.243 mmol), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (448.7 mg, 1.243 mmol) and HOBt (33.6 mg, 0.249 mmol). The resulting mixture was stirred for cyclohexylcarbon 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and 1N HCl, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, methyl trans-4-(N-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate (736.9 mg, 85%) was obtained as a light brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.72 (4H, m), 1.72-1.91 (3H, m), 2.03-2.18 (2H, m), 2.29 (1H, m), 2.50 (1H, m), 3.45-4.20

(total 13H, series of m, including 3H, s at δ: 3.68, and 3H, s at δ: 3.88), 4.67 (1H, m), 5.33 (1H, br d, J=53.2Hz), 7.28-7.45 (4H, m), 7.80 (1H, s), 8.13 (1H, m), 8.30 (1H, s), 8.52 (1H, d, J=12.0Hz).

(Step 6) Synthesis of trans-4-(N-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)amino)cyclohexanecarboxylic acid



Methyl trans-4-(N-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate (309.1 mg, 0.443 mmol) was dissolved in THF (6.0 ml). To the resulting solution was added 0.25N NaOH (6.0 ml), followed by stirring at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl and then, purified by an ion exchange resin and reverse phase middle pressure column chromatography to give the title compound (51.6 mg, 20%) as a white amorphous substance.

^{1}H-NMR (CD_3OD) δ: 1.28-1.59 (4H, m), 2.06-2.21 (4H, m), 2.21-2.35 (2H, m), 2.35-2.59 (total 1H, m), 3.10 (1H, m),

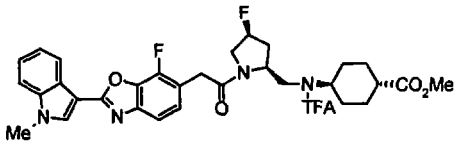
3.78 (2H, s), 3.85-4.15 (total 5H, series of m, including 3H, s at δ: 3.91), 4.48-4.70 (3H, m), 5.42 (1H, d, J=52.7Hz), 7.27 (1H, dd, J=8.0Hz), 7.32 (1H, dd, J=8.0Hz), 7.46 (1H, d, J=8.0Hz), 7.51 (1H, d, J=8.0Hz), 8.00 and 8.03 (total 1H, s), 8.06 (1H, s), 8.14 and 8.16 (total 1H, s), 8.34 (2H, br s);

MS (ESI) m/z 587 (M^++1).

Example 108

trans-4-(N-(1-((7-Fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)amino)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(N-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate

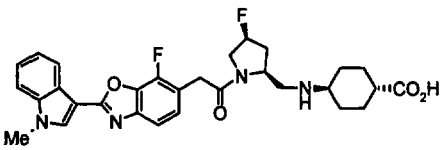


In DMF (9.0 ml), triethylamine (0.15 ml, 1.089 mmol) and EDC HCl (208.7 mg, 1.089 mmol) were added to methyl trans-4-(N-((4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate (238.7 mg, 0.726 mmol), (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (235.4 mg, 0.726 mmol) and HOBt (19.6 mg, 0.145 mmol). The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was

diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, methyl trans-4-(N-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-trifluoroacetylamino)cyclohexanecarboxylate (100%) was obtained as a light brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45-1.70 (5H, m), 1.72-1.89 (2H, m), 2.00-2.18 (2H, m), 2.30 (1H, m), 2.55 (1H, m), 3.50-4.17 (total 13H, series of m, including 3H, s at δ: 3.67, and 3H, s at δ: 3.92), 4.67 (1H, m), 5.32 (1H, br d, J=53.2Hz), 7.31-7.50 (5H, m), 7.98 (1H, m), 8.44 (1H, m).

(Step 2) Synthesis of trans-4-(N-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)amino)cyclohexanecarboxylic acid



Methyl trans-4-(N-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethyl)-

trifluoroacetylamino)cyclohexanecarboxylate (145.8 mg, 0.211 mmol) was dissolved in THF (4.0 ml). To the resulting solution was added 0.25N NaOH (4.0 ml), followed by stirring at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl and then, purified by an ion exchange resin and reverse phase middle pressure column chromatography to give the title compound (36.0 mg, 30%) as a white amorphous substance.

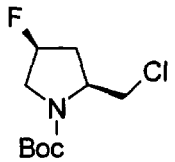
^{1}H-NMR (CD_3OD) δ: 1.20-1.56 (5H, m), 1.92-2.57 (6H, m), 3.05 (1H, m), 3.67-4.16 (total 9H, m, including 3H, s at δ: 3.94), 4.40-4.70 (1H, m), 5.43 (1H, br d, J=52.4Hz), 7.10-7.55 (5H, m), 8.11 (1H, s), 8.30 (1H, d, J=8.0Hz), 8.44 (1H, br s);

MS (ESI) m/z 551 (M^++1).

Example 109

1-(2-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylic acid:

(Step 1) Synthesis of 1-(tert-butoxycarbonyl)-(2S)-chloromethyl-(4S)-fluoropyrrolidine

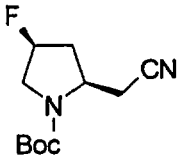


In acetonitrile (120 ml), carbon tetrachloride (3.30

ml, 34.2 mmol) was added dropwise to 1-(tert-butoxycarbonyl)-(4S)-fluoro-(2S)-pyrrolidinylmethanol (5.00 g, 22.8 mmol), potassium cyanide (2.97 g, 45.6 mmol), tributylphosphine (6.83 ml, 27.4 mmol), and 18-crown-6 (0.60 g, 2.28 mmol) under stirring at 0°C. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 19 hours and at 80°C for 9 hours. After the reaction mixture was cooled to room temperature and the crystals thus precipitated were filtered off, the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (4:1, v/v) eluate fractions, 1-(tert-butoxycarbonyl)-(2S)-chloromethyl-(4S)-fluoropyrrolidine (2.05 g, 46%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.50 (broad s, 9H), 2.16 (m, 1H), 2.53 (m, 1H), 3.41-4.17 (m, 5H), 5.24 (m, 1H).

(Step 2) Synthesis of (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetonitrile



In DMSO (50 ml), 1-(tert-butoxycarbonyl)-(2S)-chloromethyl-(4S)-fluoropyrrolidine (2.01 g, 8.46 mmol) and sodium cyanide (0.83 g, 16.9 mmol) were stirred at 80°C for

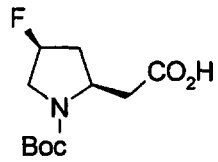
21 hours. After cooling to room temperature, the reaction mixture was added with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (3:1, v/v) eluate fractions, (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetonitrile (1.67 g, 86%) was obtained as a yellow oil.

IR (ATR) ν 2250 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.46 (broad s, 9H), 2.20-2.43 (m, 2H), 2.59 (m, 1H), 3.00 (m, 1H), 3.48-3.75 (m, 2H), 4.22 (m, 1H), 5.25 (m, 1H).

MS (ESI) m/z 229 (M^++1).

(Step 3) Synthesis of (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetic acid



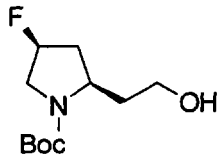
In methanol (36 ml), (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetonitrile (1.67 g, 7.32 mmol) and 0.25N NaOH (44 ml, 11.0 mmol) were heated under reflux for 24 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to

remove the solvent. The residue was dissolved in water. The aqueous solution was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent to give (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetic acid (1.37 g, 76%) as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.47 (s, 9H), 2.16-2.27 (m, 2H), 2.63 (m, 1H), 3.02 (m, 1H), 3.43-3.79 (m, 2H), 4.34 (m, 1H), 5.23 (m, 1H).

MS (ESI) m/z 248 (M^++1).

(Step 4) Synthesis of 2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethanol



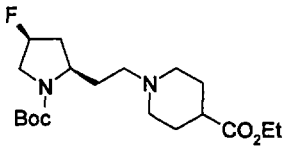
In THF (30 ml) was dissolved (1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)acetic acid (1.37 g, 5.54 mmol). To the resulting solution, a 10M borane·dimethyl sulfide solution (0.68 ml, 7.20 mmol) was added dropwise under stirring at 0°C. After completion of the dropwise addition, the reaction mixture was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature and then, distilled under reduced pressure to remove the solvent. The residue was treated with a

saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give 2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethanol (1.19 g, 92%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 9H), 1.76-2.27 (m, 4H), 3.55-3.73 (m, 4H), 4.20-4.30 (m, 2H), 5.23 (m, 1H).

MS (ESI) m/z 234 (M^++1).

(Step 5) Synthesis of ethyl 1-(2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate



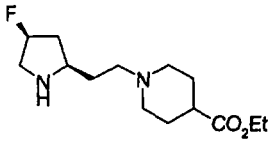
In methylene chloride (50 ml) were dissolved 2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethanol (1.19 g, 5.10 mmol) and triethylamine (1.07 ml, 7.65 mol). Under stirring at 0°C, methanesulfonyl chloride (0.43 ml, 5.61 mmol) was added dropwise to the resulting solution. After stirring at the same temperature for 1 hour, the reaction mixture was added with a saturated aqueous solution of NH_4Cl, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced

pressure to remove the solvent to afford a mesylate (1.60 g) as a yellow oil. In acetonitrile, the resulting mesylate (1.60 g), ethyl 4-piperidinacetate (1.20 ml, 7.48 mmol), and potassium carbonate (0.71 g, 5.14 mmol) were heated under reflux for 1.5 hours. The reaction mixture was cooled to room temperature. The precipitate was filtered off, and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, ethyl 1-(2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (831 mg, 44%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, J=7.1Hz, 3H), 1.46 (s, 9H), 1.62-2.47 (m, 12H), 2.83-2.90 (m, 2H), 3.49-3.93 (m, 3H), 4.12 (q, J=7.1Hz, 2H), 4.18 (m, 1H), 5.18 (m, 1H).

MS (ESI) m/z 373 (M^++1).

(Step 6) Synthesis of ethyl 1-(2-((4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate



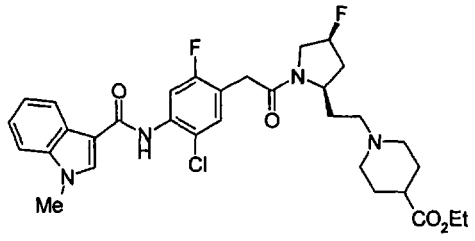
Ethyl 1-(2-(1-(tert-butoxycarbonyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (831 mg, 2.23 mmol) was dissolved in methylene chloride (10 ml). After trifluoroacetic acid (5.0 ml) was added to the resulting

solution at 0°C, the temperature of the reaction mixture was caused to rise back to room temperature and stirring was conducted for 1 hour. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue thus obtained was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give ethyl 1-(2-((4S)-fluoro-(2S)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (466 mg, 77%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.1Hz, 3H), 1.68-2.16 (m, 8H), 2.21-2.35 (m, 2H), 2.40-2.58 (m, 2H), 2.80-3.07 (m, 2H), 3.29-3.76 (m, 3H), 4.13 (q, J=7.1Hz, 2H), 4.16 (m, 1H), 5.22 (m, 1H).

MS (ESI) m/z 273 (M^++1).

(Step 7) Synthesis of ethyl 1-(2-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate



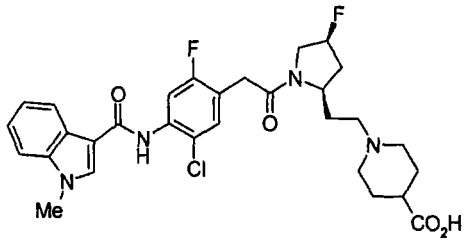
To (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (334 mg, 0.93

mmol), ethyl 1-(2-((4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (252 mg, 0.93 mmol), HOBt (25.0 mg, 0.19 mmol), and DMAP (23.0 mg, 0.19 mmol) were added DMF (9.0 ml) and EDC HCl (266 mg, 1.39 mmol). The resulting mixture was stirred at room temperature for 20 hours. Water was added to the reaction mixture, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate-acetone (1:1, v/v) eluate fractions, ethyl 1-(2-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (269 mg, 47%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.4Hz, 3H), 1.74-2.40 (m, 12H), 2.88-2.95 (m, 2H), 3.52-3.87 (m, 5H), 3.88 (s, 3H), 4.09-4.33 (m, 3H), 5.30 (m, 1H), 7.33-7.45 (m, 4H), 7.81 (s, 1H), 8.14 (m, 1H), 8.30 (m, 1H), 8.52 and 8.53 (each d, J=11.5Hz, total 1H).

MS (ESI) m/z 616 (M^++1).

(Step 8) Synthesis of 1-(2-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylic acid



To ethyl 1-(2-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2R)-pyrrolidinyl)ethyl)-4-piperidinecarboxylate (269 mg, 0.44 mmol) were added THF (4.5 ml) and 0.25N NaOH (2.62 ml, 0.66 mmol). The resulting mixture was stirred at room temperature for 21 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl, and purified by an ion exchange resin (HP-20, Mitsubishi Chemical) to give the title compound (160 mg, 62%) as a pale yellow solid.

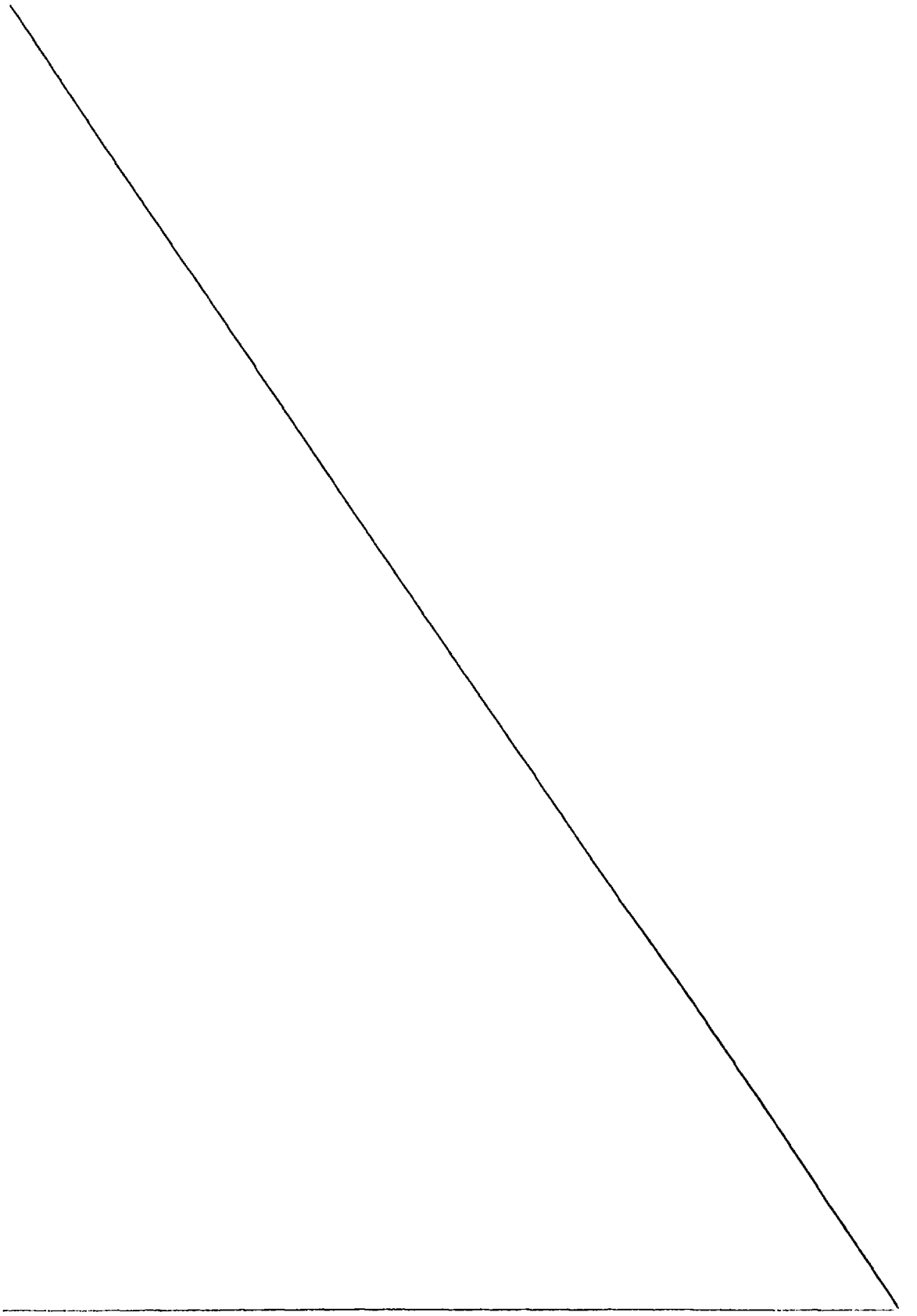
IR (ATR) ν 3419, 2940, 1644, 1583, 1511, 1465 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.45-1.58 (m, 2H), 1.74-2.36 (m, 9H), 2.73-2.87 (m, 2H), 3.41-3.87 (m, 7H), 3.88 (s, 3H), 4.09 and 4.20 (each m, total 1H), 5.32 and 5.39 (each m, total 1H), 7.21 (m, 1H), 7.27 (m, 1H), 7.44 and 7.49 (each d, J=7.6Hz, total 1H), 7.54 (d, J=8.1Hz, 1H), 7.71 (d, J=11.2Hz, 1H), 8.14 (d, J=7.6Hz, 1H), 8.30 (s, 1H), 9.29 (m, 1H).

MS (ESI) m/z 587 (M^++1);

Anal. Calcd for $C_{30}H_{33}ClF_2N_4O_4$ 0.75H_2O: C, 60.00; H, 5.79; N, 9.33.

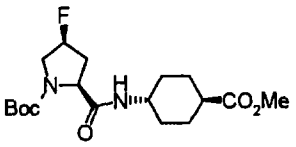
Found: C, 60.08; H, 6.00; N, 9.12.



Example 110

trans-4-(((4S)-Fluoro-1-(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate

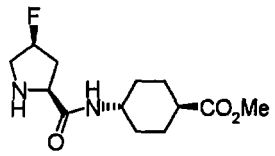


Methyl trans-4-aminocyclohexanecarboxylate (1.02 g, 6.481 mmol) and triethylamine (2.26 ml, 16.20 mmol) were dissolved in DMF (20 ml). To the resulting solution were added 1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-proline (1.51 g, 6.481 mmol), HOBt (175.2 mg, 1.296 mmol) and EDC·HCl (1.86 g, 9.722 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1 to 1:3, v/v) eluate fractions, methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (1.21 g,

50%) was obtained as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03-1.20 (2H, m), 1.32-1.63 (total 12H, m), 1.89-2.07 (5H, m), 2.23 (1H, m), 2.55 (1H, br s, NH), 3.45-3.84 (total 6H, m), 4.33 (1H, m), 5.18 (1H, d, J=52.0Hz).

(Step 2) Synthesis of methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

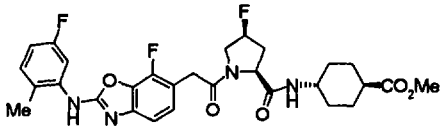


Methyl trans-4-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (1.21 g, 3.249 mmol) was dissolved in methylene chloride (20 ml). To the resulting solution was added trifluoroacetic acid (10 ml) at 0°C. The resulting mixture was stirred at room temperature for 3.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. The chloroform solution was neutralized by washing with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate. The resulting compound was provided for the subsequent reaction

without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.07-1.35 (2H, m), 1.43-1.65 (2H, m), 1.88-2.14 (5H, m), 2.15-2.49 (3H, m), 3.06-3.38 (2H, m), 3.60-3.88 (total 5H, m), 5.16 (1H, br d, J=53.2Hz), 7.39 (1H, br s, NH).

(Step 3) Synthesis of methyl trans-4-(((4S)-fluoro-1-(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

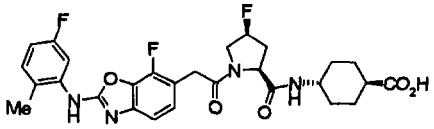


To the above-described methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (81.5 mg, 0.299 mmol), 2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetic acid (92.3 mg, 0.299 mmol) and HOBt (8.1 mg, 0.060 mmol) were added DMF (4.0 ml) and EDC HCl (86.1 mg, 0.449 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, methyl trans-4-((4S)-fluoro-1-(2-(5-

fluoro-2-methoxyphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (10%) was obtained as a crystalline powder. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.00-1.30 (2H, m), 1.42-1.63 (2H, m), 1.79-2.08 (5H, m), 2.08-2.36 (5H, m), 3.59-4.06 (total 8H, series of m), 4.59 and 4.74 (total 1H, d, J=9.6Hz), 5.27 and 5.31 (total 1H, d, J=52.4Hz), 6.74 (1H, m), 6.97-7.17 (2H, m), 7.22 (1H, m), 7.41 (1H, m), 8.01 (2H, m).

(Step 4) Synthesis of trans-4-(((4S)-fluoro-1-(2-(5-fluoro-2-methoxyphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylic acid



To the above-described methyl trans-4-(((4S)-fluoro-1-(2-(5-fluoro-2-methoxyphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate were added THF (4.0 ml) and 0.25N NaOH (4.0 ml). The resulting mixture was stirred at room temperature for 7 hours. The reaction mixture was distilled under reduced pressure to remove the solvent and the residue was neutralized with 1N

HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (142.5 mg, 85% for 2 steps) as a crystalline powder.

IR (ATR) ν 2937, 1639, 1579, 1538 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.45 (5H, m), 1.76 (2H, m), 1.90 (2H, m), 2.04-2.50 (total 5H, m), 3.42-4.01 (total 5H, series of m), 4.40 and 4.63 (total 1H, d, J=9.6Hz), 5.25 and 5.34 (total 1H, d, J=52.4Hz), 6.89 (1H, m), 7.02-7.48 (4H, m), 7.90 (1H, m), 10.03 (1H, br s), 12.05 (1H, br s, CO_2H).

MS (ESI) m/z 559 (M^++1);

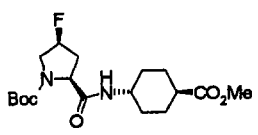
Anal. Calcd for $C_{28}H_{29}F_3N_4O_5$ H_2O: C, 58.33; H, 5.42; N, 9.72; F, 9.89.

Found: C, 58.08; H, 5.38; N, 9.45; F, 9.59.

Example 111

trans-4-((1-(5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylic acid:

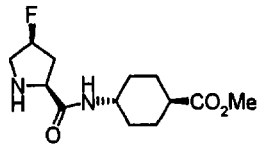
(Step 1) Synthesis of methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate



Methyl trans-4-aminocyclohexanecarboxylate (1.02 g, 6.481 mmol) was dissolved in DMF (20 ml). To the resulting solution was added triethylamine (2.26 ml, 16.20 mmol) at room temperature. After stirring for 5 minutes, 1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-proline (1.51 g, 6.481 mmol), HOBt (175.2 mg, 1.296 mmol) and EDC·HCl (1.86 g, 9.722 mmol) were added to the reaction mixture. The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1 to 1:3, v/v) eluate fractions, methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (1.21 g, 50%) as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03-1.20 (2H, m), 1.32-1.63 (total 12H, m), 1.89-2.07 (5H, m), 2.23 (1H, m), 2.55 (1H, br s, NH), 3.45-3.84 (total 6H, m), 4.33 (1H, m), 5.18 (1H, d, J=52.0Hz).

(Step 2) Synthesis of methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

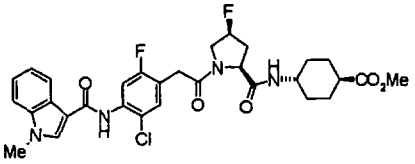


Methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylate (55.3 mg, 0.148 mmol) was dissolved in methylene chloride (2.0 ml). To the resulting solution was added trifluoroacetic acid (1.0 ml) at 0°C. The resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue thus obtained was diluted with chloroform. The chloroform solution was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate was obtained as an amorphous substance. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.07-1.35 (2H, m), 1.43-1.65 (2H, m), 1.88-2.14 (5H, m), 2.15-2.49 (3H, m), 3.06-3.38 (2H, m), 3.60-3.88 (total 5H, m), 5.16 (1H, br d, J=53.2Hz), 7.39 (1H, br s, NH).

(Step 3) Synthesis of methyl trans-4-((1-(5-chloro-2-

fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

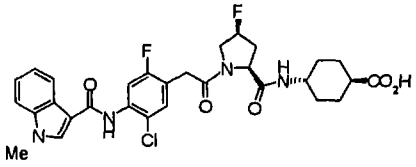


The above-described methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (40.4 mg, 0.148 mmol), 5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetic acid (53.6 mg, 0.148 mmol) and 1-HOBt (4.0 mg, 0.030 mmol) were dissolved in DMF (2.0 ml). To the resulting solution was added EDC HCl (42.7 mg, 0.223 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl trans-4-((1-(5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (62.0 mg, 68% for 2 steps) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.00-2.32 (total 12H, series of m), 3.45-

4.07 (total 11H, series of m), 4.55 and 4.71 (total 1H, d, J=10.0Hz), 5.26 and 5.29 (total 1H, d, J=52.8Hz), 7.27-7.45 (4H, m), 7.79 (1H, m), 8.12 (1H, m), 8.29 (1H, m), 8.54 (1H, dd, J=12.4Hz).

(Step 4) Synthesis of trans-4-((1-(5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylic acid



To methyl trans-4-((1-(5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (62.0 mg, 0.101 mmol) were added THF (1.5 ml) and 0.25N NaOH (1.5 ml). The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (56.3 mg, 93%) as a white amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.11-1.42 (4H, m), 1.74 (2H, m), 1.89 (2H, m), 2.05-2.52 (3H, m), 3.37-4.01 (total 8H, series of m), 4.40 and 4.64 (total 1H, d, J=10.0Hz), 5.25 and 5.36

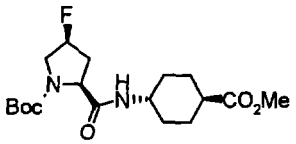
(total 1H, d, J=52.4Hz), 7.16-7.95 (total 6H, series of m), 8.15 (1H, d, J=8.0Hz), 8.31 (1H, s), 9.31 (1H, m), 12.05 (1H, s, CO_2H).

MS (ESI) m/z 601 (M^+ +1).

Example 112

trans-4-((1-(3-Chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

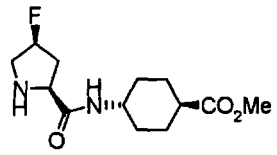


Methyl trans-4-aminocyclohexanecarboxylate (1.02 g, 6.481 mmol) was dissolved in DMF (20 ml). To the resulting solution was added triethylamine (2.26 ml, 16.20 mmol) at room temperature and the mixture was stirred for 5 minutes. To the reaction mixture were added 1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-proline (1.51 g, 6.481 mmol), HOBt (175.2 mg, 1.296 mmol) and EDC·HCl (1.86 g, 9.722 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced

pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1 to 1:3, v/v) eluate fractions, methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (1.21 g, 50%) was obtained as an oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03-1.20 (2H, m), 1.32-1.63 (total 12H, m), 1.89-2.07 (5H, m), 2.23 (1H, m), 2.55 (1H, br s, NH), 3.45-3.84 (total 6H, m), 4.33 (1H, m), 5.18 (1H, d, J=52.0Hz).

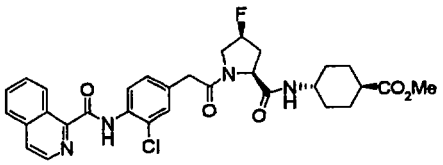
(Step 2) Synthesis of methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate



Methyl trans-4-((1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (1.21 g, 3.249 mmol) was dissolved in methylene chloride (20 ml). To the resulting solution was added trifluoroacetic acid (10 ml) at 0°C. After stirring at room temperature for 3.5 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. The resulting solution was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was

dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate as a thick sticky liquid. The resulting compound was provided for the subsequent reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.07-1.35 (2H, m), 1.43-1.65 (2H, m), 1.88-2.14 (5H, m), 2.15-2.49 (3H, m), 3.06-3.38 (2H, m), 3.60-3.88 (total 5H, m), 5.16 (1H, br d, J=53.2Hz), 7.39 (1H, br s, NH).

(Step 3) Synthesis of methyl trans-4-((1-(3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate

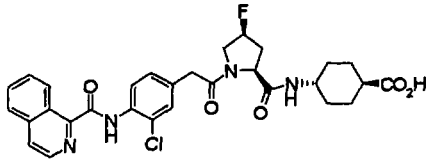


The above-described methyl trans-4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (80.6 mg, 0.296 mmol), 3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetic acid (100.9 mg, 0.296 mmol) and 1-HOBt (8.0 mg, 0.059 mmol) were dissolved in DMF (4.0 ml). To the resulting solution was added EDC HCl (85.1 mg, 0.444 mmol). The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated

aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, methyl trans-4-((1-(3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (172.1 mg, 98%) was obtained as a thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 0.98-1.23 (2H, m), 1.43-1.65 (2H, m), 1.88-2.10 (6H, m), 2.24 (1H, m), 3.52-4.06 (total 8H, series of m), 4.52 and 4.74 (total 1H, d, J=9.6Hz), 5.26 (1H, d, J=53.3Hz), 5.96 and 6.32 (total 1H, d, J=8.5Hz), 7.24 and 7.28 (total 1H, s), 7.39 and 7.44 (total 1H, s), 7.74 (2H, m), 7.89 (2H, m), 8.59 (1H, m), 8.66 (1H, d, J=8.0Hz), 8.71 (1H, d, J=8.4Hz), 9.70 (1H, d, J=8.4Hz), 11.03 and 11.07 (total 1H, s).

(Step 4) Synthesis of trans-4-((1-(3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylcarbonylamino)cyclohexanecarboxylic acid



To methyl trans-4-((1-(3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonylamino)cyclohexanecarboxylate (172.1

mg, 0.289 mmol) were added THF (4.0 ml) and 0.25N NaOH (4.0 ml). The resulting mixture was stirred at room temperature for 7 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (147.5 mg, 88%) as an amorphous substance.

IR (ATR) ν 2940, 1652, 1517 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.11-1.44 (4H, m), 1.76 (2H, m), 1.90 (2H, m), 2.07-2.62 (3H, m), 3.40-3.99 (total 5H, series of m), 4.41 and 4.61 (total 1H, d, J=9.6Hz), 5.26 and 5.34 (total 1H, d, J=53.3Hz), 7.23-7.96 (total 5H, series of m), 8.09-8.27 (3H, m), 8.67 (1H, d, J=5.6Hz), 9.32 (1H, d, J=8.8Hz), 10.83 (1H, s), 12.05 (1H, br s, CO_2H).

MS (ESI) m/z 581 (M^+ +1);

Anal. Calcd for $C_{30}H_{30}ClFN_4O_5$ 0.75H_2O: C, 60.61; H, 5.34; N, 9.42; Cl, 5.96; F, 3.20.

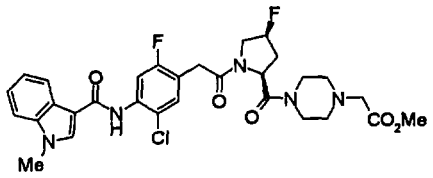
Found: C, 60.50; H, 5.31; N, 9.24; Cl, 6.09; F, 2.95.

Example 113

4-((1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonyl)-1-piperazinylacetic acid:

(Step 1) Synthesis of methyl 4-((1-((5-chloro-2-fluoro-4-

(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)- pyrrolidinyl)carbonyl)-1-piperazinylacetate



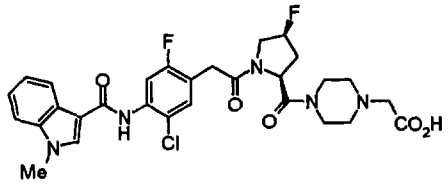
In DMF (10 ml) were dissolved (5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (300 mg, 0.832 mmol) and methyl 4-(((4S)-fluoro-(2S)-pyrrolidinyl)carbonyl)-1-piperazinylacetate (300 mg, 1.10 mmol). To the resulting solution were added EDC HCl (239 mg, 1.25 mmol), DMAP (cat.), and HOBt (catalytic amount). The resulting mixture was stirred at room temperature for 12 hours. To the reaction mixture was added water (100 ml), followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, methyl 4-((1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonyl)-1-piperazinylacetate (419 mg, 82%) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$) δ: 2.04-2.62 (series of m, 6H), 3.23-4.14 (series of m, 16H), 4.76-5.39 (m, 2H), 7.32-7.52 (m, 4H), 7.79 (s, 1H), 8.12 (dd, J=9.3,5.1Hz, 1H), 8.29 (s, 1H),

8.47-8.51 (m, 1H).

MS (ESI) m/z 616 (M^++1).

(Step 2) Synthesis of 4-((1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonyl)-1-piperazinylacetic acid



To methyl 4-((1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinyl)carbonyl)-1-piperazinylacetate (410 mg, 0.666 mmol) were added THF (10 ml) and 0.25N NaOH (5.3 ml, 1.33 mmol). The resulting mixture was stirred at room temperature for 15 hours. Water (50 ml) was added to the reaction mixture and the aqueous solution was neutralized with 1N HCl, followed by extraction with a 20% chloroform-methanol mixture (2 x 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby the title compound (240 mg, 60%) was obtained as a colorless amorphous substance.

^{1}H-NMR (DMSO) δ: 2.00-4.11 (series of m, 19H), 4.92 and 5.21 (d, J=9.8Hz, each, total 1H), 5.31 and 5.45 (m, each, total 1H), 7.20-7.30 (m, 2H), 7.41 and 7.52 (d, J=7.8Hz, each, total 1H), 7.56 (d, J=8.3Hz, 1H), 7.72 (d, J=11.0Hz,

1H), 8.16 (d, J=7.8Hz, 1H), 8.31 (s, 1H), 9.31 (s, 1H).

MS (ESI) m/z 602 (M^++1);

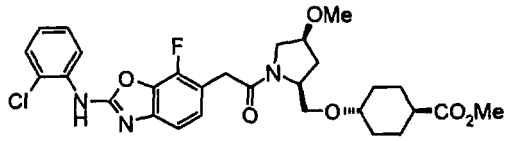
Anal. Calcd for $C_{29}H_{30}ClF_2N_5O_5$ 3.75 H_2O; C, 52.02; H, 5.64; N, 10.46.

Found: C, 51.59; H, 5.25; N, 10.13.

Example 114

trans-4-(1-((2-(2-Chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((2-(2-chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



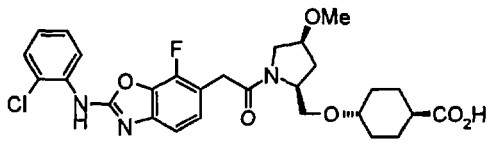
In DMF (3 ml), (2-(2-chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (100 mg, 0.369 mmol), methyl trans-4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (118 mg, 0.369 mmol), EDC HCl (106 mg, 0.554 mmol), HOBt (75 mg, 0.554 mmol) and triethylamine (0.26 ml, 1.85 mmol) were stirred at room temperature for 14 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was

purified by chromatography using a silica gel thin-layer plate, whereby from chloroform/acetone (10/1, v/v) eluate fractions, methyl trans-4-(1-((2-(2-chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (151 mg, 71%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.14-1.68 (m, 4H), 1.92-2.36 (m, 6H), 3.21-3.29 (m, 1H), 3.30 and 3.33 (each s, total 3H, amide isomers), 3.45-3.61 (m, 2H), 3.64 and 3.67 (each s, total 3H, amide isomers), 3.71(s, 1H), 3.74-4.06 (m, 5H), 4.21-4.37 (m, 1H), 7.04 (t, J=7.6Hz, 1H), 7.14 (t, J=7.1Hz, 1H), 7.24 (d, J=6.6Hz, 1H), 7.36 and 7.41 (each d, J=7.8 and 8.1Hz respectively, total 2H, amide isomers), 7.58 and 7.65 (m and br, total 1H, amide isomers), 8.52 (d, J=8.3Hz, 1H).

MS (ESI) m/z 574 (M^++1), 576 (M^++3).

(Step 2) Synthesis of trans-4-(1-((2-(2-chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(2-chlorophenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (151 mg, 0.263 mmol) was dissolved in a THF/methanol (2:1, 6 ml) mixture. To the resulting solution was added 1N NaOH (2 ml) and the

mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The resulting crude crystals were purified by chromatography using a silica gel thin-layer plate. The chloroform/methanol (20/1) fractions were collected and solidified with chloroform/methanol/ethyl acetate/n-hexane, whereby the title compound (80 mg, 54%) was obtained as a colorless solid.

IR (ATR) ν 3406, 2937, 2864, 1697, 1639, 1593, 1572, 1446 cm^{-1};

^{1}H-NMR (DMSO) δ: 1.11-1.41 (m, 4H), 1.82-2.21 (m, 7H), 3.19 (m, 1H), 3.22 and 3.25 (each s, total 3H, amide isomers), 3.28-4.31 (m, 8H), 7.03 and 7.06 (each t, each J=7.8Hz, total 1H, amide isomers), 7.15 (dd, J=7.8, 3.2Hz, 1H), 7.21 (dd, J=7.8, 1.0Hz, 1H), 7.42 (dt, J=6.6, 1.0Hz, 1H), 7.54 (dd, J=8.1, 1.0Hz, 1H), 8.05 (d, J=7.6Hz, 1H).

MS (ESI) m/z 560 (M^++1), 562 (M^++3);

Anal. Calcd for $C_{28}H_{31}ClFN_3O_6$ $0.5H_2O$: C, 59.10; H, 5.67; N, 7.38.

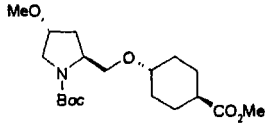
Found: C, 59.10; H, 5.65; N, 7.20.

Example 115

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-

indolylcarbonylamino)phenyl)acetyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid

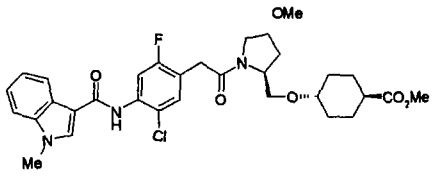


Methyl iodide (436 l, 7.00 mmol) and trans-4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (500 mg, 1.40 mmol were dissolved in DMF (10 ml). Under stirring at 0°C, sodium hydride (112 mg, 2.80 mmol) was added to the resulting solution in portions. After stirring at the same temperature for 3 hours, the reaction mixture was added with water (50 ml), followed by extraction with ethyl acetate (200 ml). The extract was washed with saturated brine (2 x 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate fractions, methyl trans-4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (441 mg, 85%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (m, 2H), 1.46 (m, 11H), 2.01-2.26 (series of m, 7H), 3.19-4.11 (series of m, 13H).

MS (ESI) m/z 372 (M^++1).

(Step 2) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

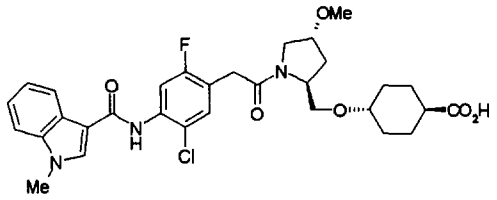


To methyl trans-4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (440 mg, 1.18 mmol) were added dioxane (10 ml) and a 4N HCl/dioxane (10 ml) mixture. The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The resulting solid was dissolved in DMF (10 ml) and triethylamine (821 µl, 5.90 mmol). To the resulting solution were added (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (426 mg, 1.18 mmol), EDC HCl (304 mg, 1.77 mmol), and HOBt (239 mg, 1.77 mmol). The resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (100 ml) and H_2O (100 ml) to separate the ethyl acetate layer. The ethyl acetate layer was washed with saturated brine (2 x 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (2:1) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (401 mg, 55%) was obtained as a colorless foam.

^{1}H-NMR ($CDCl_3$) δ: 1.08-1.28 (m, 2H), 1.31-1.59 (m, 2H), 1.93-2.28 (series of m, 7H), 3.10-4.33 (series of m, 18H), 7.34-7.44 (m, 4H), 7.82 (m, 1H), 8.14 (m, 1H), 8.30 (s, 1H), 8.48-8.53 (m, 1H).

(Step 3) Synthesis of trans4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4R)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (400 mg, 0.651 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (5.2 ml, 1.30 mmol) and the mixture was stirred for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with a chloroform-methanol (5:1, 2 x 100 ml) mixture. The extract was dried over anhydrous magnesium sulfate and distilled

under reduced pressure to remove the solvent. To the residue were added ethyl acetate and isopropyl ether to crystallize the residue. The crystals thus precipitated were collected by filtration under reduced pressure and dried under reduced pressure to give the title compound (247 mg, 63%) as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.40 (series of m, 4H), 1.83-2.18 (series of m, 7H), 3.19-4.30 (series of m, 15H), 7.19-7.29 (m, 2H), 7.41-7.45 (m, 1H), 7.55 (d, J=7.8Hz, 1H), 7.67-7.71 (m, 1H), 8.14 (d, J=7.8Hz, 1H), 8.29 (s, 1H), 9.31 (s, 1H).

MS (ESI) m/z 600 (M^++1);

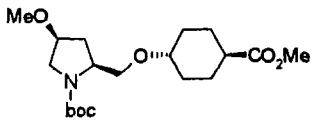
Anal. Calcd for $C_{31}H_{35}ClFN_3O_6 \cdot 0.5H_2O$: C, 61.13; H, 5.96; N, 6.90.

Found: C, 61.10; H, 6.06; N, 6.64.

Example 116

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-tert-butoxycarbonyl-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



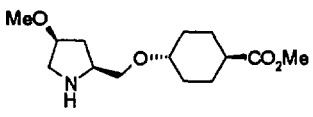
Methyl trans-4-(1-tert-butoxycarbonyl-(4S)-hydroxy-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (600 mg, 1.68 mmol) was dissolved in DMF (12 ml). To the resulting solution were added sodium hydride (60& in oil) (134 mg, 3.36 mmol) and methyl iodide (0.21 ml, 3.36 mmol) under stirring at 0°C in a nitrogen gas stream. After stirring at room temperature for 14 hours, the reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by flash column chromatography on a silica gel (Biotage flush-chromatography systems, KP-SIL 32-63 nm, 60A, n-hexane/ethyl acetate (4/1)) to give methyl trans-4-(1-tert-butoxycarbonyl-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (50 mg, 8%, more polar fraction) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.31 (m, 2H), 1.39-1.52 (m, 10H), 1.57 (s, 2H), 1.95-2.12 (m, 4H), 2.19 (d, J=13.4Hz, 1H), 2.26 (t, J=11.2Hz, 1H), 3.23 (m, 1H), 3.30 (s, 3H), 3.31-3.63 (m, 3H), 3.66 (s, 3H), 3.67-3.81 (m, 1H), 3.86-4.03 (m, 2H).

MS (ESI) m/z 372 (M^++1).

(Step 2) Synthesis of methyl trans-4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

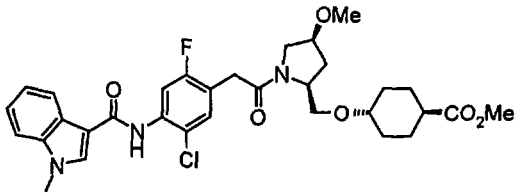


Methyl trans-4-(1-tert-butoxycarbonyl-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (50 mg, 0.135 mmol) was dissolved in methylene chloride (5 ml). To the resulting solution was added trifluoroacetic acid (0.5 ml) and the mixture was stirred at room temperature for 14 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was basified with 1N NaOH, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent to give methyl trans-4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (59 g, 100%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.57 (m, 5H), 1.96-2.20 (m, 5H), 2.32 (m, 2H), 3.33 (s, 3H), 3.34-3.57 (m, 3H), 3.66 (s, 3H), 3.67-3.81 (m, 2H), 3.94 (m, 1H), 4.11 (m, 1H).

MS (ESI) m/z 272 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

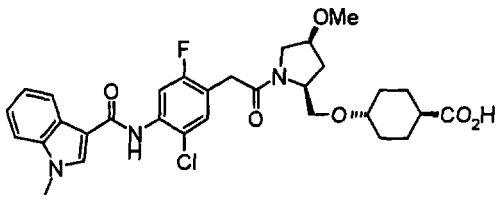


In DMF (2 ml), (5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (49 mg, 0.135 mmol), methyl trans-4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (59 mg, 0.135 mmol), EDC HCl (39 mg, 0.203 mmol), HOBt (27 mg, 0.203 mmol) and triethylamine (94 μl, 0.675 mmol) were stirred at room temperature for 20 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate, whereby from chloroform/acetone (10/1) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (117 mg, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (m, 2H), 1.46 (m, 2H), 1.94-2.14 (m, 5H), 2.19-2.14 (m, 5H), 2.19-2.33 (m, 2H), 3.25 (m, 1H), 3.30 and 3.33 (each s, total 3H, amide isomers), 3.46-3.61 (m, 3H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.67-3.86 (m ,3H), 3.88 (s, 3H), 3.95 and 4.00 (each m, total 1H, amide isomers), 4.21 and (q and m, J=7.1Hz, total 1H, amide isomers), 7.30-7.46 (m, 4H), 7.80 (s, 1H), 8.14 (d, J=5.6Hz, 1H), 8.29 (s, 1H), 8.48 and 8.51 (each d, J=9.3 and 9.5Hz respectively, total 1H).

MS (ESI) m/z 614 (M^++1), 616 (M^++3).

(Step 4) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (117 mg, 0.135 mmol) were added THF/methanol (2:1, 6 ml) and 1N NaOH (2 ml). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (78 mg, 96% (3 steps)) as a colorless solid.

IR (ATR) ν 3423, 2937, 1701, 1664, 1626, 1587, 1522, 1402 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.12-1.42 (m, 4H), 1.82-2.19 (m, 7H), 3.23 and 3.26 (each s, total 3H, amide isomers), 3.44-3.83 (m, 5H), 3.89 (s, 3H), 3.94 and 4.25 (m and q, J=5.8Hz, total 1H, amid isomers), 4.03 (br, 1H), 7.22 (t, J=7.3 hz, 1H), 7.27 (t, J=6.8Hz, 1H), 7.42 and 7.45 (each d, each

J=7.6Hz, total 1H, amide isomers), 7.65 (d, J=8.1Hz, 1H), 7.68 and 7.70 (d, J=11.2 and 11.0Hz respectively, total 1H, amide isomers), 8.15 (d, J=7.8Hz, 1H), 8.31 (d, J=2.2Hz, 1H), 9.31 (s, 1H).

MS (ESI) m/z 600 (M^++1), 602 (M^++3);

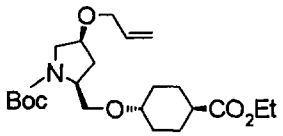
Anal. Calcd for $C_{31}H_{35}ClFN_3O_6$ $0.8H_2O$: C, 60.59; H, 6.00; N, 6.84.

Found: C, 60.60; H, 5.97; N, 6.74.

Example 117

trans-4-((4S)-Allyloxy-1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl trans-4-((4S)-allyloxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

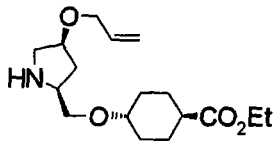


Ethyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (810 mg, 2.18 mmol) was dissolved in DMF (15 ml). Under stirring at 0°C, allyl bromide (0.378 ml, 4.36 mmol) and sodium hydride (60% in oil, 175 mg, 4.37 mmol) were added to the resulting solution in portions. After the reaction mixture was stirred at room temperature for 2.5 hours, allyl bromide (0.189 ml, 2.18 mmol) and sodium hydride (60% in oil, 88

mg, 2.18 mmol) were added further thereto. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was poured in ice water and then, acidified with 1N HCl. The reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2:1, v/v) eluate fractions, ethyl trans-4-((4S)-allyloxy-1-(tert-butoxycarbonyl)- (2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (626 mg, 70%) was obtained as a pale yellow oil.

MS (ESI) m/z 412 (M^++1).

(Step 2) Synthesis of ethyl trans-4-((4S)-allyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



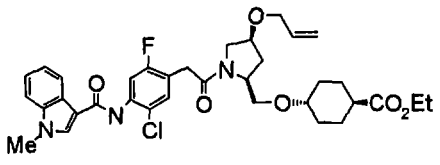
Ethyl trans-4-((4S)-allyloxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (308 mg, 0.75 mmol) was dissolved in methylene chloride (5 ml). To the resulting solution was added trifluoroacetic acid (1 ml) and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure to remove the solvent.

The residue was neutralized with a saturated aqueous solution of sodium bicarbonate. The mixture was extracted with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent to give ethyl trans-4-((4S)-allyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (230 mg, 99%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (m, total 4H), 1.45 (q, J=11.6Hz, 2H), 1.55 (m, 1H), 1.85-1.58 (series of m, total 4H), 2.25 (m, 2H), 2.92 and 2.95 (dd, J=5.2, 2.8Hz, each, total 1H), 3.06-3.09 (m, 1H), 3.62 (m, 2H), 3.51 (m, 2H), 4.93 (m, 2H), 4.06 (m, 1H), 4.10 (q, J=7.2Hz, 2H), 4.46 (m, 1H), 5.15 (m, 1H), 5.25 (m, 2H), 5.88 (m, 1H).

MS (LC-MS) m/z 312 (M^++1).

(Step 3) Synthesis of ethyl trans-4-((4S)-allyloxy-1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



Ethyl trans-4-((4S)-allyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (202 mg, 0.65 mmol) and (5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (234 mg, 0.65 mmol)

were dissolved in DMF (7 ml). To the resulting solution were added EDC HCl (188 mg, 0.98 mmol), HOBt (2.5 mg, 0.02 mmol) and DMAP (2.5 mg, 0.02 mmol), and the resulting mixture was stirred at room temperature for 14 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, ethyl trans-4-((4S)-allyloxy-1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (358 mg, 84%) was obtained as a yellow oil.

IR (ATR) ν 1724, 1643, 1514 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.24 (m, 3H), 1.26 (m, 2H), 1.46 (m, 2H), 1.96-2.10 (series of m, total 4H), 2.26 (m, 2H), 3.24 (m, 1H), 3.50-3.59 (series of m, total 3H), 3.72 (m, 2H), 3.82 (m, 1H), 3.89 (s, 3H), 3.96 (d, J=5.2Hz, 1H), 4.04 (m, 1H), 4.10 (m, 3H), 4.24 (m, 1H), 4.56 (m, 1H), 5.20 (m, 1H), 5.28 (m, 1H), 5.88 (m, 1H), 7.35 (m, 2H), 7.41 (m, 2H), 7.81 (d, J=2.0Hz, 1H), 8.13 (m, 1H), 8.30 (m, 1H), 8.50 (dd, J=12.4, 9.6Hz, 1H).

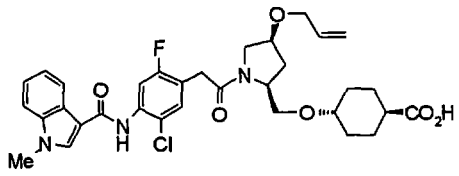
MS (ESI) m/z 655 (M^++1);

Anal. Calcd for $C_{35}H_{41}ClFN_3O_6$ 0.25 H_2O: C, 63.82; H, 6.35; N,

6.38.

Found: C, 63.86; H, 6.32; N, 6.23.

(Step 4) Synthesis of trans-4-((4S)-allyloxy-1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Ethyl trans-4-((4S)-allyloxy-1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (244 mg, 0.37 mmol) was dissolved in THF (3.5 ml). To the resulting solution was added 0.25N NaOH (3.5 ml), followed by stirring at 50°C for 5 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The concentrate was neutralized with 1N HCl, followed by extraction with a chloroform-methanol (5:1, v/v) mixture. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, the title compound (145 mg, 63%) was obtained as a white solid.

IR (KBr) ν 2935, 1724, 1616, 1513 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.60 (m, 2H), 1.31 (m, 2H), 1.83-1.99 (series of m, total 4H), 2.09 (m, 2H), 3.14 (m, 1H), 3.23 (m, 1H), 3.35-3.79 (series of m, total 5H), 3.85 (s, 3H), 3.88-3.96 (series of m, total 3H), 4.02-4.13 (series of m, total 2H), 5.13 (m, 1H), 5.23 (m, 1H), 5.87 (m, 1H), 7.20 (t, J=7.2Hz, 1H), 7.26 (t, J=7.2Hz, 1H), 7.40 (t, J=8.0Hz, 1H), 7.53 (d, J=8.0Hz, 1H), 7.67 and 7.68 (d, J=10.8Hz, total 1H), 8.12 (d, J=8.0Hz, 1H), 8.24 (d, J=6.0Hz, 1H), 9.29 (s, 1H).

MS (ESI) m/z 27 (M^++1);

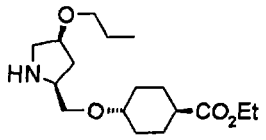
Anal. Calcd for $C_{33}H_{37}ClFN_3O_6$ 0.5 H_2O: C, 62.41; H, 6.03; N, 6.62.

Found: C, 62.33; H, 5.96; N, 6.46.

Example 118

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl trans-4-((4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



Ethyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-allyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (318 mg, 0.77 mmol) was dissolved in ethanol (8 ml). To the resulting solution was added 5% palladium-carbon (50 mg).

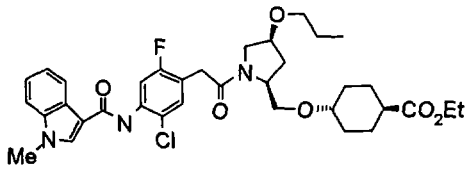
The resulting mixture was subjected to catalytic hydrogenation at room temperature for 48 hours under a hydrogen gas of 1 atm. After removal of the catalyst from the reaction mixture by filtration, the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (4:1, v/v) eluate fractions, an oil (275 mg) was obtained. The resulting oil was dissolved in methylene chloride (7 ml). Trifluoroacetic acid (2 ml) was added to the resulting solution and the mixture was stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform-methanol (10:1, v/v). The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent to afford ethyl trans-4-((4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (208 mg, 86%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, J=7.2Hz, 3H), 1.24 (t, J=7.2Hz, 3H), 1.27 (m, 2H), 1.38-1.66 (series of m, total 6H), 1.99 (m, 3H), 2.07 (m, 2H), 2.24 (m, 1H), 2.89 and 2.92 (d, J=5.6Hz, each, total 1H), 3.02 and 3.05 (d, J=2.4Hz, each, total 1H), 3.24 (m, 2H), 3.32 (dt, J=6.8, 1.2Hz, 2H), 3.49

(m, 2H), 3.98 (m, 1H), 4.11 (q, J=7.2Hz, 2H).

MS (ESI) m/z 314 (M^++1).

(Step 2) Synthesis of ethyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (7 ml) were dissolved (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (238 mg, 0.66 mmol) and ethyl trans-4-((4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (208 mg, 0.66 mmol). To the resulting solution were added EDC HCl (190 mg, 0.99 mmol), HOBt (5 mg, 0.04 mmol), and DMAP (5 mg, 0.04 mmol). The resulting mixture was stirred at room temperature for 14 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, ethyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (424 mg, 98%)

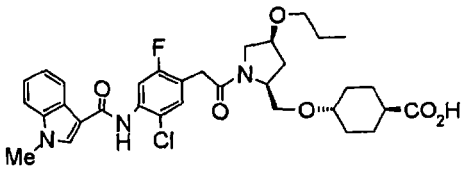
was obtained as a white crystalline powder.

IR (ATR) 2935, 1726, 1647, 1514 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 0.93 (m, 3H), 1.25 (m, 4H), 1.46 (m, 2H), 1.58 (m, 2H), 1.97-2.06 (series of m, total 6H), 2.24 (m, 2H), 3.24 (m, 1H), 3.35 (m, 2H), 3.43 (m, 1H), 3.49-3.59 (series of m, total 3H), 3.72 (m, 1H), 3.86 (m, 1H), 3.89 and 3.90 (series of s, total 3H), 4.02 (m, 1H), 4.11 (m, 2H), 4.26 (m, 1H), 7.35 (m, 2H), 7.41 (m, 2H), 7.81 (m, 1H), 8.14 (m, 1H), 8.30 (br s, 1H), 8.50 (m, 1H).

Anal. Calcd for $C_{35}H_{43}ClFN_3O_6$: C, 64.06; H, 6.61; N, 6.40. Found: C, 63.92; H, 6.70; N, 76.24.

(Step 3) trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Ethyl trans-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-(4S)-propoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (411 mg, 0.63 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (5 ml). The resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure and acidified with 1N HCl, followed by extraction with chloroform-methanol (5:1, v/v). The extract was dried over

anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, the title compound (253 mg, 64%) was obtained as a white solid.

IR (ATR) 2935, 1724, 1616, 1513 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.84 (m, 3H), 1.15 (m, 2H) 1.30 (m, 2H), 1.47 (m, 3H), 1.85-1.98 (m, 4H), 2.02 (m, 1H), 2.11 (m, 1H), 3.12 (m, 1H), 3.23 (m, 2H), 3.35 (m, 3H), 3.44-3.52 (m, 2H), 3.84 (s, 3H), 4.00 (m, 3H), 4.20 (m, 1H), 7.20 (dt, J=7.6, 2.2Hz, 1H), 7.25 (dt, J=7.7, 2.2Hz, 1H), 7.39 (dt, J=8.0, 3.4Hz, 1H), 7.52 (dd, J=8.0, 2.2Hz, 1H), 7.66 (ddd, J=11.0, 6.6, 3.4Hz, 1H), 8.11 (dd, J=7.8, 2.2Hz, 1H), 8.82 (m, 1H), 9.29 (s, 1H).

MS (ESI) m/z 629 (M^++1);

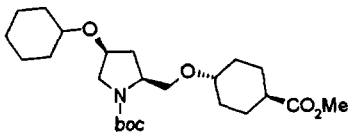
Anal. Calcd for $C_{33}H_{39}ClFN_3O_6$ 0.75H_2O: C, 61.77; H, 6.36; N, 6.55.

Found: C, 61.73; H, 6.18; N, 6.42.

Example 119

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-tert-butoxycarbonyl-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In methanol/HCl (40/1, 20.5 ml), methyl 4-((4S)-phenoxy-(2S)-pyrrolidinylmethoxy)benzoate (560 mg, 1.71 mmol) and rhodium-alumina (1.30 g) were subjected to catalytic hydrogenation at room temperature under 4 kg/cm^2 of hydrogen atmosphere for 4 days. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent to give methyl 4-((4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate hydrochloride as a solid. The resulting compound was provided for the subsequent reaction without further purification.

In 1,4-dioxane/water (1:1, 20 ml), di-tert-butyl dicarbonate (448 mg, 2.15 mmol) was added to methyl 4-((4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate hydrochloride (1.71 mmol) and sodium bicarbonate (862 mg, 10.3 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2/1) eluate fractions, methyl 4-(1-tert-butoxycarbonyl-

(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (642 mg, 85%) was obtained as a colorless oil.

The methyl 4-(1-tert-butoxycarbonyl-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (642 mg, 1.46 mmol) thus obtained was dissolved in methanol. To the resulting solution was added sodium methoxide (789 mg, 14.6 mmol) and the mixture was heated under reflux for 19 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (20/1, v/v) eluate fractions, the target methyl trans-4-(1-tert-butoxycarbonyl-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (90 mg, 14% (3 steps)) was obtained as a colorless oil.

In addition, a cis-isomer (90 mg, 14% (3 steps); non-polar fraction) as a colorless oil and a mixture (30 mg) of both isomers were obtained.

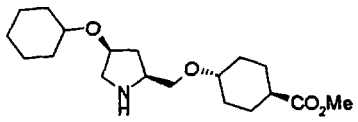
Trans-isomer : ^{1}H-NMR ($CDCl_3$) δ: 1.16-1.31 (m, 8H), 1.42 (s, 9H), 1.63-2.31 (m, 14H), 3.21-3.33 (m, 3H), 3.42-3.63 (m,

2H), 3.66 (s, 3H), 3.71-4.00 (m, 1H), 4.11(m, 1H); MS (ESI) m/z 440 (M^++1).

Cis-isomer : ^{1}H-NMR ($CDCl_3$) δ: 1.19-1.32 (m, 8H), 1.45 (s, 9H), 1.57-2.18 (m, 13H), 2.34 (br, 1H), 3.22-3.99 (m, 1H), 4.13 (m, 1H);

MS (ESI) m/z 440 (M^++1).

(Step 2) Synthesis of methyl trans-4-((4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



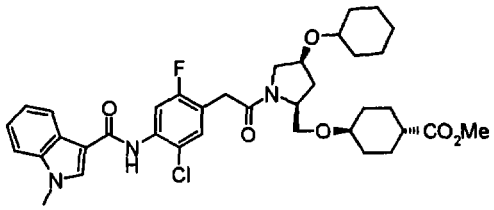
Methyl trans-4-(1-tert-butoxycarbonyl-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (90 mg, 0.205 mmol) was dissolved in methylene chloride (10 ml). To the resulting solution was added trifluoroacetic acid (1 ml) and the mixture was stirred at room temperature for 19 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was basified with methylene chloride and 1N NaOH, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent whereby methyl trans-4-((4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (16 mg, 23%) was obtained as a yellow oil. The resulting compound was

provided for subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.14-1.38 (m, 7H), 1.41-1.63 (m, 4H), 1.86 (s, 2H), 1.99-2.21 (m, 5H), 2.22-2.36 (m, 1H), 2.43 (m, 2H), 2.92-3.07 (m, 2H), 3.44-3.56 (m, 2H), 3.66 (s, 3H), 4.15 (m, 1H).

MS (ESI) m/z 340 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



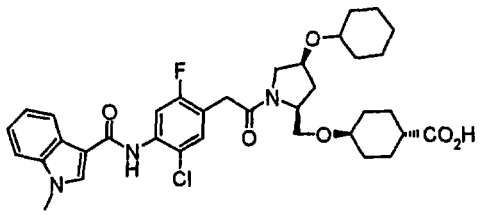
In DMF (1 ml), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (17 mg, 47.1 μmol), methyl trans-4-((4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate (16 mg, 47.1 μmol), EDC HCl (13.5 mg, 70.7 μmol), HOBt (9.6 mg, 70.0 μmol) and triethylamine (32.8 μl, 236 μmol) were stirred at room temperature for 17 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under

reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate, whereby from chloroform/acetone (10/1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (38 mg, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.32 (m, 8H), 1.38-1.52 (m, 2H), 1.72 (m, 2H), 1.83 (m, 2H), 1.94-2.31 (m, 6H), 3.20-3.34 (m, 2H), 3.42-3.59 (m, 3H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.69-3.76 (m, 2H), 3.80 (dd, J=8.6, 4.9Hz, 1H), 3.87 (m, 1H), 3.880 and 3.883 (each s, total 3H, amide isomers), 4.18-4.28 (m, 2H), 7.33-7.42 (m, 4H), 7.80 (d, J=2.2Hz, 1H), 8.11-8.14 (m, 1H), 8.27 and 8.29 (each s, total 1H, amide isomers), 8.47 and 8.50 (each d, each J=10.5Hz, total 1H, amide isomers).

MS (ESI) m/z 682 (M^++1), 684 (M^++3).

(Step 4) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-cyclohexyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (38 mg, 47.1 μmol) were added THF/methanol (2:1, 3 ml) and 1N NaOH (1 ml). The resulting mixture was stirred at room temperature for 13 hours. The reaction mixture was distilled under reduced pressure to remove the solvent and the residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (34 mg, 100%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.13-2.22 (m, 14H), 3.22 (m, 1H), 3.50-3.86 (m, 4H), 3.89 (s, 3H), 3.99-4.33 (m, 2H), 7.22 (t, J=7.1Hz, 1H), 7.42 and 7.45 (each d, each J=7.1Hz total 1H, amide isomers), 7.56 (d, J=8.3Hz, 1H), 7.68 and 7.70 (each d, J=11.0 and 10.5Hz respectively, total 1H, amide isomers), 8.15 (d, J=7.8Hz, 1H), 8.30 and 8.31 (each s, total 1H, amide isomers), 9.31 (s, 1H).

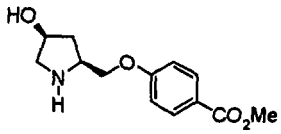
MS (ESI) m/z 669 (M^++1), 671 (M^++3).

Example 120

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-((4S)-hydroxy-(2S)-

pyrrolidinylmethoxy)benzoate hydrochloride

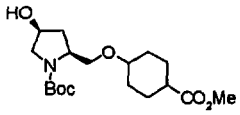


To methyl 4-(1-tert-butoxycarbonyl-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)benzoate (1.0 g, 2.85 mmol) was added 4N HCl-dioxane (10 m). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The resulting residue was crystallized by the addition of ether. The crystals thus precipitated were collected by filtration under reduced pressure, and dried under reduced pressure to give methyl 4-((4S)-hydroxy-(2S)-pyrrolidinylmethoxy)benzoate hydrochloride (660 mg, 80%) as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.75 (m, 1H), 2.33 (m, 1H), 3.09-3.23 (m, 2H), 3.82 (s, 3H), 4.01 (m, 1H), 4.34 (m, 2H), 4.43 (m, 1H), 5.56 (d, J=3.4Hz, 1H), 7.09 (d, J=8.8Hz, 2H), 7.95 (d, J=8.8Hz, 2H).

MS (ESI) m/z 252 (M^++1).

(Step 2) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexane-carboxylate

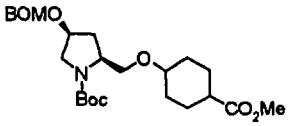


Methyl 4-((4S)-hydroxy-(2S)-

pyrrolidinylmethoxy)benzoate hydrochloride (660 mg, 2.29 mmol) was dissolved in methanol-acetic acid (10:1, 33 ml). To the resulting solution was added rhodium-alumina (500 mg) and the resulting mixture was subjected to catalytic hydrogenation at room temperature for 48 hours under 4 atm. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. The resulting residue was dissolved in acetonitrile-water (1:1, 50 ml). To the resulting solution were added triethylamine (637 µl, 4.58 mmol) and di-tert-butyl dicarbonate (600 mg, 2.75 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was extracted with chloroform (2 × 200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (818 mg, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.26-2.36 (series of m, 20 H), 3.34-4.21 (series of m, 8H), 4.81-5.08 (m, 2H).

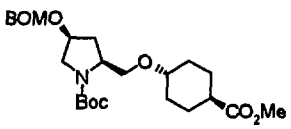
(Step 3) Synthesis of methyl 4-((4S)-benzyloxymethoxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



Methyl 4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (818 mg, 2.29 mmol) was dissolved in methylene chloride (20 ml). To the resulting solution were added benzyl chloromethyl ether (476 μl, 3.44 mmol) and DIEA (599 μl, 3.44 mmol). The resulting mixture was heated under reflux for 15 hours. After cooling to room temperature, the reaction mixture was added with water (50 ml), followed by extraction with chloroform (200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate fractions, methyl 4-((4S)-benzyloxymethoxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1- cyclohexanecarboxylate (1.07 g, 98%) as a colorless oil.

MS (ESI) m/z 478 (M^++1).

(Step 4) Synthesis of methyl trans-4-((4S)-benzyloxymethoxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

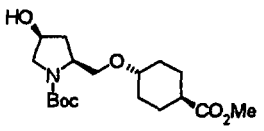


Methyl 4-((4S)-benzyloxymethoxy-1-(tert-

butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (1.07 g, 2.24 mmol) was dissolved in methanol (50 ml). To the resulting solution was added sodium methoxide (363 mg, 6.72 mmol). The resulting mixture was heated under reflux for 15 hours in a nitrogen gas stream. After cooling to room temperature, the reaction mixture was poured in 1N HCl (100 ml), followed by extraction with chloroform (2 x 200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent to give a mixture (about 1:1) of methyl 1,4-cis and trans-cyclohexanecarboxylates. The trans isomer was purified by flash column chromatography on silica gel, whereby from hexane-ethyl acetate (4:1) eluate fractions, methyl trans-4-((4S)-benzyloxymethoxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (400 mg, 37%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 2H), 1.45 (m, 11H), 1.98-2.25 (m, 7H), 3.24-3.96 (series of m, total 9 H), 4.60 (s, 2H), 4.77 (m, 2H), 7.28-7.38 (m, 5H).

(Step 5) Synthesis of methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexane carboxylate

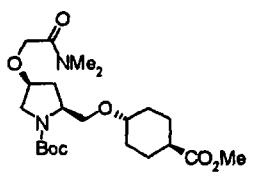


Methyl trans-4-((4S)-benzyloxymethoxy-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (390 mg, 0.817 mmol) was dissolved in methanol (50 ml). To the resulting solution was added 5% palladium/carbon (40 mg). The reaction mixture was subjected to catalytic hydrogenation at room temperature for 15 hours. The reaction mixture was filtered to remove the catalyst and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (281 mg, 96%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (m, 2H), 1.46 (m, 11H), 1.86-2.36 (series of m, 7H), 3.31-3.63 (series of m, 4H), 3.66 (s, 3H), 3.92-4.21 (series of m, 3H), 4.85 and 5.06 (d, J=11.5Hz, each, total 1H).

MS (ESI) m/z 358 (M^++1).

(Step 6) Synthesis of methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



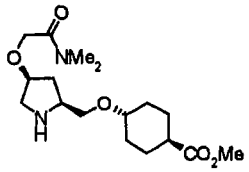
To methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-

hydroxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (280 mg, 0.780 mmol) were added DMF (10 ml) and N,N-dimethyl bromoacetamide (195 mg, 1.18 mmol). Under stirring at 0°C, sodium hydride (62 mg, 1.56 mmol) was added in portions. After the reaction mixture was stirred at room temperature for 1 hour, 1N HCl (50 ml) was poured therein, followed by extraction with ethyl acetate (200 ml). The extract was washed with saturated brine (2 x 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (1:1) eluate fractions, methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (247 mg, 72%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 2H), 1.45 (m, 11H), 1.98 (m, 5H), 2.25 (m, 2H), 2.95 (s, 3H), 3.01 (s, 3H), 3.22 (m, 1H), 3.43 (m, 2H), 3.50-3.96 (series of m, 6H, including s, 3H, at δ: 3.66), 4.12 (m, 3H).

MS (ESI) m/z 443 (M^++1).

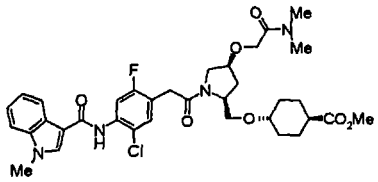
(Step 7) Synthesis of methyl trans-4-((4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



To methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (245 mg, 0.554) were added dioxane (10 ml) and 4N HCl/dioxane (10 ml). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (210 mg, 100%) was obtained as a colorless oil.

MS (ESI) m/z 343 (M^++1).

(Step 8) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)- dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

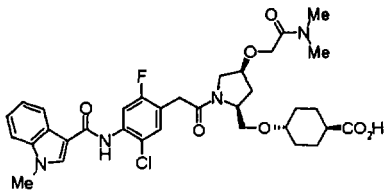


In DMF (10 ml), triethylamine (771 µl, 5.54 mmol), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.554 mmol), EDC HCl (159 mg, 0.831 mmol), and HOBt (112 mg,

0.831 mmol) were added to methyl trans-4-((4S)-dimethylcarbamoylmethoxy-(2S)- pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (210 mg, 0.554 mmol) and the resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (200 ml) and water (100 ml). The organic layer thus separated was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (288 mg, 76%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (m, 2H), 1.45 (m, 2H), 1.84-2.31 (series of m, 7H), 2.96-3.01 (m, 6H), 3.22 (m, 1H), 3.50-4.23 (series fo m, 17H), 7.27 (m, 4H), 7.80 (s, 1H), 8.12-8.14 (m, 1H), 8.29 (s, 1H), 8.49 (dd, J=12.0, 8.6Hz, 1H). MS (ESI) m/z 685 (M^++1).

(Step 9) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid



To methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-dimethylcarbamoylmethoxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (280 mg, 0.409 mmol) were added THF (5 ml) and 0.25N NaOH (3.3 ml, 0.825 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with chloroform-methanol (5:1, 2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform and to this solution was added hexane in portions until precipitation occurred. The crystals thus precipitated were collected by filtration under reduced pressure and dried under reduced pressure to give the title compound (180 mg, 66%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.37 (m, 4H), 1.85-2.17 (m, 7H), 2.82 (d, J=4.4Hz, 3H), 2.92 (d, J=6.8Hz, 3H), 3.17-4.22 (series of m, 14H), 7.20-7.30 (m, 2H), 7.44 (dd, J=11.2, 6.8Hz, 1H), 7.56 (d, J=8.1Hz, 1H), 7.70 (dd, J=11.2, 6.8Hz, 1H), 8.15 (d, J=7.8Hz, 1H), 8.31 (s, 1H), 9.31 (s, 1H).

MS (FAB) m/z 671(M^++1);

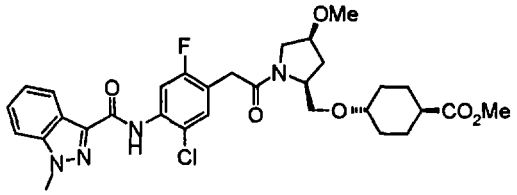
Anal. Calcd for $C_{34}H_{40}ClFN_4O_7$ 0.75 H_2O: C, 59.64; H, 6.11; N, 8.18.

Found: C, 60.03; H, 6.16; N, 7.82.

Example 121

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



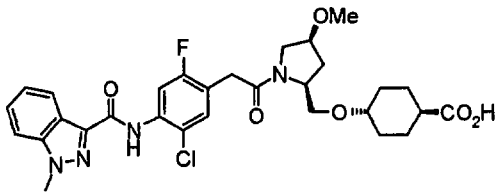
In DMF (3 ml), (5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetic acid (133 mg, 0.369 mmol), methyl trans-4-((4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (100 mg, 0.369 mmol), EDC HCl (106 mg, 0.554 mmol), HOBt (75 mg, 0.554 mmol) and triethylamine (0.26 ml, 1.85 mmol) were stirred at room temperature for 14 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using

a silica gel thin-layer plate (developed in chloroform/acetone (20/1)) to give methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (166 mg, 73%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.13-1.52 (m, 4H), 1.90-2.16 (m, 6H), 2.89 (m, 1H), 3.21-3.27 (m, 1H), 3.30 and 3.33 (each s, total 3H, amide isomers), 3.42-3.59 (m, 3H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.67-4.03 (m, 1H), 7.34 (m, 1H), 7.46 (s, 2H), 8.39 (d, J=8.3Hz, 1H), 8.48 and 8.52 (each d, each J=10.0Hz, total 1H, amide isomers), 9.49 (d, J=4.2Hz, 1H).

MS (ESI) m/z 615 (M^++1), 617 (M^++3).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (166 mg, 0.270 mmol) was dissolved in a THF/methanol (2:1, 6 ml) mixture. To the resulting solution was added 1N NaOH (2 ml). After

the reaction mixture was stirred at room temperature for 17 hours, the solvent was distilled off under reduced pressure. To the residue was added 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (130 mg, 80%) as a pale yellow solid.

IR (ATR) ν 3363, 2937, 2862, 1726, 1685, 1643, 1621, 1587, 1527, 1406 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.12-1.42 (m, 4H), 1.82-2.22 (m, 7H), 3.16 (m, 1H), 3.22 and 3.26 (each s, total 3H, amide isomers), 3.43-3.99 (m, 6H), 4.02 (s, 1H), 4.21 (s, 3H), 4.24 (m, 1H), 7.37 (t, J=7.3Hz, 1H), 7.46 and 7.50 (each d, each J=7.3Hz, total 1H, amide isomers), 7.82 (d, J=8.3Hz, 1H), 8.04 and 8.06 (each d, each J=11.3Hz, 1H, amide isomers), 8.20 (d, J=8.1Hz, 1H), 9.72 (s, 1H);

MS (ESI) m/z 601 (M^++1), 603 (M^++3);

Anal. Calcd for $C_{30}H_{34}ClFN_4O_6$ 0.5H_2O: C, 59.06; H, 5.78; N, 9.18; Cl, 5.81; F, 3.11.

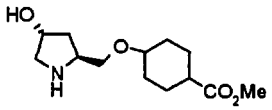
Found: C, 58.80; H, 5.64; N, 9.03; Cl, 6.00; F, 3.08.

Example 122

trans-4-((4R)-Hydroxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-((4R)-hydroxy-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate

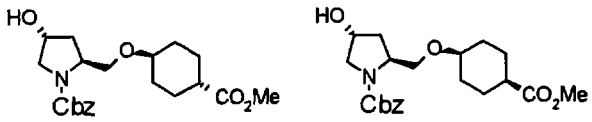


Methyl 4-(N-(tert-butoxycarbonyl)-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)benzoate (4.016 g, 11.43 mmol) was dissolved in methylene chloride (60.0 ml). Under stirring at 0°C, trifluoroacetic acid (30 ml) was added to the resulting solution. The resulting mixture was stirred at room temperature for 3 hours. The solvent was then distilled off under reduced pressure. The residue was dissolved in ethanol (80 ml), followed by catalytic hydrogenation in an autoclave for 20 hours with rhodium-alumina (5%, 1.01 g) under 9.5 kgf/cm^2 of hydrogen atmosphere. The reaction mixture was filtered through Celite to remove the catalyst and the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform-methanol (10:1, v/v). The resulting solution was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give methyl 4-((4R)-hydroxy-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate (2.46 g, 86%) as a brown oil. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.10-2.45 (total 11H, series of m), 3.13-

3.90 (total 9H, series of m, including 3H, s at δ: 3.65), 4.17 (1H, m), 4.65 (1H, m), 9.37 (1H, bs, NH).

(Step 2) Synthesis of methyl trans- and cis-4-(N-carbobenzoxy-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylates



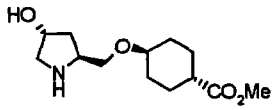
Methyl 4-((4R)-hydroxy-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate (2.46 g, 9.790 mmol) was dissolved in methylene chloride (50.0 ml). Under stirring at 0°C, carbobenzoxy chloride (a 30 to 35% toluene solution, 8.70 ml, 14.68 mmol) and a saturated aqueous solution of sodium bicarbonate (2.5 ml) were added to the resulting solution, followed by stirring at room temperature for 2 days. The reaction mixture was diluted with chloroform. The diluted mixture was washed with 1N HCl, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, a trans- and cis- diastereomer mixture was obtained. The mixture was separable by medium pressure chromatography on a silica gel column. From hexane-ethyl acetate (1:3, v/v) eluate fractions, methyl trans-4-(N-carbobenzoxy-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (555.1 mg, 15%)

and methyl cis-4-(N-carbobenzoxy-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (2.14 g, 57%) were obtained.

^{1}H-NMR ($CDCl_3$) (trans-isomer) δ: 1.09-1.30 (2H, m), 1.31-1.52 (2H, m), 1.55-1.83 (3H, m), 1.83-2.09 (3H, m), 2.11-2.29 (2H, m), 3.13 (1H, m), 3.40-3.73 (total 7H, m, including 3H, s at δ: 3.67), 4.12 (1H, bs), 4.49 (1H, bs), 5.01-5.28 (2H, m), 7.33 (5H, m, ArH);

^{1}H-NMR ($CDCl_3$) (cis-isomer) δ: 1.30-1.51 (2H, m), 1.52-1.88 (total 6H, m), 1.90-2.12 (2H, m), 2.19 (1H, m), 2.31 (1H, m), 3.27-3.78 (total 8H, m, including 3H, s at δ: 3.64), 4.12 (1H, bs), 4.52 (1H, bs), 5.00-5.28 (2H, m), 7.31 (5H, m, ArH).

(Step 3) Synthesis of methyl trans-4-((4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

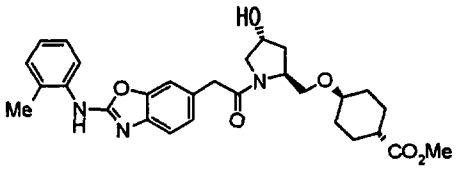


Methyl trans-4-(N-carbobenzoxy-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (555.1 mg, 1.418 mmol) was dissolved in ethanol (11 ml). To the resulting solution was added 5% palladium/carbon (wet, 100 mg) and the mixture was subjected to catalytic reduction at room temperature under normal pressure. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent to

give methyl trans-4-((4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (361.6 mg, crude). The compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.32 (3H, m), 1.35-1.55 (2H, m), 1.65 (1H, m), 1.74-1.93 (3H, m), 1.93-2.30 (3H, m), 2.82-3.58 (total 6H, series of m), 3.66 (3H, s, OMe), 4.40 (1H, bs).

(Step 4) Synthesis of methyl trans-4-((4R)-hydroxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

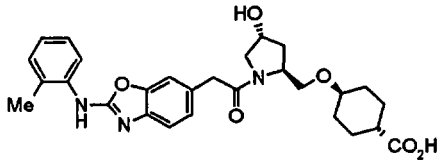


Methyl trans-4-((4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (50.5 mg, 0.201 mmol), (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid (56.7 mg, 0.201 mmol), and HOBt (5.4 mg, 0.040 mmol) were dissolved in DMF (2.0 ml). To the resulting solution was added EDC HCl (57.8 mg, 0.301 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with 1N HCl, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography using a silica gel thin-layer plate, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl trans-4-

((4R)-hydroxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (55.5 mg, 53%) was obtained as a clear oil.

^{1}H-NMR ($CDCl_3$) δ: 1.01-1.19 (2H, m), 1.29-1.50 (2H, m), 1.79-2.06 (6H, m), 2.10-2.23 (2H, m), 2.35 (3H, s, ArMe), 3.12 (1H, m), 3.32-3.59 (3H, m), 3.61 (3H, s, OMe), 3.71 (2H, s, CH_2), 3.79 (1H, dd, J=4.4, 10.0Hz, CH_2), 4.36 (1H, m), 4.52 (1H, m), 7.01-7.45 (total 8H, series of m, ArH, NH).

(Step 5) Synthesis of trans-4-((4R)-hydroxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-((4R)-hydroxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (55.5 mg, 0.106 mmol) was dissolved in THF (1.0 ml). To the resulting solution was added 0.25N NaOH (1.0 ml), followed by stirring at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl (0.3 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C

under reduced pressure to give the title compound (39.3 mg, 73%) as a light brown solid.

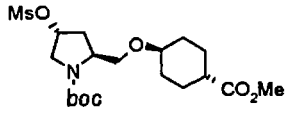
^{1}H-NMR (DMSO-d_6) δ: 0.98-1.39 (4H, m), 1.72-2.03 (6H, m), 2.11 (1H, m), 2.29 (3H, s, ArMe), 3.04-3.95 (8H, m), 4.09 (1H, m), 4.25, 4.32 (total 1H, m), 7.00-7.87 (total 8H, series of m, ArH, NH), 9.75 (1H, bs, CO_2H).

MS (ESI) m/z 508 (M^+ +1).

Example 123

trans-4-(1-((2-(2-Methylphenylamino)-6-benzoxazolyl)acetyl))-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(N-(tert-butoxycarbonyl)-(4R)-methanesulfonyloxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

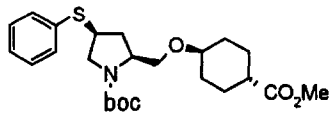


Methyl trans-4-(N-(tert-butoxycarbonyl)-(4R)-hydroxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (301.6 mg, 0.844 mmol) was dissolved in methylene chloride (6.0 ml). Under stirring at 0°C, triethylamine (0.47 ml, 3.375 mmol) and methanesulfonyl chloride (0.13 ml, 1.687 mmol) were added to the resulting solution. The reaction mixture was stirred at the same temperature for 2.5 hours. The reaction mixture was diluted with chloroform. The diluted mixture was washed with 1N HCl, dried over anhydrous sodium

sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, methyl trans-4-(N-(tert-butoxycarbonyl)-(4R)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (361.1 mg, 98%) was obtained as a colorless clear oil.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.27 (2H, m), 1.35-1.52 (10H, m, including 9H, s at δ: 1.45), 1.64 (1H, m), 1.90-2.05 (4H, m), 2.18-2.40 (3H, m), 3.01 (3H, s, $MeSO_3$), 3.17 (1H, m), 3.43-3.85 (total 7H, m, including 3H, s at δ: 3.64), 3.95-4.12 (1H, m), 5.25 (1H, m, MsOCH).

(Step 2) Synthesis of methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

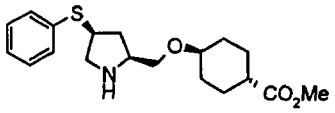


Cesium fluoride (125.9 mg, 0.829 mmol) was dried under reduced pressure at 180°C for 40 minutes. The reaction vessel was allowed to cool down to room temperature in a nitrogen gas stream. To the reaction mixture were added DMF (2.0 ml) and thiophenol (0.11 ml, 1.078 mmol). Under stirring at room temperature, a solution of methyl trans-4-(N-(tert-butoxycarbonyl)-(4R)-methanesulfonyl-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (361.1 mg, 0.829 mmol) in DMF (3.5 ml) was added dropwise. The reaction mixture was stirred further for 18 hours at 50°C and then, diluted with ethyl acetate. The diluted mixture was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (8:1, v/v) eluate fractions, methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (367.2 mg, 98%) was obtained as a colorless clear oil.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.32 (2H, m, CH_2), 1.35-1.56 (11H, m, including 9H, s at δ: 1.46), 1.93-2.10 (5H, m, CH_2, CH), 2.27 (1H, m, CH_2), 2.45 (1H, m, CH_2), 3.14-3.27 (2H, m), 3.44-3.79 (total 6H, m, including 3H, s at δ: 3.67), 3.81-4.07 (2H, m), 7.20-7.45 (total 5H, series of m, ArH).

(Step 3) Synthesis of methyl trans-4-((4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

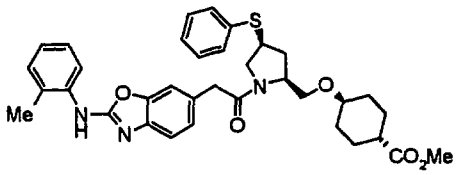


Methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (367.2 mg, 0.817 mmol) was dissolved in methylene chloride (7.0 ml). To the resulting solution was added trifluoroacetic acid (3.5 ml) under stirring at 0°C. The

reaction mixture was stirred further at room temperature for 1.5 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was diluted with chloroform, followed by washing with a saturated aqueous solution of sodium bicarbonate, drying over anhydrous sodium sulfate and distillation under reduced pressure to remove the solvent, whereby methyl trans-4-((4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (256.3 mg, 90%) was obtained. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.33 (2H, m), 1.35-1.55 (3H, m), 1.91-2.18 (5H, m, CH_2, CH, NH), 2.19-2.39 (2H, m), 2.95 (1H, dd, J=4.8, 11.6Hz, CH_2), 3.13-3.33 (3H, m), 3.38-3.54 (2H, m), 3.65 (3H, s, OMe), 3.68 (1H, m), 7.11-7.40 (total 5H, series of m, ArH).

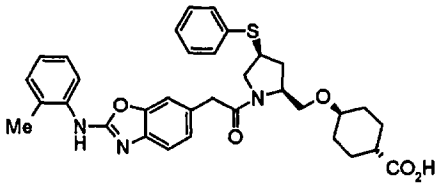
(Step 4) Synthesis of methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



Methyl trans-4-((4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (256.3 mg, 0.733 mmol), (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid

(207.0 mg, 0.733 mmol), and HOBt (19.8 mg, 0.147 mmol) were dissolved in DMF (9.0 ml). Under stirring at room temperature, EDC HCl (210.9 mg, 1.100 mmol) was added. The resulting mixture was stirred further at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with 1N HCl, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (15:1, v/v) eluate fractions, methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (quantitative yield) was obtained as a light brown amorphous substance. ^{1}H-NMR ($CDCl_3$) δ: 1.04-1.29 (2H, m), 1.30-1.51 (2H, m), 2.78-2.12 (5H, m), 2.19 (1H, m), 2.34 (3H, s, ArMe), 2.37 (1H, m), 3.12 (1H, m), 3.23 (1H, dd, J=10.0Hz), 3.49 (1H, m), 3.55-3.67 (6H, m, including 3H, s at δ: 3.61), 3.71 (1H, m), 3.88 (1H, m), 4.22 (1H, m), 6.95-7.10 (2H, m, ArH), 7.15-7.40 (9H, m, ArH), 7.90 (1H, d, J=8.0Hz, ArH), 7.99 (1H, s, NH).

(Step 5) Synthesis of trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (187.2 mg, 0.305 mmol) was dissolved in THF (4.0 ml). To the resulting solution was added 0.25N NaOH (4.0 ml), followed by stirring at room temperature for 2 days. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was acidified with 1N HCl (1.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (160.3 mg, 88%) as an amorphous substance.

IR (ATR) ν 1693, 1639, 1573, 1438 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ 1.00-1.21 (2H, m), 1.22-1.38 (2H, m), 1.75-1.97 (5H, m), 2.11 (1H. m), 2.30 (3H, s, ArMe), 2.42 (1H, m), 3.01-4.15 (total 9H, series of m), 7.01 (1H, d, J=8.0Hz, ArH), 7.08 (1H, dd, J=7.6Hz, ArH), 7.20-7.44 (9H, m, ArH), 7.79 (1H, d, J=8.0Hz, ArH), 9.62 (1H, br s).

MS (ESI) m/z 600 (M^+ +1);

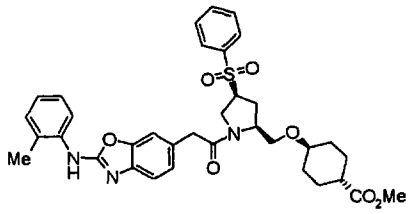
Anal. Calcd for $C_{34}H_{37}N_3O_5S$ $0.5H_2O$: C, 67.08; H, 6.29; N, 6.90; S, 5.27.

Found: C, 67.02; H, 6.05; N, 6.84; S, 5.29.

Example 124

trans-4-(1-((2-(2-Methylphenylamino)-6-benzoxazolyl)acetyl)- (4S)-phenylsulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-phenylsulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



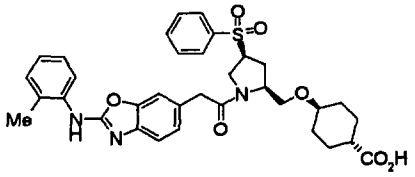
Methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (282.9 mg, 0.461 mmol) was dissolved in methylene chloride (6.0 ml). To the resulting solution was added m-chloroperbenzoic acid (198.9 mg, 1.152 mmol) under stirring at 0°C. The reaction mixture was stirred at the same temperature for 3.5 hours and at room temperature for 5 hours. The reaction mixture was diluted with chloroform-methanol (10:1, v/v). The diluted mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (15:1,

v/v) eluate fractions, methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazoly)acetyl)-(4S)-phenylsulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (quantitative yield) was obtained as a light brown amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 0.95-1.55 (4H, m), 1.70-2.50 (total 10H, series of m, including total 3H, s at δ: 2.34 and 2.37), 3.00-4.34 (total 12H, series of m, including 3H, s at δ: 3.63), 6.85-8.15 (total 13H, series of m, ArH, NH).

MS (ESI) m/z 646 (M^+ +1).

(Step 2) Synthesis of trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylsulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-phenylsulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (297.6 mg, 0.461 mmol) was dissolved in THF (6.0 ml). To the resulting solution was added 0.25N NaOH (6.0 ml), followed by stirring at room temperature for 18 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was acidified with 1N HCl

(1.7 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (268.4 mg, 92%) as an amorphous substance.

IR (ATR) ν 1695, 1639, 1575, 1446 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.97-1.22 (2H, m), 1.22-1.40 (2H, m), 1.73-1.98 (4H, m), 2.07-2.25 (3H, m), 2.30 (3H, s, ArMe), 3.03-4.45 (total 9H, series of m), 6.99 (1H, d, J=8.0Hz, ArH), 7.08 (1H, dd, J=7.2Hz, ArH), 7.24 (4H, m, ArH), 7.65-7.96 (total 6H, series of m, ArH), 9.64 (1H, br s).

MS (ESI) m/z 632 (M^+ +1);

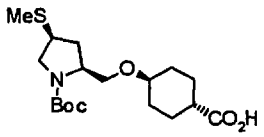
Anal. Calcd for $C_{34}H_{37}N_3O_7S$ 0.75H_2O: C, 63.29; H, 6.01; N, 6.51; S, 4.97.

Found: C, 63.15; H, 5.71; N, 6.33; S, 4.95.

Example 125

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid

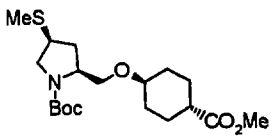


Methyl trans-4-(N-(tert-butoxycarbonyl)-(4R)-methanesulfonyloxy-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (95.3 mg, 0.219 mmol) was dissolved in DMF (2.0 ml). To the resulting solution was added sodium thiomethoxide (46.0 mg, 0.656 mmol) at room temperature under a nitrogen gas stream. After stirring for 18 hours at 60°C, the reaction mixture was cooled and then, diluted with ethyl acetate. The ethyl acetate solution was washed with 1N HCl, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:1, v/v) eluate fractions, trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (77.2 mg, 95%) was obtained as a clear oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.34 (2H, m), 1.37-1.55 (11H, m, including 9H, s at δ: 1.46), 1.91 (1H, m), 1.96-2.10 (4H, m), 2.13 (3H, s, SMe), 2.30 (1H, m), 2.38 (1H, m), 3.07-3.18 (2H, m), 3.23 (1H, m), 3.43-4.06 (total 4H, series of m).

(Step 2) Synthesis of methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

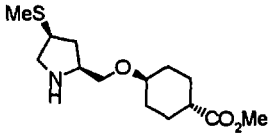


In benzene (5.0 ml) and methanol (0.5 ml) was

dissolved trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (77.2 mg, 0.207 mmol). Under stirring at 0°C, trimethylsilyldiazomethane (a 2M-hexane solution, 1 ml) was added and the resulting mixture was stirred at room temperature for 30 minutes. Acetic acid was added to the reaction mixture at 0°C. From the resulting mixture, the solvent was distilled off under reduced pressure, followed by dilution with ethyl acetate. The ethyl acetate solution was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (75.6 mg, 94%) was obtained as a pale yellow oil. The compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.32 (2H, m), 1.36-1.54 (11H, m, including 9H, s at δ: 1.46), 1.85-2.08 (5H, m), 2.13 (3H, s, SMe), 2.26 (1H, m), 2.38 (1H, m), 3.05-3.16 (2H, m), 3.21 (1H, m), 3.42-4.05 (total 7H, series of m, including 3H, s at δ: 3.66).

(Step 3) Synthesis of methyl trans-4-((4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



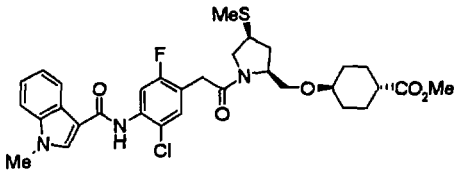
Methyl trans-4-(N-(tert-butoxycarbonyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (75.6 mg, 0.195 mmol) was dissolved in methylene chloride (4.0 ml). To the resulting solution was added trifluoroacetic acid (2.0 ml) at 0°C. The resulting mixture was stirred for 2.5 hours at room temperature. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was diluted with chloroform. The chloroform solution was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate was obtained as a pale yellow oil. The compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.52 (6H, m), 1.94-2.12 (7H, m, including 3H, s at δ: 2.10), 2.20-2.31 (2H, m), 2.90 (1H, dd, J=8.0, 14.0Hz), 3.11-3.32 (4H, m), 3.43 (1H, dd, J=6.2, 9.4Hz), 3.49 (1H, dd, J=5.0, 9.4Hz).

(Step 4) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-

(4S)-methylthio-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate

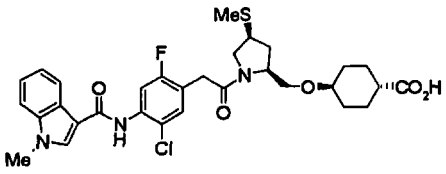


Methyl trans-4-((4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (161.6 mg, 0.562 mmol) was dissolved in DMF (7.0 ml). To the resulting solution were added (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (202.8 mg, 0.562 mmol), HOBt (15.2 mg, 0.112 mmol) and EDC HCl (161.7 mg, 0.843 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:2, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (328.8 mg, 93%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.33 (2H, m), 1.36-1.54 (2H, m), 1.90-2.11 (5H, m), 2.15 (3H, s, SMe), 2.17-2.59 (total 2H, series of m), 3.11-3.23 (2H, m), 3.30 (1H, dd, J=10.0Hz),

3.52-3.98 (total 11H, series of m, including 3H, s at δ: 3.62 and 3H, s at 3.89), 4.19-4.44 (total 1H, m), 7.30-7.46 (4H, m), 7.81 (1H, d, J=4.4Hz), 8.14 (1H, m), 8.30 (1H, s), 8.51 (1H, dd, J=10.8Hz).

(Step 5) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (146.6 mg, 0.234 mmol) was dissolved in THF (3.0 ml). To the resulting solution were added 0.25N NaOH (3.0 ml) and methanol (0.5 ml), followed by stirring at room temperature for .5 hour. The reaction mixture was concentrated under reduced pressure and the concentrate was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (135.0 mg, 94%) as a white amorphous substance.

IR (ATR) ν 2935, 1641, 1517 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.08-1.43 (4H, m), 1.76-2.05 (5H, m),

2.14 (3H, s, SMe), 2.16 (1H, m), 2.35 (1H, m), 3.09-3.47 (4H, m), 3.55-3.66 (2H, m), 3.71 (1H, s), 3.80-4.38 (total 5H, series of m, including 3H, s, at δ 3.89), 7.22 (1H, dd, J=7.2Hz), 7.28 (1H, dd, J=7.2Hz), 7.43 (1H, d, J=7.2Hz), 7.56 (1H, d, J=7.2Hz), 7.70 (1H, m), 8.15 (1H, d, J=7.2Hz), 8.31 (1H, s), 9.32 (1H, s).

MS(ESI) m/z 616 (M^++1);

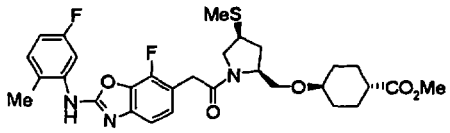
Anal. Calcd for $C_{31}H_{35}ClFN_3O_5S$ $0.5H_2O$: C, 59.56; H, 5.80; N, 6.72; Cl, 5.67; F, 3.04; S, 5.13.

Found: C, 59.39; H, 5.53; N, 6.78; Cl, 5.74; F, 2.99; S, 5.12.

Example 126

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

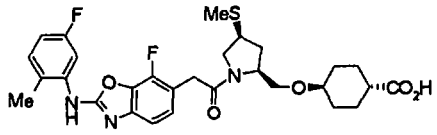


Methyl trans-4-((4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (169.4 mg, 0.589 mmol) was dissolved in DMF (7.0 ml). To the resulting solution were added (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (187.6 mg, 0.589 mmol),

HOBt (15.9 mg, 0.118 mmol) and EDC HCl (169.5 mg, 0.884 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:2, v/v) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (336.0 mg, 97%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.35 (2H, m), 1.36-1.55 (2H, m), 1.90-2.61 (total 13H, series of m, including 3H, s at δ: 2.15 and 3H, s at δ: 2.32), 3.13-3.25 (2H, m), 3.31 (1H, dd, J=9.6Hz), 3.54-3.80 (total 7H, series of m, including 3H, s at δ: 3.65), 3.87-4.00 (1H, m), 4.20-4.45 (total 1H, m), 6.75 (1H, m), 6.98 (1H, br s), 7.07-7.18 (2H, m), 7.24 (1H, m), 8.11 (1H, dd, J=2.8, 11.2Hz).

(Step 2) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (153.5 mg, 0.261 mmol) was dissolved in THF (3.0 ml). To the resulting solution was added 0.25N NaOH (3.0 ml). The resulting mixture was stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure and the concentrate was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (138.8 mg, 93%) as a white amorphous substance.

IR (ATR) ν 2935, 1639, 1577 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.05-1.43 (4H, m), 1.64-2.04 (5H, m), 2.13 (3H, s, SMe), 2.15 (1H, m), 2.30 (3H, s, ArMe), 2.33 (1H, m), 2.95-3.40 (3H, m), 3.54-3.82 (total 4H, series of m), 3.83-4.38 (total 2H, series of m), 6.90 (1H, m), 7.08 (1H, m), 7.21 (1H, dd, J=3.2,8.4Hz), 7.26 (1H, dd, J=7.6Hz), 7.93 (1H, dd, J=3.2,11.2Hz), 10.05 (1H, br s, NH), 12.05 (1H, br s, CO_2H).

MS(ESI) m/z 574 (M^++1);

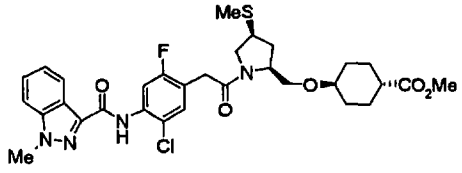
Anal. Calcd for $C_{29}H_{33}F_2N_3O_5S$ 0.5H_2O: C, 59.78; H, 5.88; N, 7.21; F, 6.52; S, 5.50.

Found: C, 59.89; H, 5.65; N, 7.21; F, 6.43; S, 5.44.

Example 127

trans-4-(1-((5-Chloro2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro 2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

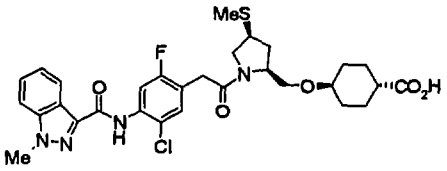


Methyl trans-4-((4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexylcarboxylate (163.2 mg, 0.568 mmol) was dissolved in DMF (7.0 ml). To the resulting solution were added (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (205.4 mg, 0.568 mmol), HOBt (15.3 mg, 0.114 mmol) and EDC HCl (163.3 mg, 0.852 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1:2, v/v) eluate

fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (348.7 mg, 97%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.33 (2H, m), 1.37-1.55 (2H, m), 1.92-2.11 (5H, m), 2.15 (3H, s, SMe), 2.25 (1H, m), 2.33-2.59 (total 1H, m), 3.12-3.36 (3H, m), 3.52-3.99 (total 8H, series of m, including 3H, s at δ: 3.62), 4.17 (3H, s), 4.19-4.45 (total 1H, m), 7.29-7.42 (2H, m), 7.45-7.54 (2H, m), 8.38 (1H, d, J=8.0Hz), 8.51 (1H, dd, J=12.0Hz), 9.50 (1H, s).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (154.7 mg, 0.245 mmol) was dissolved in THF (3.0 ml). To the resulting solution were added 0.25N NaOH (3.0 ml) and methanol (1.0 ml). The resulting mixture was stirred at

room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the concentrate was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (132.2 mg, 87%) as a white amorphous substance.

IR (ATR) ν 2937, 1621, 1529 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.07-1.42 (4H, m), 1.62-2.41 (total 10H, series of m, including 3H, s, at δ: 2.14), 2.95-3.47 (total 3H, series of m), 3.52-3.92 (total 4H, series of m), 4.00-4.39 (total 5H, series of m, including 3H, s, at δ: 4.22), 7.37 (1H, dd, J=7.6Hz), 7.49 (1H, d, J=7.6Hz), 7.54 (1H, dd, J=7.6Hz), 7.83 (1H, d, J=8.4Hz), 8.06 (1H, dd, J=6.4,11.2Hz), 8.21 (1H, d, J=8.4Hz), 9.73 (1H, s, NH), 12.05 (1H, br s, CO_2H).

MS(ESI) m/z 617 (M^++1);

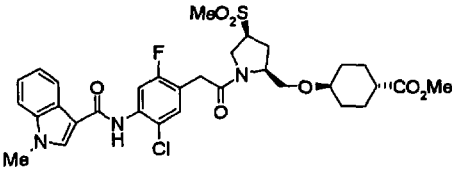
Anal. Calcd for $C_{30}H_{34}ClFN_4O_5S$ 0.5H_2O: C, 57.55; H, 5.63; N, 8.95; Cl, 5.66; F, 3.03; S, 5.12.

Found: C, 57.69; H, 5.43; N, 8.92; Cl, 5.67; F, 3.04; S, 5.18.

Example 128

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

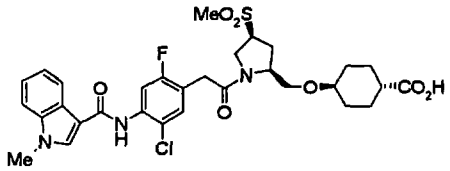
(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (182.2 mg, 0.289 mmol) was dissolved in methylene chloride (4.0 ml). To the resulting solution was added m-chloroperbenzoic acid (149.7 mg, 0.867 mmol) under stirring at 0°C. The stirring was conducted further at the same temperature for 2 hours. The reaction mixture was diluted with chloroform-methanol (10:1, v/v). The diluted mixture was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (159.1 mg, 83%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.34 (2H, m), 1.35-1.55 (2H, m), 1.88-2.14 (5H, m), 2.27 (1H, m), 2.42-2.67 (total 1H, m), 2.92 and 2.94 (total 3H, s, SO_2Me), 3.14-3.33 (2H, m), 3.44-3.95 (total 11H, series of m, including total 3H, s at δ: 3.62 and 3.67, and 3H, s at 3.90), 4.04-4.60 (total 2H, series of m), 7.30-7.47 (4H, m), 7.83 (1H, s), 8.13 (1H, m), 8.31 (1H, s), 8.53 (1H, dd, J=12.0Hz).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (159.1 mg, 0.240 mmol) was dissolved in THF (3.0 ml). To the resulting solution was added 0.25N NaOH (3.0 ml). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 35°C under reduced pressure for 3 days. The crude crystals were

purified by chromatography on silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, the title compound (107.4 mg, 69%) was obtained as a pale brown amorphous substance.

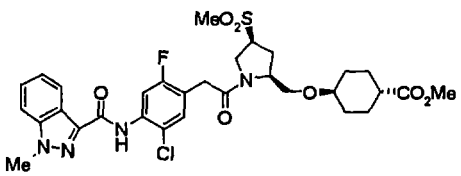
^{1}H-NMR (DMSO-d_6) δ: 1.07-1.45 (4H, m), 1.72-2.06 (5H, m), 2.06-2.49 (2H, m), 3.04 and 3.06 (total 3H, s, SO_2Me), 3.13-4.50 (total 12H, series of m, including 3H, s at δ: 3.89), 7.22 (1H, dd, J=7.6Hz), 7.28 (1H, dd, J=7.6Hz), 7.44 (1H, d, J=7.6Hz), 7.56 (1H, d, J=7.6Hz), 7.71 (1H, m), 8.15 (1H, d, J=7.6Hz), 8.31 (1H, s), 9.33 (1H, s, NH), 12.09 (1H, br s, CO_2H).

MS(ESI) m/z 648 (M^+ +1).

Example 129

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

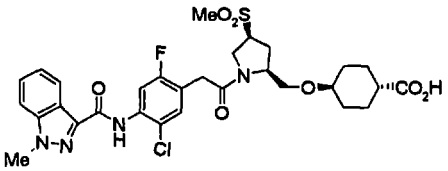


Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methylthio-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (194.0 mg, 0.307 mmol) was dissolved in methylene chloride (4.0 ml). Under stirring at 0°C, m-chloroperbenzoic acid (159.1 mg, 0.922 mmol) was added to the resulting solution. Stirring was conducted further at the same temperature for 3 hours. The reaction mixture was diluted with ethyl acetate. The ethyl acetate solution was washed successively with an aqueous solution of sodium sulfite and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (quantitative yield) was obtained as a white amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.33 (2H, m), 1.37-1.55 (2H, m), 1.92-2.13 (4H, m), 2.20-2.67 (total 3H, series of m), 2.92 and 2.95 (total 3H, s, SO_2Me), 3.25 (1H, m), 3.46-3.92 (total 9H, series of m, including total 3H, s at δ: 3.63 and 3.66), 4.14 (1H, m), 4.18 (3H, s, NMe), 4.39 and 4.55

(total 1H, m), 7.30-7.42 (2H, m), 7.42-7.54 (2H, m), 8.39 (1H, d, J=8.0Hz), 8.53 (1H, dd, J=12.4Hz), 9.51 (1H, s).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-methanesulfonyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (203.8 mg, 0.307 mmol) was dissolved in THF (4.0 ml). To the resulting solution were added 0.25N NaOH (4.0 ml) and methanol (0.5 ml). The resulting mixture was stirred at room temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure. After the residue was neutralized with 1N HCl, the mixture was diluted with water, followed by extraction with a chloroform-methanol (10:1, v/v) mixture. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, the title compound (quantitative yield) was obtained as a white amorphous substance.

IR (ATR) ν 2935, 1621, 1525 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.11-1.34 (2H, m), 1.38-1.57 (2H, m), 1.80-2.14 (5H, m), 2.30 (1H, m), 2.49 and 2.60 (total 1H, m), 2.92 and 2.95 (total 3H, s, SO_2Me), 3.25 (1H, m), 3.46-3.92 (6H, m), 4.06-4.60 (total 5H, series of m, including 3H, s at δ: 4.17), 7.29-7.42 (2H, m), 7.42-7.55 (2H, m), 8.38 (1H, d, J=8.0Hz), 8.53 (1H, dd, J=12.0Hz), 7.44 (1H, d, J=7.6Hz), 7.56 (1H, d, J=7.6Hz), 7.71 (1H, m), 8.15 (1H, d, J=7.6Hz), 9.51 (1H, s).

MS(ESI) m/z 649 (M^++1);

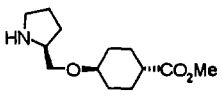
Anal. Calcd for $C_{30}H_{34}ClFN_4O_7S$ $0.5H_2O$ 1.5HCl: C, 50.55; H, 5.16; N, 7.86; Cl, 12.43; F, 2.67; S, 4.50.

Found: C, 50.53; H, 4.75; N, 7.62; Cl, 12.43; F, 2.62; S, 4.40.

Example 130

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



Methyl 4-((2S)-pyrrolidinylmethoxy)benzoate (2.0 g, 7.36 mmol) was dissolved in acetic acid-methanol (1:10, 55 ml). To the resulting solution was added rhodium/alumina

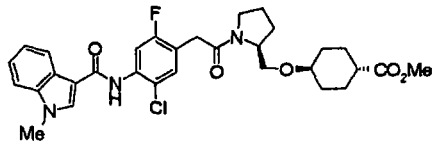
(1 g), followed by catalytic hydrogenation at room temperature under 3.8 atm for 15 hours. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent, whereby methyl 4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (1.71 g) was obtained as a colorless oil. The resulting compound was dissolved in acetonitrile-water (1:1, 40 ml). To the resulting solution were added triethylamine (1.5 ml, 10.6 mmol) and di-tert-butyl dicarbonate (1.7 g, 7.80 mmol) and the resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (300 ml). The diluted mixture was washed successively with 1N HCl (100 ml) and saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl 4-(1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (2.26 g) was obtained as a colorless oil. The resulting oil was dissolved in methanol (50 ml). To the resulting solution was added sodium methoxide (1.07 g, 19.9 mmol), followed by heating under reflux for 15 hours. The reaction mixture was cooled and poured in 1N HCl (100 ml), followed by extraction with chloroform (2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The oily residue was dissolved in

methanol/benzene (1:4, 60 ml) and under stirring at room temperature, (trimethylsilyl)diazomethane (a 2M-hexane solution) was added in portions to the resulting solution until the disappearance of carboxylic acid was confirmed by TLC. The resulting mixture was distilled under reduced pressure to remove the solvent to give a 1:1 cis-trans mixture of methyl 4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate as an oil. The resulting mixture was purified by flash column chromatography (Biotage) whereby from hexane-ethyl acetate (4:1) eluate fractions, the trans-isomer was obtained. The trans isomer was dissolved in trifluoroacetic acid (5 ml) and methylene chloride (5 ml). The mixture was stirred at room temperature for 15 minutes. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform (200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (504 mg) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.29 (m, 2H), 1.34-1.51 (m, 3H), 1.66-2.10 (series of m, 7H), 2.23-2.31 (m, 1H), 2.83-2.89 (m, 1H), 2.95-3.01 (m, 1H), 3.20-3.28 (m, 2H), 3.32-3.36 (m, 1H), 3.44-3.48 (m, 1H), 3.66 (s, 3H).

MS (ESI) m/z 242 (M^++1).

(Step 2) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



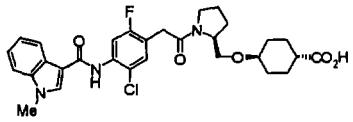
In DMF (10 ml), EDC·HCl (274 mg, 1.43 mmol), DMAP (catalytic amount), and HOBt (catalytic amount) were added to (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (344 mg, 0.953 mmol) and methyl trans-4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (230 mg, 0.953 mmol) and the resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (200 ml) and saturated brine (100 ml). The organic layer thus separated was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. From chloroform-ethyl acetate (4:1) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (556 mg, 100%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.12-2.32 (series of m, 13H), 3.15-4.25 (series of m, 14H), 7.32-7.44 (m, 4H), 7.81 (m, 1H), 8.14

(m, 1H), 8.29 (br s, 1H), 8.48-8.52 (m, 1H).

MS (ESI) m/z 584 (M^++1).

(Step 3) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid



To methyl 4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-pyrrolidinyl methoxy)-1-cyclohexanecarboxylate (556 mg, 0.953 mmol) were added THF (10 ml) and 0.25N NaOH (10 ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with chloroform-methanol (5:1, 2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. To the residue were added chloroform and hexane. The crystals thus precipitated were collected by filtration under reduced pressure and dried under reduced pressure to give the title compound (400 mg, 74%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.13-2.34 (series of m, 13H), 3.16-4.24 (series of m, total 11H), 7.32-7.44 (m, 4H), 7.81 (s, 1H), 8.11-8.14 (m, 1H), 8.29 (s, 1H), 8.46-8.51 (m, 1H).

MS (FAB) m/z 570 (M^++1);

Anal. Calcd for $C_{30}H_{33}ClN_3O_5$ 0.25 H_2O: C, 62.71; H, 5.88; N,

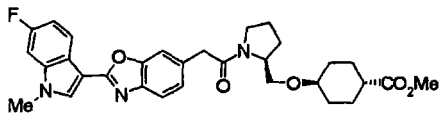
6.96.

Found: C, 62.55; H, 5.99; N, 6.96.

Example 131

trans-4-(1-((2-(6-Fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



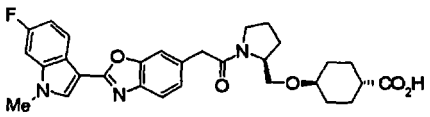
In DMF (10 ml), EDC HCl (177 mg, 0.926 mmol), DMAP (catalytic amount), and HOBt (catalytic amount) were added to (2-(6-fluoro-1-methyl-3-indolylcarbonylamino)-6-benzoxazoly)acetic acid (200 mg, 0.617 mmol) and methyl trans-4-((2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (149 mg, 0.617 mmol) and the resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (200 ml) and saturated brine (100 ml). The organic layer thus separated was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-

pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (338 mg, 100 %) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.11-1.48 (series of m, 4H), 1.86-2.06 (m, 8H), 2.18-2.35 (m, 1H) 3.16-4.27 (series of m, 14H), 7.05-7.24 (m, 3H), 7.50-7.52 (m, 1H), 7.62-7.67 (m, 1H), 7.90 (s, 1H), 8.38 (dd, J=8.8,5.4Hz, 1H).

MS (ESI) m/z 549 (M^++1).

(Step 2) Synthesis of trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid



To methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolylcarbonylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (338 mg, 0.617 mmol) were added THF (10 ml) and 0.25N NaOH (10 ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with chloroform-methanol (5:1, 2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, the title compound (202 mg, 49%) was obtained as a colorless

amorphous substance.

^{1}H-NMR (DMSO) δ: 1.07-1.35 (m, 4H), 1.83-1.93 (m, 8H), 2.13 (m, 1H), 3.12-4.21 (series of m, 11H), 7.14-7.22 (m, 2H), 7.51-7.54 (m, 2H), 7.63 (d, J=8.1Hz, 1H), 8.28-8.33 (m, 2H).

MS (FAB) m/z 534 (M^++1);

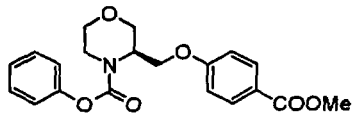
Anal. Calcd for $C_{30}H_{32}N_3O_5$ 0.5 H_2O: C, 66.41; H, 6.13; N, 7.74.

Found: C, 66.60; H, 6.23; N, 7.46.

Example 132

trans-4-(4-(5-Chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(3S)-morpholinylmethoxy)cyclohexanecarboxylic acid :

(Step 1) Synthesis of methyl 4-(4-N-benzyloxycarbonyl-(3S)-morpholinylmethoxy)benzoate



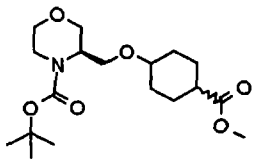
In THF (15 ml) were dissolved 4-N-benzyloxycarbonyl-(3S)-morpholinemethanol (1.42 g, 5.65 mmol), methyl 4-hydroxybenzoate (860 mg, 5.65 mmol), and triphenylphosphine (1.93 g, 7.35 mmol). To the resulting solution was added DIAD (1.44 ml, 7.35 mmol). The resulting mixture was heated under reflux for 18 hours. The reaction mixture was cooled to room temperature and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column (middle pressure chromatography system: YAMAZEN YFLC-5404-FC, chloroform, ϕ 37 mm x 300 mm, 12 ml/min) to give methyl 4-(4-N-benzyloxycarbonyl-(3S)-morpholinylmethoxy)benzoate (2.18 g, 100%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.20-4.40 (m, 9H), 3.88 (d, J=7.8Hz, 3H), 4.96 (m, 2H), 6.88 (d, J=8.8Hz, 2H), 7.54 (m, 5H), 7.90 (d, J=8.8Hz, 2H).

MS (ESI) m/z, 386 (M^++ 1).

(Step 2) Synthesis of methyl 4-(4-tert-butoxycarbonyl-(3S)-morpholinylmethoxy)cyclohexanecarboxylate

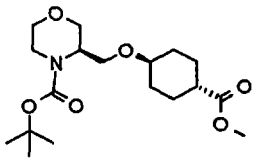


In methanol/trifluoroacetic acid (40 ml, 1:1) was dissolved methyl 4-(4-N-benzyloxycarbonyl-(3S)-morpholinylmethoxy)benzoate (2.18 g, 5.65 mmol). To the resulting solution was added 50% rhodium-alumina/carbon (1 g), followed by catalytic hydrogenation at room temperature for 48 hours under hydrogen of 5 atm. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. The residue was dissolved in THF (20 ml). Triethylamine (3.9 ml, 28.3 mmol) and di-tert-butyl dicarbonate (1.85 g, 8.5 mmol) were added and the resulting mixture was stirred

for 18 hours at room temperature. From the reaction mixture, the solvent was distilled off under reduced pressure. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column (middle pressure chromatography system: YAMAZEN YFLC-5404-FC) to give methyl 4-(4-tert-butoxycarbonyl-(3S)-morpholinylmethoxy)cyclohexanecarboxylate as a thick sticky liquid.

MS (ESI) m/z 252 (M^++ 1).

(Step 3) Synthesis of methyl trans-4-(4-tert-butoxycarbonyl-(3S)-morpholinylmethoxy)cyclohexanecarboxylate



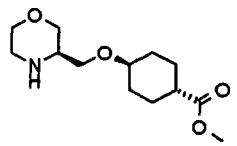
The cis- and trans- mixture of methyl 4-(4-tert-butoxycarbonyl-(3S)-morpholinylmethoxy)cyclohexanecarboxylate (450 mg, 1.21 mmol) prepared in the above-described step was separated by silica gel column chromatography (Biotage, flush chromatography No.2, 195-s, toluene/ethyl acetate, 9:1) to give methyl trans-4-(4-tert-butoxycarbonyl-(3S)-

morpholinylmethoxy)cyclohexanecarboxylate (45 mg, 10%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (m, 2H), 1.42 (m, 2H), 1.48 (s, 9H), 2.05 (m, 4H), 2.28 (m, 1H), 3.02 (m, 1H), 3.25 (m, 1H), 3.48 (m, 4H), 3.65 (s, 3H), 3.70 (t, J=9.1Hz, 1H), 3.83 (d, J=8.3Hz, 1H), 3.96 (d, J=11.3Hz, 2H).

MS (ESI) m/z 357 (M^++ 1).

(Step 4) Synthesis of methyl trans-4-((3S)-morpholinylmethoxy)cyclohexanecarboxylate



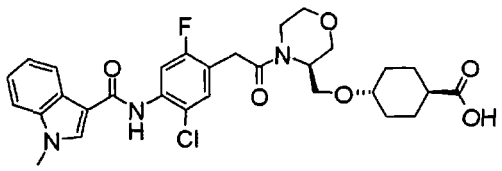
Methyl trans-4-(4-tert-butoxycarbonyl-(3S)-morpholinylmethoxy)cyclohexanecarboxylate (45 mg, 0.13 mmol) was dissolved in methylene chloride/trifluoroacetic acid (15 ml, 2:1). The resulting solution was stirred for 2 hours at room temperature. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate. After extraction with ethyl acetate, the extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent to give methyl trans-4-((3S)-morpholinylmethoxy)cyclohexanecarboxylate (29 mg, 91%) as a colorless oil.

^{1}H-NMR (DMSO) δ: 1.20 (m, 2H), 1.48 (AB type q, J=10.5Hz,

2H), 2.05 (m, 4H), 2.88 (m, 1H), 2.95 (m, 1H), 3.00 (m, 1H), 3.20 (m, 1H), 3.25 (m, 2H), 3.40 (dd, J=4.0,8.8Hz, 1H), 3.53 (dt, J=3.0,10.5Hz, 1H), 3.66 (s, 3H), 3.77 (dt, J=2.5,8.8Hz, 2H).

MS (ESI) m/z 258 $(M+1)^+$.

(Step 5) Synthesis of trans-4-(4-(5-chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(3S)-morpholinylmethoxy)cyclohexanecarboxylic acid



In DMF (2.5 ml), methyl trans-4-((3S)-morpholinylmethoxy)cyclohexanecarboxylate (29 mg, 0.11 mmol), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (41 mg, 0.1 mmol), EDC HCl (33 mg, 0.17 mmol), HOBt (29 mg, 0.21 mmol), and DMAP (catalytic amount) were stirred for 18 hours at room temperature. The resulting mixture was diluted with ethyl acetate (50 ml). The diluted mixture was washed with 1N HCl and saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure. To the residue were added THF (6 ml) and 0.25M NaOH (0.68 ml, 0.17 mmol) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl. The crystals thus precipitated were

collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (57 mg, 86%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ 1.20 (m, 3H), 1.35 (m, 3H), 1.92 (m, 3H), 2.18 (m, 1H), 2.90 (m, 1H), 3.52 (m, 2H), 3.50-3.85 (m, 7H), 3.88 (s, 3H), 4.05 and 4.30 (2m, total, 2H), 7.22 (t, J=7.0Hz, 1H), 7.28 (t, J=7.5Hz, 1H), 7.40 (dd, J=7.8Hz, 19.1Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 7.70 (dd, J=5.8Hz, 10.7Hz, 1H), 8.15 (d, J=8.6Hz, 1H), 8.31 (s, 1H), 9.31 (s, 1H).

MS (ESI) m/z 587 $(M+1)^+$;

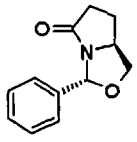
Anal. Calcd for $C_{30}H_{33}ClFN_3O_6$: C, 61.48; H, 5.68; N, 7.17.

Found: C, 61.06; H, 5.73; N, 6.88.

Example 133

trans-4-(1-(5-Chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

(Step 1) Synthesis of (2R,5S)-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one



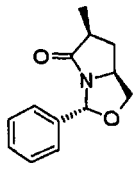
In toluene (500 ml), (5S)-hydroxymethylpyrrolidin-2-one (72 g, 0.63 mol), benzaldehyde (79.6 g, 0.75 mol) and p-toluenesulfonic acid (1.6 g, 9.4 mmol) were heated under reflux for 48 hours by using a Dean-Stark water separator.

After the reaction mixture was cooled to room temperature, water (300 ml) was added thereto, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was distilled under reduced pressure to give (2R,5S)-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (71 g, 56%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.95 (m, 1H), 2.30 (m, 1H), 2.58 (m, 1H), 2.80 (m, 1H), 3.48 (t, J=8.0Hz, 1H), 4.15 (m, 1H), 4.24 (m, 1H), 6.32 (s, 1H), 7.32 (m, 3H), 7.40 (m, 2H).

MS (ESI) m/z 204 $(M+1)^+$.

(Step 2) Synthesis of (2R,5S,7S)-7-methyl-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one



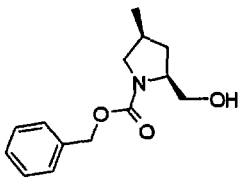
To a solution of (2R,5S)-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (5.08 g, 25 mmol) in THF (30 ml), lithium diisopropylamide (a 2.0M solution in THF, 13.1 ml, 26.3 mmol) was added dropwise at -78°C under stirring. After the reaction mixture was stirred at the same temperature for 15 minutes, methyl iodide (7.78 ml, 125 mmol) was added thereto and stirring was conducted further

for 30 minutes at -40°C. The reaction mixture was poured in an ice - saturated aqueous solution of ammonium chloride, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate form 4:1 to 1:1, 30 ml/min, ϕ 50 mm x 300 mm, range 0.32) to give (2R,5S,7S)-7-methyl-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (3.8 g, 70%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.23 (d, J=7.3Hz, 3H), 1.54 (m, 1H, 3-H), 2.62 (m, 1H), 2.95 (m, 1H, 4-H), 3.52 (t, J=7.5Hz, 1H), 4.09 (t, J=7.5Hz, 1H, 2-H), 4.22 (dd, J=6.5,8.0Hz), 6.33 (s, 1H), 7.32 (m, 3H), 7.46 (m, 2H).

MS (ESI) m/z 218 $(M+1)^+$.

(Step 3) Synthesis of 1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethanol



Lithium aluminum hydride (1.05 g, 26.2 mmol) was suspended in THF (10 ml). To the resulting suspension, a solution of (2R,5S,7S)-7-methyl-2-phenyl-3-oxa-1-

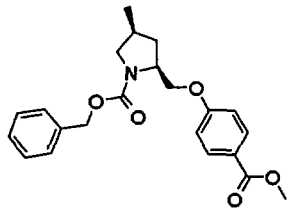
azabicyclo(3.3.0)octan-8-one (3.79 g, 17.5 mmol) in THF (30 ml) was added dropwise under stirring at 60°C. After completion of the dropwise addition, the reaction mixture was heated under reflux for 1 hour. The reaction mixture was cooled to room temperature and then, poured in sodium thiosulfate (6.5 g, 26.2 mmol) and ice (500 cm^3), followed by extraction with ethyl acetate (500 ml). The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. Ethanol/acetic acid (45 ml, 1:2) and 10% palladium carbon (400 mg) were added to the residue and the resulting mixture was subjected to catalytic reduction for 24 hours under a hydrogen gas of 3.5 atm. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. Toluene was added to the residue to azeotropically remove water. To the residue were added THF/water (4:1, 35 ml) and potassium carbonate (2.54 g, 18.4 mmol). Benzyloxycarbonyl chloride (a 30-35% toluene solution, 10.2 ml, 17.9 mmol) was added dropwise while stirring the resulting mixture at 0°C. After completion of the dropwise addition, the reaction mixture was stirred further for 30 minutes at the same temperature. The reaction mixture was poured in a cooled solution of ethyl acetate and a saturated aqueous solution of ammonium chloride and the mixed solution was extracted with ethyl

acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate form 4:1 to 7:3, 30 ml/min, ϕ 50 mm x 150 mm, range 0.32) to give 1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethanol (2.46 g, 56%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (d, J=6.1Hz, 3H), 1.12 (AB type q, J=12.5Hz, 4-H), 1.70 (br, 1H), 2.18 (m, 2H), 2.82 (t, J=10.5Hz), 3.63 (dd, J=7.4Hz,11.8Hz, 1H), 3.72 (m, 1H), 3.79 (t, J=8.5Hz), 3.98 (m, 1H), 5.14 (s, 2H), 7.36 (m, 5H).

MS (ESI) m/z 250 $(M+1)^+$.

(Step 4) Synthesis of methyl 4-(1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate



In methylene chloride (40 ml) were dissolved 1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethanol (2. 06 g, 8.26 mmol) and triethylamine (3.45 ml, 24.8 mmol). Under stirring at 0°C, methanesulfonyl chloride (1.15 ml, 14.9 mmol) was added dropwise to the resulting

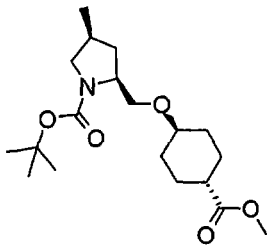
solution. The reaction mixture was diluted with ethyl acetate and the diluted mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. To the residue were added DMF (40 ml), potassium carbonate (1.71 g, 12.4 mmol) and methyl 4-hydroxybanzoate (3.77 g, 24.8 mmol). The resulting mixture was stirred at 100°C for 2 hours. The reaction mixture was cooled to room temperature, and ether and water were added thereto, followed by extraction with ether. The extract was washed with 1M NaOH (3 times) and saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography, whereby from n-hexane/ethyl acetate (9:1 to 7:3) eluate fractions, 4-(1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate (2.27 g, 72%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.08 (m, 3H), 1.61 (m, 1H), 2.20 (m, 1H), 2.31 (m, 1H), 2.88 (t, J=10.2Hz, 1H), 3.80-4.00 (m, 2H), 3.89 (s, 3H), 4.20 (m, 2H), 5.12 (m, 2H), 6.78 and 6.92 (d, J=8.1Hz, total 2H), 7.32 (m, 5H), 7.90 and 7.92 (d, J=7.8Hz, total 2H).

MS (ESI) m/z 384 $(M+1)^+$.

(Step 5) Synthesis of methyl trans-4-(1-N-tert-

butoxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



To methyl 4-(1-N-benzyloxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate (2.27 g, 5.92 mmol) and 5% palladium carbon (389 mg) was added methanol/acetic acid (30 ml, 10:1) and the resulting mixture was subjected to catalytic reduction at room temperature under a hydrogen gas of 2 atm for 18 hours. From the reaction mixture, the catalyst was filtered off. To the filtrate were added acetic acid (10 ml) and rhodium-alumina (700 mg) and catalytic hydrogenation was effected at room temperature under a hydrogen gas of 4 atm for 24 hours. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. To the residue were added methylene chloride (30 ml), triethylamine (2.48 ml, 17.8 mmol) and di-tert-butyl dicarbonate (1.94 g, 8.89 mmol). The resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture was added 15% citric acid, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue

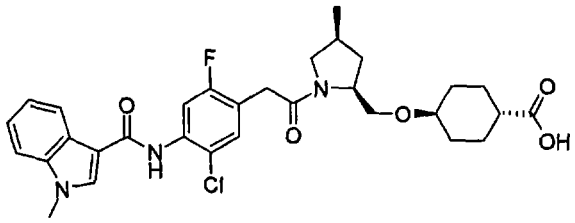
was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate form 9:1 to 1:1). To the purified product were added ethanol (50 ml) and sodium ethoxide (3.02 ml, 8.9 mmol) and the mixture was heated under reflux for 18 hours. The reaction mixture was basified with 1M NaOH. The reaction mixture was heated under reflux further for 3 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 15% citric acid, followed by extraction with a chloroform/methanol mixture. The extract was dried over sodium sulfate and distilled under reduced pressure to remove the solvent. To the residue were added THF/DMF (30 ml, 2:1), ethyl iodide (2.4 ml, 29.5 mmol) and DBU (1.33 ml, 8.8 mmol) and the resulting mixture was stirred for 18 hours. To the reaction mixture was added 15% citric acid, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (Biotage, KP-SIL, 32-63 m, 1000 g, n-hexane/ethyl acetate 9:1) to give methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (404 mg, 19%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.03 (d, J=6.6Hz, 3H), 1.25 (t, J=7.3Hz,

3H), 1.25-1.70 (m, 6H), 1.46 (s, 9H), 1.82 (m, 3H), 2.10 (m, 1H), 2.20 (m, 1H), 2.32 (m, 1H), 2.70 (t, J=10.0Hz, 1H), 3.35-3.90 (m, 4H), 3.62 (dd, J=3.0,9.0Hz, 1H), 4.12 (q, J=7.3Hz, 2H).

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

(Step 6) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (147 mg, 0.397 mmol) were added methylene chloride (15 ml) and trifluoroacetic acid (15 ml). The resulting mixture was stirred at room temperature for 1 hour. From the reaction mixture, the solvent was distilled off under reduced pressure. To the residue was added chloroform/a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (5 ml) and (5-chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (143 mg, 0.397 mmol), HOBt (102 mg, 0.75 mmol), DMAP (catalytic amount)

and EDC·HCl salt (114 mg, 0.6 mmol) were added to the solution. The mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine and dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography using silica gel (middle pressure Yamazen, chloroform, 10 ml/min, ϕ 15 mm x 300 mm). To the purified product were added THF (6 ml) and 0.25M NaOH (3.6 ml, 0.9 mmol) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was poured in water. The solution was acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (110 mg, 48%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.12 (d, J=5.5Hz, 3H), 1.10-1.50 (m, 6H), 1.85-2.15 (m, 6H), 2.60 (m, 1H), 2.90 (t, J=10.5Hz, 1H), 3.12 (m, 1H), 3.50-4.20 (m, 5H), 2.90 (s, 3H), 7.21 (t, J=7.5Hz, 1H), 7.29 (t, J=7.5Hz, 1H), 7.42 (d, J=7.5Hz, 1H), 7.57 (d, J=8.1Hz, 1H), 7.70 (m, 1H), 8.16 (d, J=7.8Hz, 1H), 8.32 (s, 1H).

MS (ESI) m/z 585 $(M+1)^+$;

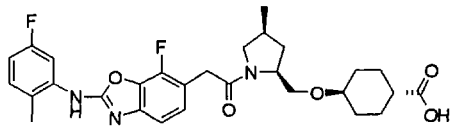
Anal. Calcd for $C_{31}H_{35}ClFN_3O_5 \cdot 0.5\ H_2O$: C, 62.78; H, 6.12; N, 7.08.

Found: C, 62.58; H, 5.98; N, 7.35.

Example 134

trans-4-(1-(7-Fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans4-(1-(7-fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (147 mg, 0.397 mmol) were added methylene chloride (15 ml) and trifluoroacetic acid (15 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added chloroform/a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (5 ml) and to the resulting solution, 7-fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetic acid (126 mg, 0.397 mmol), HOBt (102 mg, 0.75 mmol), DMAP (catalytic

amount) and EDC·HCl salt (114 mg, 0.6 mmol) were added. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform, 10 ml/min, ϕ 15 mm x 300 mm). To the purified product were added THF (6 ml) and 0.25M NaOH (3.6 ml, 0.9 mmol) and the mixture was stirred for 18 hours at room temperature. The reaction mixture was poured in water. The solution was acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (129 mg, 60%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.01 (d, J=6.0Hz, 3H), 1.05-1.50 (m, 6H), 1.80-2.20 (m, 6H), 2.30 (s, 3H), 2.50 (m, 1H), 2.95 (t, J=9.8Hz, 1H), 3.12 (m, 1H), 3.40-3.60 (m, 3H), 5.71 (s, 1H), 5.80-4.00 (m, 1H), 6.90 (dt, J=2.5,8.3Hz, 1H), 7.06 (d, J=7.8Hz, 1H), 7.20 (d, J=8.0Hz, 1H), 7.26 (t, J=7.5Hz, 1H), 7.92 (dd, J=2.5,11.3Hz, 1H).

MS (ESI) m/z 542 $(M+1)^+$;

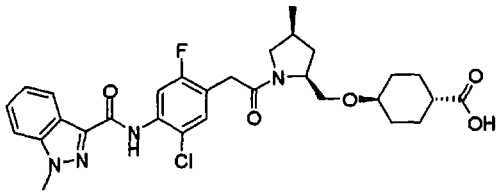
Anal. Calcd for $C_{29}H_{33}F_2N_3O_5 \cdot 0.5\ H_2O$: C, 63.26; H, 6.32; N, 7.63.

Found: C, 63.34; H, 6.17; N, 7.64.

Example 135

trans-4-(1-(5-Chloro-2-fluoro-4-((1-methyl-1H-3-indazolylcarbonyl)amino)phenylacetyl)(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((1-methyl-1H-3-indazolylcarbonyl)amino)phenylacetyl)(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (147 mg, 0.397 mmol) were added methylene chloride (15 ml) and trifluoroacetic acid (15 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added chloroform/a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (5 ml). To the resulting solution were added (2-fluoro-5-chloro-4-((1-methyl-1H-3-indazolylcarbonyl)amino)phenyl)acetic acid (144 mg, 0.397

mmol), HOBt (102 mg, 0.75 mmol), DMAP (catalytic amount) and EDC·HCl (114 mg, 0.6 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform, 10 ml/min, ϕ 15 mm x 300 mm). To the purified product were added THF (6 ml) and 0.25M NaOH (3.6 ml, 0.9 mmol) and mixture was stirred for 18 hours at room temperature. The reaction mixture was poured in water and the solution was acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (89 mg, 38%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.03 (d, J=6.1Hz, 3H), 1.10-1.50 (m, 6H), 1.83-2.20 (m, 6H), 2.50 (m, 1H), 2.90 (t, J=9.5Hz, 1H), 3.13 (m, 1H), 3.50-4.05 (m, 5H), 4.21 (s, 3H), 7.39 (t, J=7.5Hz, 1H), 7.48 (d, J=7.5Hz, 1H), 7.54 (t, J=7.5Hz, 1H), 7.82 (d, J=8.6Hz, 1H), 8.08 (d, J=7.5Hz, 1H), 8.21 (d, J=8.3Hz, 1H).

MS (ESI) m/z 586 $(M+1)^+$;

Anal. Calcd for $C_{30}H_{34}ClFN_4O_5 \cdot 0.75\ H_2O$: C, 60.20; H, 5.98; N,

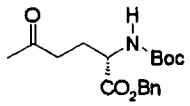
9.36.

Found: C, 60.49; H, 5.99; N, 9.10.

Example 136

trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

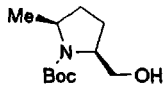
(Step 1) Synthesis of benzyl (2S)-N-tert-butoxycarbonylamino-5-oxohexanoate



Benzyl N-tert-butoxycarbonyl-(2S)-pyroglutamate (20.5 g, 64.2 mmol) was dissolved in THF (500 ml). Methyl lithium (a 1.04M ether solution, 61.7 ml, 64.2 mmol) was added dropwise at -78°C. The temperature of the reaction mixture was caused to rise back gradually to room temperature under stirring, and the resulting mixture was stirred for 18 hours. A saturated aqueous solution of ammonium chloride was added and the resulting mixture was concentrated under reduced pressure. The concentrate was extracted with ether. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (3/1) eluate fractions, benzyl (2S)-N-tert-butoxycarbonylamino-5-oxohexanoate (8.37 g, 39%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.43 (s, 9H), 1.61-2.15 (series of m, 3H), 2.09 (s, 3H), 2.41-2.55 (m, 2H), 4.30 (brs, 1H), 4.70 (d, J=5.6Hz, 1H), 5.12-5.21 (m, 2H), 7.29-7.37 (m, 5H); MS (ESI) m/z 336 (M^++H).

(Step 2) Synthesis of N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethanol

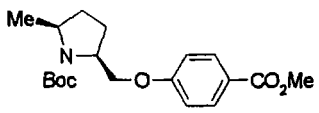


To (2S)-N-tert-butoxycarbonylamino-5-oxohexanoate (7.61 g, 22.7 mmol) were added methylene chloride (50 ml) and trifluoroacetic acid (20 ml). The mixture was stirred at room temperature for 1 hour. The reaction mixture was distilled under reduced pressure to remove the solvent. Toluene was added to the residue to azeotropically remove excessive trifluoroacetic acid under reduced pressure. To the residue were added 10%-palladium/carbon (500 mg) and methanol (100 ml) to conduct catalytic reduction at room temperature under normal pressure. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent to obtain a brown oil. To the resulting oil were added di-tert-butyl dicarbonate (7.43 g, 34.0 mmol), methanol/water (6/1, 140 ml) and 1N NaOH (56.7 ml, 56.7 mmol). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, followed by extraction with a

chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (1/3) eluate fractions, an oil was obtained. The oil was dissolved in THF (100 ml) and under stirring at room temperature, borane-dimethyl sulfide (an about 10M solution, 4.54 ml, 45.4 mmol) was added. The resulting mixture was stirred at 60°C for 1 hour. After cooling, ice water and 1N HCl were added, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (1/1) eluate fractions, N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethanol (2.03 g, total 42%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, J=6.0Hz, 3H), 1.48 (s, 9H), 1.48-1.64 (m, 2H), 1.90-2.11 (m, 2H), 3.52-3.57 (m, 1H), 3.68-3.70 (m, 1H), 3.94-4.13 (m, 2H).

(Step 3) Synthesis of methyl 4-(N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate

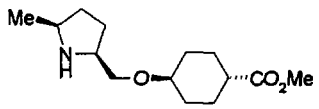


In THF (50 ml were dissolved N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethanol (2.02 g, 9.38 mmol), triphenylphosphine (2.95 g, 11.3 mmol) and methyl 4-hydroxybenzoate (1.43 g, 9.38 mmol). To the resulting solution was added diisopropyl azodicarboxylate (2.14 ml, 10.3 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (3/1) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate (3.27 g, 100 %) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24 (brs, 3H), 1.49 (s, 9H), 1.55-1.70 (m, 2H), 1.94-2.11 (m, 2H), 3.88 (s, 3H), 3.88 (overlap, 1H), 4.06-4.20 (m, 2H), 6.93-6.96 (m, 2H), 7.97 (d, J=8.8Hz, 2H).

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

(Step 4) Synthesis of methyl trans-4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



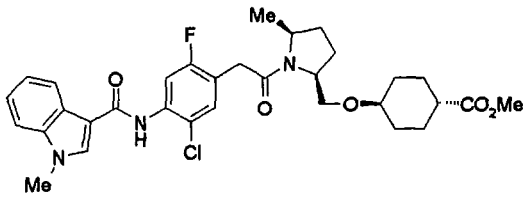
In methanol/acetic acid (10/1, 55 ml), methyl 4-(N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethoxy)benzoate (3.27 g, 9.34 mmol) and 5%

rhodium-alumina (0.52 g) were stirred at room temperature for 18 hours under a hydrogen gas of 20 atm. From the reaction mixture, the catalyst was filtered off and then, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (3/1) eluate fractions, methyl 4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.74 g, 52%) was obtained as a colorless oil. Under a nitrogen gas stream, methyl 4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.73 g, 4.87 mmol) was dissolved in methanol (50 ml). To the resulting solution was added sodium methoxide (800 mg, 14.6 mmol) and the mixture was stirred for 24 hours. After cooling, 1N HCl was added and the resulting mixture was concentrated under reduced pressure. The concentrate was extracted with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in benzene/methanol (5/1, 30 ml). Under stirring at 0°C, trimethylsilyldiazomethane (a 2.0M hexane solution) was added dropwise to the solution. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was then distilled under reduced pressure to remove the solvent, and the residue was purified by flash column

chromatography using silica gel, whereby from hexane/ethyl acetate (8/1) eluate fractions, methyl trans-4-(N-tert-butoxycarbonyl-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (700 mg, 40%) was obtained as an oil. The product was dissolved into methylene chloride (30 ml), and trifluoroacetic acid (10 ml) was added to the resulting solution. The mixture was stirred at room temperature for 7 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. To the residue was added a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform/methanol (10/1). The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give methyl trans-4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (502 mg, 100 %) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, J=6.0Hz, 3H), 1.94-1.33 (m, 3H), 1.41-1.54 (m, 3H), 1.76-1.90 (m, 2H), 1.98-2.08 (m, 3H), 2.22-2.29 (m, 3H), 3.14-3.30 (m, 3H), 3.39 (dd, J=6.4, 9.2Hz, 1H), 3.52 (dd, J=4.4,9.6Hz, 1H), 3.66 (s, 3H).

(Step 5) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

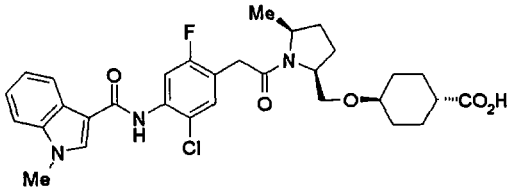


In DMF (10 ml), HOBt (21.0 mg, 0.16 mmol) was added to (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (283 mg, 0.78 mmol), methyl trans-4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexylcarboxylate (205 mg, 0.78 mmol) and EDC-HCl (165 mg, 0.86 mmol) and the resulting mixture was stirred for cyclohexylcarbon 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate, whereby from hexane/ethyl acetate (1/5) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (404 mg, 86%) was obtained as a colorless amorphous substance. ^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.20-1.34 (m, overlap, 2H), 1.29 and 1.33 (d, J=6.4Hz, total 3H), 1.42-2.31 (series of m, 11H), 3.23-3.27 (m, 1H), 3.44-3.51 (m, 1H), 3.66-3.83 (m, 3H), 3.66 and 3.68 (s, total 3H), 4.14 (brs, 2H), 7.35-7.37 (m, 2H), 7.42-7.44 (m, 2H), 7.82 (s,

1H), 8.13-8.16 (m, 1H), 8.30 (s, 1H), 8.49 and 8.52 (d, J=4.8Hz, total 1H).

MS (ESI) m/z 598 (M^++1).

(Step 6) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (388 mg, 0.65 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (7.80 ml, 1.95 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (389 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ 1.15-1.27 (m,

overlap, 2H), 1.22 and 1.26 (d, J=6.0Hz, total 3H), 1.37-2.30 (series of m, 11H), 3.16-3.22 (m, 1H), 3.35-3.45 (m, 1H), 3.52-3.79 (m, 3H), 3.82 (s, 3H), 4.09 (brs, 2H), 7.26-7.31 (m, 2H), 7.34-7.37 (m, 2H), 7.75 (s, 1H), 8.05-8.08 (m, 1H), 8.23 (s, 1H), 8.41 and 8.44 (d, J=5.6Hz, total 1H).

MS (ESI) m/z 584 (M^++1);

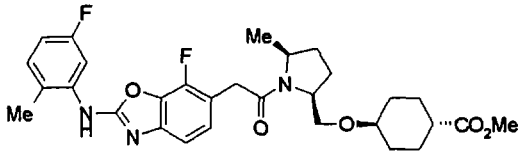
Anal. calcd for $C_{31}H_{35}ClFN_3O_5 \cdot 1/4H_2O$: C, 63.26; H, 6.08; N, 7.14.

Found : C, 63.33; H, 6.18; N, 7.14.

Example 137

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

(Step 1) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



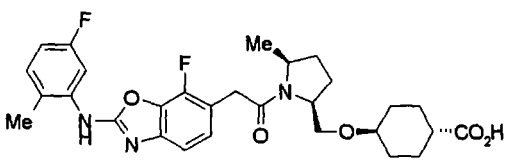
In DMF (10 ml) were dissolved (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (182 mg, 0.57 mmol), methyl trans-4-((5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexylcarboxylate (146 mg, 0.57 mmol) and EDC-HCl (121 mg, 0.63 mmol). To the resulting solution was added HOBt (15.0 mg, 0.11 mmol), and the

resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC), whereby from hexane-ethyl acetate (1/5) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (276 mg, 87%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.22-2.24 (series of m, 13H), 1.31 and 1.33 (d, J=6.4Hz, total 3H), 3.20-3.29 (m, 1H), 3.43-3.52 (m, 1H), 3.63-3.83 (series of m, 3H), 3.67 and 3.68 (s, total 3H), 3.89 (s, 1H), 4.17 (brs, 2H), 6.74-6.78 (m, 1H), 7.10-7.17 (m, 2H), 7.23 and 7.26 (d, J=2.0Hz, total 1H), 8.09 and 8.12 (d, J=4.0Hz, total 1H).

MS (ESI) m/z 556 (M^++2).

(Step 2) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-

7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (264 mg, 0.48 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (5.70 ml, 1.43 mmol) and the mixture was stirred at room temperature for 17 hours. The reaction mixture was poured in 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (173 mg, 67%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.14-2.25 (series of m, 13H), 1.31 and 1.33 (d, J=6.4Hz, total 3H), 3.15-3.21 (m, 1H), 3.35-3.44 (m, 1H), 3.58-3.75 (series of m, 3H), 3.82 (s, 1H), 4.10 (brs, 2H), 6.68-6.72 (m, 1H), 7.03-7.14 (m, 3H), 7.80-7.83 (m, 1H).

MS (ESI) m/z 542 (M^++1);

Anal. calcd. for $C_{29}H_{33}ClF_2N_3O_5$: C, 64.31; H, 6.14; N, 7.76.

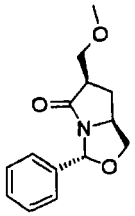
Found : C, 64.02; H, 6.25; N, 7.52.

Example 138

trans-4-(1-(5-Chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid

(Step 1) Synthesis of (2R,5S,7S)-7-methoxymethyl-2-phenyl-

3-oxa-1-azabicyclo(3.3.0)octan-8-one



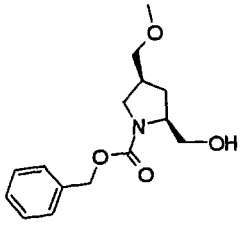
To a solution of lithium diisopropylamide (110 mmol, 100 ml of THF, prepared from diisopropylamine (15.6 ml, 110 mmol) and n-butyl lithium (70.1 ml, 1.57M, 110 mmol)) was added (2R,5S)-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (10.2 g, 50 mmol) under stirring at -78°C. After stirring at the same temperature for 1 hour, a solution of chloromethyl methyl ether (5.7 ml, 75 mmol) in THF (50 ml) was added to the reaction mixture and stirring was conducted further at -78°C for 90 minutes. The reaction mixture was poured in a saturated aqueous solution of ammonium chloride, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate from 9:1 to 7:3, 30 ml/min, ϕ 80 mm x 300 mm, range 0.08) to give (2R,5S,7S)-7-methoxymethyl-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (1.06 g, 9%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.94 (m, 1H, H-6), 2.52 (m, 1H, H-6), 3.09

(m, 1H, H-7), 3.38 (s, 3H, OMe), 3.53 (t, J=8.1Hz, 1H, H-4), 3.58 (dd, J=4.0,9.5Hz, 1H, CH_2OMe), 3.67 (dd, J=5.4Hz, 9.4Hz, 1H, CH_2OMe), 4.08 (m, 1H, H-5), 4.22 (AB type d, J=6.4Hz, 1H, H-4), 6.30 (s, 1H, H-2), 7.32 (m, 3H, Ph), 7.43 (d, J=6.6Hz,2H, Ph).

MS (ESI) m/z 248 $(M+1)^+$.

(Step 2) Synthesis of 1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethanol



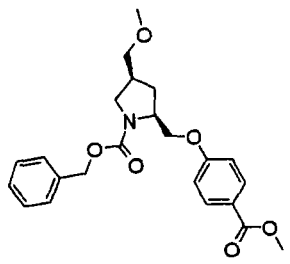
Lithium aluminum hydride (0.56 ml, 12.8 mmol) was suspended in THF (7 ml). To the resulting suspension was added a solution of (2R,5S,7S)-7-methoxymethyl-2-phenyl-3-oxa-1-azabicyclo(3.3.0)octan-8-one (2.11 g, 8.5 mmol) in THF (10 ml) under stirring at 60°C. The reaction mixture was heated under reflux for 1 hour. The reaction mixture was cooled and sodium thiosulfate (6.5 g, 26.2 mmol) and water (10 ml) were added thereto. The reaction mixture was filtered through Celite under reduced pressure. From the filtrate, the solvent was distilled off under reduced pressure. To the residue were added ethanol (10 ml), acetic acid (20 ml) and palladium·carbon and the resulting mixture was subjected to catalytic hydrogenation under normal pressure for 3 days. The reaction mixture was

filtered to remove the catalyst and then the solvent was removed from the filtrate under reduced pressure. To the residue were added THF/water (4:1, 20 ml) and potassium carbonate (2.35 g, 17 mmol). Under stirring of the mixture at 0°C, benzyloxycarbonyl chloride (a 30 to 35% toluene solution, 9.7 ml, 17 mmol) was added. The reaction mixture was stirred further at room temperature for 24 hours. The reaction mixture was poured in ethyl acetate and a saturated aqueous solution of ammonium chloride, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate from 4:1 to 1:9, 30 ml/min, ϕ 50 mm x 150 mm, range 0.32) to give 1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethanol (1.61 g, 69%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 3.01 (m, 1H, 3-H), 2.18 (m, 1H, 3-H), 2.40 (m, 1H, 4-H), 3.08 (t, J=10.5Hz, 1H, 5-H), 3.30 (m, 1H, CH_2OMe), 3.31 (s, 3H, OMe), 3.38 (dd, J=4.5,9.1Hz, 1H, CH_2OMe), 3.62 (dd, J=7.2,11.7Hz, 1H, CH_2OH), 3.70 (m, 1H, CH_2OH), 3.81 (t, J=9.0Hz, 1H, 5-H), 4.00 (m, 1H, 2-H), 4.88 (br, 1H, OH), 5.12 (AB type d, J=13.0Hz, 2H), 7.35 (m, 5H, Ph).

MS (ESI) m/z 280 $(M+1)^+$.

(Step 3) Synthesis of methyl 4-(1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate



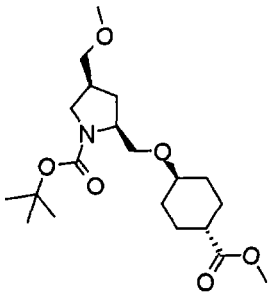
In methylene chloride (20 ml) were dissolved 1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethanol (1.6 g, 5.7 mmol) and triethylamine (4.8 ml, 34 mmol). To the resulting solution was added a solution of methanesulfonyl chloride (1.6 ml, 21 mmol) in methylene chloride (8 ml) under stirring at 0°C. The reaction mixture was stirred for 1 hour at the same temperature. The reaction mixture was diluted with ethyl acetate and the solution was poured in 1M HCl. The mixed solution was extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (28 ml) and to the resulting solution were added potassium carbonate (1.2 g, 8.6 mmol) and methyl 4-hydroxybenzoate (2.6 g, 17 mmol). The resulting mixture was stirred at 100°C for 2 hours. After cooling, ether and water were added to the reaction mixture, followed by extraction with ether. The extract

was washed with 1M NaOH (3 times), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate from 9:1 to 7:3, ϕ 50 mm × 300 mm) to give methyl 4-(1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.46 g, 62%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.78 (m, 1H), 2.32 (m, 1H), 2.48 (m, 1H), 3.10 (t, J=10.2Hz, 1H), 3.30 (s, 3H), 3.42 (m, 3H), 3.85 (s, 3H), 4.20 (m, 3H), 5.10 (m, 2H), 6.90 (m, 2H), 7.32 (m, 5H), 7.90 (m, 2H).

MS (ESI) m/z 414 $(M+1)^+$.

(Step 4) Synthesis of methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In a methanol/acetic acid (100 ml, 10:1) mixed solvent, methyl 4-(1-N-benzyloxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.45 g, 3.51 mmol) and 10% palladium·carbon (300 mg) were subjected

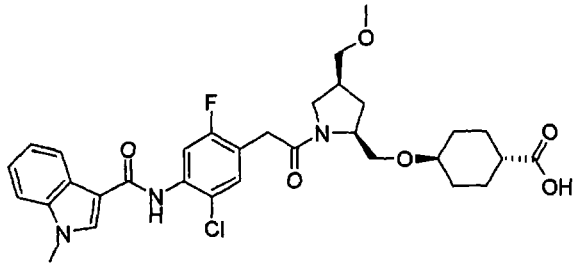
to catalytic hydrogenation for 3 hours at room temperature under normal pressure. From the reaction mixture, the catalyst was filtered off. To the filtrate were added acetic acid (10 ml) and rhodium/aluminum (435 mg) and the mixture was subjected to catalytic hydrogenation for 24 hours under a hydrogen gas of 4 atom. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (18 ml) and to the resulting solution, triethylamine (1.47 ml, 10.5 mmol) and di-tert-butyl-dicarbonate (1.15 g, 5.3 mmol) were added. Stirring was conducted for 6 hours at room temperature. The reaction mixture was poured in a 15% aqueous citric acid solution, followed by extraction with chloroform. The extract was washed with saturated brine and dried over anhydrous magnesium sulfate. After removal of the solvent by distillation under reduced pressure, the residue was dissolved in methanol and sodium methoxide (285 mg, 5.27 mmol) was added to the solution. The resulting mixture was heated under reflux for 18 hours. After cooling, the reaction mixture was poured in a saturated aqueous solution of citric acid, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate. After removal of the solvent by distillation under reduced pressure, the residue was dissolved in methanol/benzene (1:4, 18 ml). Under stirring

at 0°C, trimethylsilyldiazomethane (2.64 ml, a 2.0M n-hexane solution, 5.27 mmol) was added to the solution. The reaction mixture was stirred further for 3 hours at room temperature, followed by distillation under reduced pressure to remove the solvent. The residue was purified by medium-pressure column chromatography using silica gel (Biotage, KP-SIL, 32-63 μm, 75M, n-hexane/ethyl acetate 4:1 v/v) to give methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexane carboxylate (473 mg, 35%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (m, 3H), 1.48 (s, 9H), 2.00 (m, 4H), 2.20 (m, 2H), 2.38 (m, 1H), 2.92 (t, J=9.5Hz, 1H), 3.20 (m, 1H), 3.33 (s, 3H), 3.40-3.90 (m, 8H), 3.62 (s, 3H).

MS (ESI) m/z 386 $(M+1)^+$.

(Step 5) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In methylene chloride (15 ml) was dissolved methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (157 mg, 0.406

mmol). To the resulting solution was added trifluoroacetic acid (15 ml). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure to remove the solvent and the residue was dissolved in chloroform/a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (2 ml). To the resulting solution were added (5-chloro-2-fluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl] acetic acid (146 mg, 0.406 mmol), HOBt (104 mg, 0.77 mmol), DMAP (catalytic amount) and EDC·HCl salt (117 mg, 0.61 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by medium-pressure silica gel column chromatography (middle pressure Yamazen, chloroform/methanol 10:0 to 20:1, 20 ml/min, ϕ 50 mm × 150 mm). The purified product was dissolved in THF (4 ml) and 0.25M NaOH (2.4 ml, 0.61 mmol) was added to the solution. The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was acidified with 1M

HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (140 mg, 56%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20-2.80 (m, 15H), 3.10-4.30 (m, 7H), 3.30 (s, 3H), 3.90 (s, 3H), 7.21 (t, J=7.5Hz, 1H), 7.27 (t, J=7.5Hz, 1H), 7.41 (d, J=7.3Hz, 1H), 7.55 (d, J=8.1Hz, 1H), 7.70 (d, J=11.2Hz, 1H), 8.14 (d, J=7.5Hz, 1H), 8.31 (s, 1H), 9.30 (s, 1H).

MS (ESI) m/z 615 $(M+1)^+$;

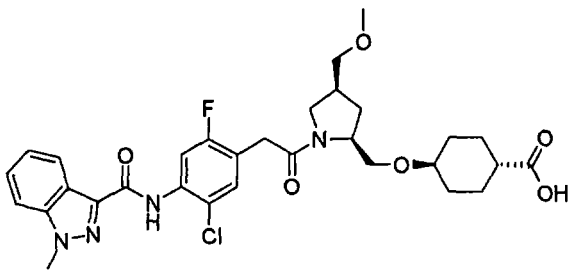
Anal. Calcd for $C_{30}H_{32}ClF_2N_3O_5 \cdot 0.75H_2O$: C, 59.90; H, 5.61; N, 7.31.

Found: C, 59.97; H, 5.55; N, 7.31.

Example 139

trans-4-(1-(5-Chloro-2-fluoro-4-((1-methyl-1H-indazole-3-indazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((1-methyl-1H-indazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To a solution of methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (157 mg, 0.406 mmol) in methylene chloride (15 ml), trifluoroacetic acid (15 ml) was added. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added chloroform/a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (2 ml) and (5-chloro-2-fluoro-4-((1-methyl-1H-indazolylcarbonyl)amino)phenyl)acetic acid (147 mg, 0.406 mmol), HOBt (104 mg, 0.77 mmol), DMAP (catalytic amount) and EDC·HCl salt (117 mg, 0.61 mmol) were added to the solution. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform/methanol 10:0 to 20:1, 20 ml/min, ϕ 50 mm x 150 mm). The purified product was dissolved in THF (4 ml) and 0.25M NaOH (2.4 ml, 0.61 mmol) was added to the

solution. The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure, whereby a white solid (154 mg, 62%) was obtained.

^{1}H-NMR (DMSO-d_6) δ: 1.20-2.80 (m, 15H), 3.10-4.30 (m, 7H), 3.30 (s, 3H), 3.90 (s, 3H), 7.37 (t, J=7.5Hz, 1H), 7.46 (d, J=7.1Hz, 1H), 7.53 (t, J=8.0Hz, 1H), 7.82 (d, J=8.3Hz, 1H), 8.06 (d, J=11.5Hz, 1H), 8.20 (d, J=7.6Hz, 1H), 9.71 (s, 1H).

MS (ESI) m/z 616 $(M+1)^+$;

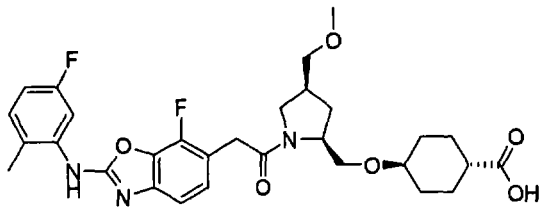
Anal. Calcd for $C_{31}H_{36}ClFN_4O_6 \cdot 0.25H_2O$: C, 62.13; H, 6.11; N, 6.79.

Found: C, 62.04; H, 6.15; N, 6.75.

Example 140

trans-4-(1-(7-Fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(7-fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolylacetyl)-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To a solution of methyl trans-4-(1-N-tert-butoxycarbonyl-(4S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (157 mg, 0.406 mmol) in methylene chloride (15 ml), trifluoroacetic acid (15 ml) was added. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform/saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (2 ml). To the resulting solution were added 7-fluoro-2-(5-fluoro-2-methylphenylamino)-6-benzoxazolacetic acid (147 mg, 0.406 mmol), HOBt (104 mg, 0.77 mmol), DMAP (catalytic amount) and EDC·HCl salt (129 mg, 0.61 mmol). The mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle

pressure Yamazen, chloroform/methanol 10:0 to 20:1, 20 ml/min, ϕ 50 mm x 150 mm). The purified product was dissolved in THF (4 ml) and 0.25 M NaOH (2.4 ml, 0.61 mmol) was added to the solution. The resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (110 mg, 47%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.60 (m, 6H), 1.80-3.80 (m, 9H), 2.31 (s, 3H), 3.10-4.30 (m, 7H), 3.25 (s, 3H), 6.88 (dt, J=2.4,8.5Hz, 1H), 7.05 (t, J=7.5Hz, 1H), 7.20 (d, J=8.1Hz, 1H), 7.25 (t, J=7.5Hz, 1H), 7.92 (d, J=10.8Hz, 1H).

MS (ESI) m/z 572 $(M+1)^+$;

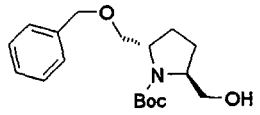
Anal. Calcd for $C_{30}H_{35}F_2N_3O_6 \cdot 0.25H_2O$: C, 62.54; H, 6.21; N, 7.29.

Found: C, 62.46; H, 6.23; N, 7.29.

Example 141

trans-4-((1-(5-Chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-hydroxymethylpyrrolidine

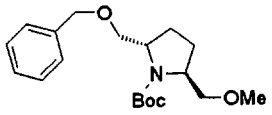


In methanol/THF/water (5/3/2, 100ml) was dissolved (2S)-benzoyloxymethyl-(5S)-benzyloxymethyl-N-tert-butoxycarbonylpyrrolidine (3.34 g, 7.85 mmol). To the resulting solution was added 1N NaOH (25.0 ml, 25.0 mmol) and the resulting mixture was stirred at room temperature for 7 hours. The reaction mixture was concentrated under reduced pressure. The residue was extracted with chloroform/methanol (10/1). The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (3/1 to EtOAc) eluate fractions, (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-hydroxymethylpyrrolidine (1.46 g, 58%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.41 (s, 9H), 1.57 (brs, 1H), 1.95-1.97 (m, 2H), 2.05-2.18 (m, 1H), 3.36 (t, J=8.4Hz, 1H), 3.56-3.62 (m, 2H), 3.67-3.72 (m, 2H), 3.95 (brs, 1H), 4.03 (brs, 1H), 4.51 (s, 1H), 7.28-7.37 (m, 5H).

MS (FAB) m/z 322 (M^++1).

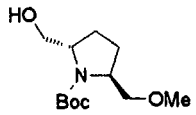
(Step 2) Synthesis of (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-methoxymethylpyrrolidine



In DMF (50 ml) was dissolved (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-hydroxymethylpyrrolidine (1.46 g, 4.55 mmol). Under stirring at 0°C, sodium hydride (60% in oil, 218 mg, 5.46 mmol) was added to the resulting solution in portions. After stirring at the same temperature for 10 minutes, methyl iodide (1.42 ml, 22.8 mmol) was added and the resulting mixture was stirred further at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction with ether. The extract was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (5/1) eluate fractions, (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-methoxymethylpyrrolidine (1.13 g, 74%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.40 and 1.47 (s, total 9H), 1.86-2.02 (m, 4H), 3.20-3.68 (series of m, 4H), 3.34 (s, 3H), 3.86-4.00 (m, 2H), 4.46-4.58 (m, 2H), 7.27-7.34 (m, 5H).

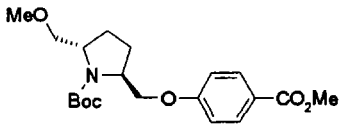
(Step 3) Synthesis of N-tert-butoxycarbonyl-(5S)-hydroxymethyl-(2S)-methoxymethylpyrrolidine



In methanol (30 ml), (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-methoxymethylpyrrolidine (1.12 g, 3.34 mmol) and 10% palladium/carbon (163 mg) were subjected to catalytic hydrogenation at room temperature under normal pressure for 18 hours. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent, whereby N-tert-butoxycarbonyl-(5S)-hydroxymethyl-(2S)-methoxymethylpyrrolidine (866 mg, 100 %) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.57-1.70 (m, 1H), 1.87-1.98 (m, 2H), 2.014-2.14 (m, 1H), 3.17-4.02 (series of m, 6H), 3.35 (s, 3H).

(Step 4) Synthesis of methyl 4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate

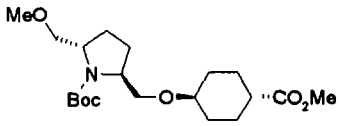


In THF (30 ml) were dissolved N-tert-butoxycarbonyl-(5S)-hydroxymethyl-(2S)-methoxymethylpyrrolidine (865 mg, 3.53 mmol), triphenylphosphine (1.11 g, 4.23 mmol) and methyl 4-hydroxybenzoate (536 mg, 3.53 mmol). To the resulting solution was added DIAD (803 µl, 3.88 mmol) and the resulting mixture was stirred at 60°C for 2 hours.

After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (3/1) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.13 g, 84%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.48 (s, 9H), 1.94-2.14 (m, 4H), 3.26-4.27 (series of m, 6H), 3.36 (s, 3H), 3.88 and 3.89 (s, total 3H), 6.93 and 6.96 (d, J=8.8Hz, total 2H), 7.96 and 7.99 (d, J=4.0Hz, total 2H).

(Step 5) Synthesis of methyl trans-4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

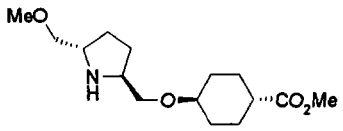


In ethanol/acetic acid (10/1, 55 ml), methyl 4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.02 g, 2.69 mml) and 5% rhodium-alumina (500 mg) were subjected to catalytic hydrogenation at room temperature for 2.5 hours under a hydrogen gas of 8 atom. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column,

whereby from hexane/ethyl acetate (3/1) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (771 mg, 74%) was obtained as a colorless oil. The oil was dissolved in methanol (770 mg, 1.20 mmol). To the resulting solution was added sodium methoxide (324 mg, 5.99 mmol), followed by heating under reflux for 18 hours. After cooling, the reaction mixture was neutralized with 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give an oil. The oil was dissolved in a benzene/methanol (10/1, 22 ml) mixture, followed by the dropwise addition of trimethylsilyl diazomethane (a 2.0M hexane solution, 0.50 ml, 0.25 mmol). After the reaction mixture was stirred at room temperature for 1 hour, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatography using silica gel, whereby from hexane/ethyl acetate (5/1) eluate fractions, methyl trans-4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (178 mg, 23%) was obtained as a colorless oil.

MS (ESI) m/z 386 (M^++1).

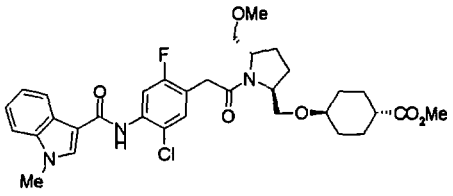
(Step 6) Synthesis of methyl trans-4-((5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



Methyl trans-4-(N-tert-butoxycarbonyl-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)-cyclohexanecarboxylate (175 mg, 0.45mmol) was dissolved in methylene chloride (20 ml). To the resulting solution was added trifluoroacetic acid (7 ml). The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)-cyclohexanecarboxylate (130 mg, 100 %) was obtained as a pale yellow oil.

MS (ESI) m/z 286 (M^++1).

(Step 7) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (10 ml), HOBt (18.2 mg, 0.14 mmol) was added to (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (162 mg, 0.45 mmol), methyl trans-4-((5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (128 mg, 0.45 mmol) and EDC·HCl (103 mg, 0.54 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (1/5) eluate fractions, methyl trans-4-((1-(5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (244 mg, 87%) was obtained as a colorless amorphous substance.

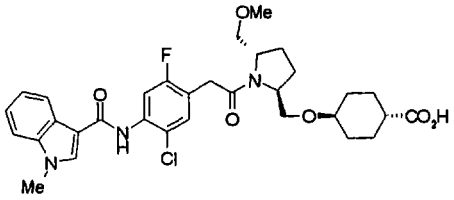
^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.09-2.25 (series of m, 12H), 3.05-4.20 (series of m, 10H), 3.27 and 3.31 (s, total 3H), 3.55 and 3.61 (s, total 3H), 3.84 (s, 3H), 7.28-7.32 (m, 2H), 7.36-7.41 (m, 2H), 7.76 (d, J=2.4Hz, 1H), 8.01-8.10 (m, 1H), 8.24 (s, 1H), 8.43 and 8.46 (s, total 1H).

MS (ESI) m/z 628 (M^++1).

(Step 8) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-

methoxymethyl-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (1/1, 20 ml) was dissolved methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolyl)carbonylamino)phenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (241 mg, 0.39 mmol). To the resulting solution was added 0.25N NaOH (7.67 ml, 1.92 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction with a chloroform/methanol (10/1) mixture. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (204 mg, 87%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.05-2.32 (series of m, 12H), 3.10-4.25 (series of m, 10H), 3.30 and 3.35 (s, total 3H), 3.85 and 3.86 (s, total 3H), 7.30-7.35 (m, 2H), 7.38-7.44 (m, 2H), 7.79 (d, J=1.2Hz, 1H), 8.08-8.12 (m, 1H), 8.28 (s, 1H), 8.45 and 8.48 (d, J=6.0Hz, total 1H).

MS (ESI) m/z 613 (M^++1);

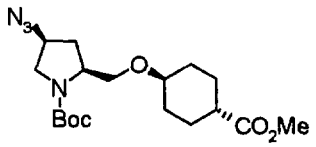
Anal. calcd for $C_{32}H_{37}ClFN_3O_6$: C, 62.59; H, 6.07; N, 6.84.

Found : C, 62.45; H, 6.30; N, 6.65.

Example 142

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-(N-methylacetamido)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-((4S)-azido-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

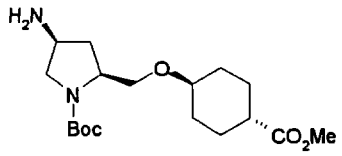


Methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-methanesulfonyloxy-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (530 mg, 1.22 mmol) was dissolved in DMF (10 ml) and LiN_3 (119 mg, 2.43 mmol) was added to the resulting solution. The mixture was stirred at 80°C for 5 hours. After cooling, the reaction mixture was diluted with ethyl acetate (300 ml). The ethyl acetate solution was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (20:1 to 10:1) eluate fractions,

methyl trans-4-((4S)-azido-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (423 mg, 91%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.30 (m, 2H), 1.46 (m, 11 H, including s, 9H, at δ: 1.46), 2.00-2.36 (series of m, 7H), 3.20-4.13 (series of m, 10H, including s, 3H, at δ: 3.66).

(Step 2) Synthesis of methyl trans-4-((4S)-amino-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

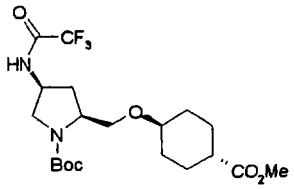


In methanol (20 ml), 5% palladium/carbon (400 mg) was added to methyl trans-4-((4S)-azido-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (420 mg, 1.10 mmol) and catalytic hydrogenation was effected for 15 hours at room temperature under normal pressure. After removal of the catalyst by filtration, the filtrate was distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((4S)-amino-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (391 mg, 100 %) was obtained as a pale yellow oil.

MS (ESI) m/z 357 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-trifluoroacetamido-(2S)-

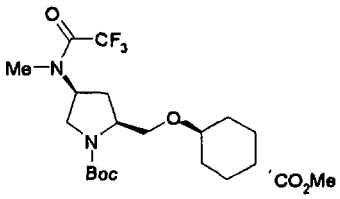
pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



Methyl trans-4-((4S)-amino-1-(tert-butoxycarbonyl)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (390 mg, 1.09 mmol) was dissolved in methylene chloride (10 ml). Under stirring at 0°C, diisopropylethylamine (381 µl, 2.19 mmol) and trifluoroacetic anhydride (227 µl, 1.64 mmol) were added to the resulting solution. After stirring for 2 hours at the same temperature, the reaction mixture was added with water (50 ml), followed by extraction with ethyl acetate (200 ml). The extract was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate fractions, methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-trifluoroacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (375 mg, 76%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.22-2.50 (series of m, 20H), 3.27-3.69 (series of m, 7H, including s, 3H, at d 3.67), 3.96-4.15 (m, 2H), 4.62 (m, 1H), 8.45 and 8.56 (m, each, total 1H).
MS (ESI) m/z 453 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-N-methyltrifluoroacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

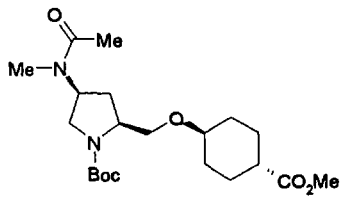


In DMF (10 ml) were dissolved methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-trifluoroacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (375 mg, 0.829 mmol) and MeI (258 μl, 4.15 mmol). To the resulting solution was added sodium hydride (40 mg, 0.995 mmol) in portions under stirring at 0°C. After stirring for 1 hour at the same temperature, the reaction mixture was added with 1N HCl (50 ml), followed by extraction with ethyl acetate (200 ml). The extract was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-ethyl acetate (10:1) eluate fractions, methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-N-methyltrifluoroacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (202 mg, 52%) was obtained as a yellow oil.

MS (ESI) m/z 467 (M^++1).

(Step 5) Synthesis of methyl trans-4-(1-(tert-

butoxycarbonyl)-(4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate

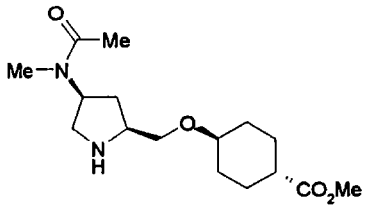


Methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-N-methyltrifluoroacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (200 mg, 0.429 mmol) was dissolved in THF-methanol (5:1, 6 ml). To the resulting solution was added a 2M aqueous solution (4 ml) of Na_2CO_3. After stirring for 3 hours, the reaction mixture was diluted with ethyl acetate (100 ml). The ethyl acetate solution was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (20 ml). To the resulting solution were added triethylamine (119 µl, 0.859 mmol) and acetylene chloride (46 µl, 0.644 mmol) under stirring at 0°C. The reaction mixture was stirred at room temperature for hour and diluted with ethyl acetate (100 ml). The diluted mixture was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, methyl trans-

4-(1-(tert-butoxycarbonyl)-(4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (90 mg, 51%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (m, 2H), 1.45 (m, 11H), 1.98-2.29 (series of m, 10H), 2.86 and 2.92 (s, each, total 3H), 3.02-3.30 (m, 2H), 3.62-3.92 (series of m, 7H, including s, 3H, at δ: 3.66), 4.29 and 5.14 (m, each, total 1H).

(Step 6) Synthesis of methyl trans-4-((4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate hydrochloride

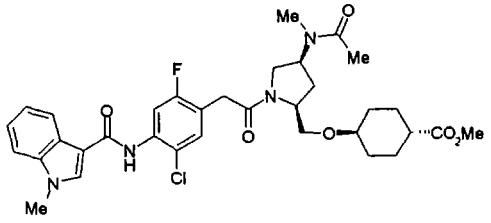


Methyl trans-4-(1-(tert-butoxycarbonyl)-(4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (90 mg, 0.218 mmol) was dissolved in dioxane (5 ml). To the resulting solution was added a 4N HCl/dioxane solution (10 ml). The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate hydrochloride (80 mg) was obtained as a pale yellow oil.

MS (ESI) m/z 313 (M^++1).

(Step 7) Synthesis of methyl trans-4-(1-((5-chloro-2-

fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-(N-methylacetamido)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate



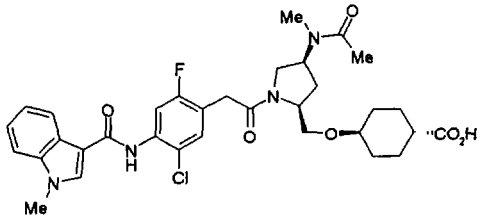
Methyl trans-4-((4S)-N-methylacetamido-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate hydrochloride (80 mg, crude) was dissolved in DMF (10 ml). To the resulting solution were added 5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (79 mg, 0.218 mg), triethylamine (303 µl, 2.18 mmol), EDC HCl (63 mg, 0.327 mmolI), and HOBt (44 mg, 0.327 mmol). The resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (100 ml) and water (100 ml) to separate an ethyl acetate layer. The ethyl acetate layer was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-(methylacetamido)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (120 mg, 84%) was obtained as a

yellow thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.07-2.23 (series of m, 14H), 2.87 and 2.94 (s, each, total 3H), 3.18 (m, 2H), 3.40-3.95 (series of m, 11H), 4.25 (m, 1H), 4.36 and 5.22 (m, each, total 1H), 7.33-7.42 (m, 4H), 7.82 (s, 1H), 8.13-8.15 (m, 1H), 8.29 (s, 1H), 8.49-8.54 (m, 1H).

MS (ESI) m/z 655 (M^++1).

(Step 8) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-(N-methylacetamido)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(4S)-(methylacetamido)-(2S)-pyrrolidinylmethoxy)-1-cyclohexanecarboxylate (115 mg, 0.176 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (4 ml, 1 mmol). After stirring at room temperature for 15 hours, the reaction mixture was poured in 1N HCl (100 ml), followed by extraction with chloroform-methanol (5:1, 2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. Hexane was added

to the resulting solution until precipitation of crystals occurred. The solid thus precipitated was collected by filtration under reduced pressure and dried to give the title compound (87 mg, 77%) as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.38 (m, 4H), 1.87-2.16 (m, 10H), 2.75 and 2.91 (s, each, total 3H), 3.17-5.05 (series of m, 12H), 7.20-7.30 (m, 2H), 7.40-7.44 (m, 1H), 7.56 (d, J=8.1Hz, 1H), 7.70 (m, 1H), 8.15 (d, J=7.8Hz, 1H), 8.31 (s, 1H), 9.31 (s, 1H).

MS (ESI) m/z 642 (M^++1);

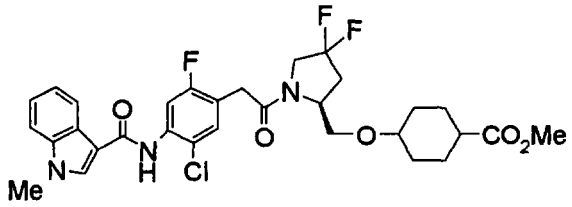
Anal. Calcd for $C_{33}H_{38}ClFN_4O_6$, C, 61.82; H, 5.97; N, 8.74.

Found: C, 59.72; H, 6.26; N, 7.68.

Example 143

trans-4-(1-(5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid and cis-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (5 ml) were dissolved (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (208 mg, 0.58 mmol) and methyl 4-(4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (160 mg, 0.58 mmol). To the resulting solution were added EDC HCl (167 mg, 0.87 mmol), HOBt (2.5 mg, 0.02 mmol), and DMAP (2.5 mg, 0.02 mmol), and the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel

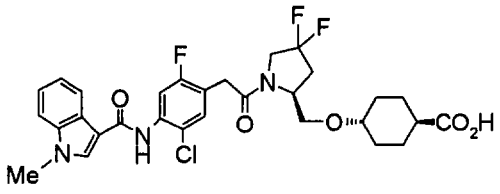
column, whereby from chloroform-methanol (30:1, v/v) eluate fractions, methyl 4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (a mixture of two diastereomers) (335 mg, 93%) was obtained as a pale brown crystalline powder.

IR (ATR) ν 1726, 1658, 1518 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 1.26 (m, 1H), 1.46 (m, 2H), 1.63-1.85 (series of m, total 5H), 1.99 (m, 2H), 2 35 (m, 1H), 2.55 (m, 2H), 3.51 (m, 1H), 3.58 (dd, J=10.8,6.8Hz, 1H), 3.66 and 3.67 (s, total 3H), 3.71 (m, 1H), 3.83 (m, 1H), 3.88 (s, 3H), 4.49 (m, 1H), 7.33-7.42 (series of m, total 4H), 7.80-7.81 (series of s, total 1H), 8.00 (s, 1H), 8.12 (m, 1H), 8.30 (s, 1H), 8.49-8.55 (series of d, J=12.0Hz, total 1H).

MS (LC-MS) m/z 621 (M^++1).

(Step 2) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid and cis-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl 4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (620 mg, 0.53 mmol) were added THF (4.5 ml) and 0.25N NaOH (4.5 ml). The resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl, followed by extraction with chloroform-methanol (5:1, v/v). The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. By chromatography using a silica gel thin-layer plate (Whatman TLC), two diastereomers were separated from the residue, whereby from chloroform-methanol (40:1, v/v×3) eluate fractions, trans-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (53 mg, 16%) was obtained as a white solid.

IR (ATR) ν 1653, 1518 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.11-1.31 (series of m, total 3H), 1.44 (m, 2H), 1.99 (m, 4H), 2.25 (m, 1H), 2.52 (m, 2H), 3.18 (m, 1H), 3.54 (m, 2H), 3.72 (m, 1H), 3.85 (s, 3H), 3.90 (m, 1H), 4.46 (m, 1H), 7.34 (m, 3H), 7.38 (m, 2H), 7.80 (s, 1H), 8.11 (m, 1H), 8.29 (s, 1H), 8.51 (dd, J=12.0,6.0Hz, 1H), 8.49 and 8.50 (d, J=12.0Hz, total 1H).

MS (ESI) m/z 607 (M^++1).

The further elution gave cis-4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenylacetyl)-4,4-difluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (246 mg, 67%) as a white solid.

IR (KBr) ν 1653, 1521cm^{-1};

^{1}H-NMR (DMSO-d_6) δ 1.47 (m, 2H), 1.65-1.86 (series of m, total 6H), 2.34 (m, 1H), 2.51-2.60 (series of m, total 2H), 3.44 (m, 2H), 3.52 and 3.58 (AB q, J=12.3Hz, 2H), 3.75 (m, 1H), 3.83 (m, 1H), 3.85 (s, 3H), 3.93 (m, 1H), 4.49 (m, 1H), 7.34 (m, 3H), 7.39 (d, J=6.4Hz, 2H), 7.79 and 7.81 (s, total 1H), 8.11 (m, 1H), 8.28 (s, 1H), 8.48 (d, J=12.0Hz, 1H).

MS (ESI) m/z 607 (M^++1);

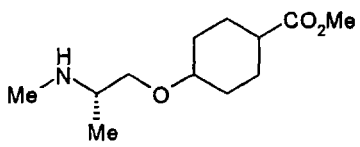
Anal. Calcd for $C_{30}H_{31}ClF_3N_3O_5$ H_2O: C, 57.74; H, 5.33; N, 6.73.

Found: C, 57.55; H, 5.06; N, 6.52.

Example 144

trans-4-((2S)-((5-Chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 4-((2S)-N-methylamino-1-propoxy)-1-cyclohexanecarboxylate

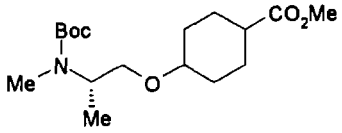


In methanol (30 ml), rhodium/alumina (2 g) was added to methyl 4-((2S)-N-methylamino-1-propoxy)benzoate (1.83 g, 8.20 mmol) and trifluoroacetic acid (1.9 ml, 24.6 mmol) and the resulting mixture was subjected to catalytic hydrogenation for 15 hours under a hydrogen gas of 20 atom. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was basified with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform (2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 4-((2S)-N-methylamino-1-propoxy)-1-cyclohexanecarboxylate (1.56 g, 83%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.99-1.02 (m, 3H), 1.20-2.03 (series of m, 8H), 2.24-2.44 (m, 4H), 2.74 (m, 1H), 3.18-3.44 (series of m, 3H), 3.67 (m, 3H).

MS (ESI) m/z 230 (M^++1).

(Step 2) Synthesis of methyl 4-((2S)-(N-(tert-butoxycarbonyl)-N-methylamino)-1-propoxy)-1-cyclohexanecarboxylate



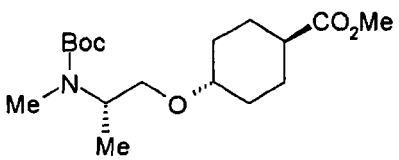
The methyl 4-((2S)-N-methylamino-1-propoxy)-1-

cyclohexanecarboxylate obtained in the above-described step was dissolved in acetonitrile (25 ml) and water (25 ml). To the resulting solution were added triethylamine (1.9 ml, 13.5 mmol) and di-tert-butyl dicarbonate (2.2 g, 10.1 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was extracted with ethyl acetate (100 ml). The extract was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, methyl 4-((2S)-(N-(tert-butoxycarbonyl)-N-methylamino)-1-propoxy)-1-cyclohexanecarboxylate (1.83 g, 82%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.12 (m, 3H), 1.24-2.33 (series of m, 18H), 2.75 (m, 3H), 3.20-3.44 (m, 3H), 3.66 (m, 3H), 4.10-4.34 (m, 1H).

MS (ESI) m/z 330 (M^++1).

(Step 3) Synthesis of methyl trans-4-((2S)-(N-(tert-butoxycarbonyl)-N-methylamino)-1-propoxy)-1-cyclohexanecarboxylate



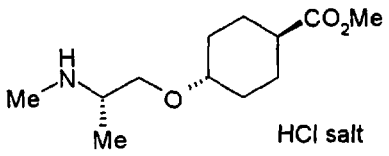
Methyl 4-((2S)-(N-(tert-butoxycarbonyl)-N-

methylamino)-1-propoxy)-1-cyclohexanecarboxylate (1.83 g, 5.56 mmol) was dissolved in dry methanol (30 ml). To the resulting solution was added sodium methoxide (900 mg, 16.7 mmol) and the mixture was heated under reflux for 15 hours. After cooling to room temperature, the reaction mixture was poured in 1N HCl (100 ml), followed by extraction with ethyl acetate (2 × 100 ml). The extract was washed with saturated brine (100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was dissolved in a 20% methanol-benzene mixture (20 ml) and to the resulting solution, trimethylsilyldiazomethane (a 2.0M hexane solution) was added in portions until the disappearance of raw material carboxylic acid was confirmed on TLC. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, methyl trans-4-((2S)-(N-(tert-butoxycarbonyl)-N-methylamino)-1-propoxy)-1-cyclohexanecarboxylate (786 mg, 43%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.09 (d, J=6.8Hz, 3H), 1.21 (m, 2H), 1.46 (m, 11 H, including s, 9H, at δ: 1.46), 2.02 (m, 4H), 2.26 (m, 1H), 2.73 (br s, 3H), 3.18-3.47 (m, 3H), 3.66 (s, 3H), 4.11-4.34 (m, 1H).

MS (ESI) m/z 330 (M^++1).

(Step 4) Synthesis of methyl trans-4-((2S)-methylamino-1-propoxy)-1-cyclohexanecarboxylate hydrochloride

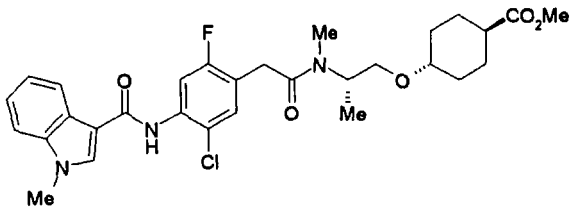


Methyl trans-4-((2S)-(N-(tert-butoxycarbonyl)-N-methylamino)-1-propoxy)-1-cyclohexanecarboxylate (786 mg, 2.39 mmol) was dissolved in dioxane (10 ml). To the resulting solution was added a 4N HCl/dioxane solution (15 ml). The mixture was stirred at room temperature for 15 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was solidified by treating it with ether, whereby methyl trans-4-((2S)-methylamino-1-propoxy)-1-cyclohexanecarboxylate hydrochloride (500 mg, 79%) was obtained as a colorless amorphous substance.

^{1}H-NMR (DMSO) δ: 1.16-1.24 (m, 5H), 1.31-1.40 (m, 2H), 1.87-1.91 (m, 2H), 1.96-1.99 (m, 2H), 2.24-2.30 (m, 1H), 2.49 (s, 3H), 3.21-3.28 (m, 2H), 3.47-3.60 (series of m, 7H), 8.73 (br s, 2H).

MS (ESI) m/z 230 (M^++1).

(Step 5) Synthesis of methyl trans-4-((2S)-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate



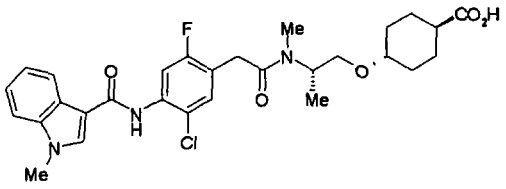
Methyl trans-4-((2S)-methylamino-1-propoxy)-1-cyclohexanecarboxylate hydrochloride (200 mg, 0.753 mmol) and (5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (272 mg, 0.753 mmol) were dissolved in DMF (10 ml). To the resulting solution were added and triethylamine (523 μl, 3.76 mmol), EDC HCl (217 mg, 1.13 mmol), and HOBt (153 mg, 1.13 mmol). The resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (100 ml) and water (100 ml) to separate it into layers. The ethyl acetate layer thus separated was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1) eluate fractions, methyl trans-4-((2S)-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate (400 mg, 93%) was obtained as a yellow viscous oil.

^{1}H-NMR ($CDCl_3$) δ: 1.11-1.14 (m, 3H), 1.15-1.29 (m, 2H), 1.40-1.49 (m, 2H), 2.00 (m, 4H), 2.21-2.30 (m, 1H), 2.81

and 2.90 (s, each, total 3H), 3.17 (m, 1H), 3.36-3.49 (m, 2H), 3.59-3.89 (series of m, 8H, including s, 3H, at δ: 3.85), 4.12 and 4.80 (m, each, total 1H), 7.31-7.41 (m, 4H), 7.78 (d, J=1.7Hz, 1H), 8.13 (dd, J=6.1,3.2Hz, 1H), 8.27 (s, 1H), 8.49 (d, J=12.9Hz, 1H).

MS (ESI) m/z 572 (M^++1).

(Step 6) Synthesis of trans-4-((2S)-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylic acid



Methyl trans-4-((2S)-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)-N- methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate (400 mg, 0.699 mmol) was dissolved in THF (10 ml). To the resulting solution was added 0.25N NaOH (5.6 ml, 1.40 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (50 ml), followed by extraction with chloroform (2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. Hexane was added to the resulting solution in portions to cause crystallization. The crystals thus precipitated were collected by filtration

under reduced pressure and dried to give the title compound (260 mg, 67%) as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.01-1.34 (series of m, 7H), 1.89 (m, 4H), 2.15 (m, 1H), 2.70 and 2.90 (s, each, total 3H, due to double bond character of the C(O)-N bond in amide), 3.21-3.92 (series of m, 8H), 4.18 and 4.61 (m, each, 1H, due to double bond character of the C(O)-N bond in amide), 7.20-7.69 (series of m, 5H), 8.16 (m, 1H), 8.31 (s, 1H), 9.30 (s, 1H), 12.04 (s, 1H).

MS (FAB) m/z 558 (M^++1);

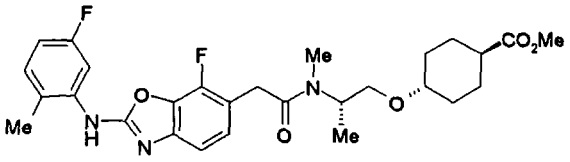
Anal. Calcd for $C_{29}H_{33}ClFN_3O_5$: C, 62.42; H, 5.96; N, 7.53.

Found: C, 62.09; H, 6.09; N, 7.26.

Example 145

trans-4-((2S)-((7-Fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-((2S)-((7-fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate



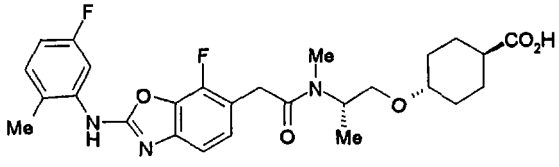
In DMF (10 ml), triethylamine (523 µl, 3.76 mmol), EDC HCl (217 mg, 1.13 mmol), and HOBt (153 mg, 1.13 mmol) were added to methyl trans-4-((2S)-N-methylamino-1-propoxy)-1-cyclohexanecarboxylate hydrochloride (200 mg,

0.753 mmol) and methyl 7-fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)acetate (239 mg, 0.753 mmol) and the resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (100 ml) and water (100 ml) to separate it into layers. The ethyl acetate layer thus obtained was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, methyl trans-4-((2S)-((7-fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate (399 mg, 100%) was obtained as a yellow viscous oil.

^{1}H-NMR ($CDCl_3$) δ: 1.08-1.48 (m, 7H), 1.99 (m, 4H), 2.28 (m, 4H), 2.77-3.94 (series of m, 11H), 4.19 and 4.83 (m, each, total 1H), 6.73 (m, 1H), 7.03-7.21 (m, 3H), 7.44 (m, 1H), 8.00-8.04 (m 1H).

MS (ESI) m/z 572 (M^++1).

(Step 2) Synthesis of trans-4-((2S)-((7-fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)-N-methylacetamido)-1-propoxy)-1-cyclohexanecarboxylic acid



Methyl trans-4-((2S)-(7-fluoro-2-((5-fluoro-2-methylphenyl)amino)-6-benzoxazolyl)-N- methylacetamido)-1-propoxy)-1-cyclohexanecarboxylate (399 mg, 0.753 mmol) was dissolved in THF (10 ml). To the resulting solution was added 0.25N NaOH (6 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (50 ml), followed by extraction with chloroform (2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. Hexane was added until the precipitation of a solid occurred. The precipitate thus obtained was collected by filtration under reduced pressure and dried to give the title compound (210 mg, 54%) as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.00-1.40 (series of m, 7H), 1.89 (m, 4H), 2.15 (m, 1H), 2.30 (s, 3H), 2.69 and 2.90 (s, each, total 3H, due to double bond character of the C(O)-N in amide), 3.19 (m, 1H), 3.33-3.47 (m, 4H), 3.73-3.84 (m, 2H), 4.19 and 4.63 (m, each, total 1H, due to double bond character of the C(O)-N in amide), 6.89 (dt, J=8.3,2.7Hz, 1H), 7.03 and 7.07 (t, J=7.8Hz, total 1H, due to double bond character of the C(O)-N in amide), 7.21 (d, J=7.8Hz, 1H), 7.27 (t, J=7.8Hz, 1H), 7.94 (dd, J=11.5,2.5Hz, 1H), 10.04 (br s, 1H), 12.06 (br s, 1H).

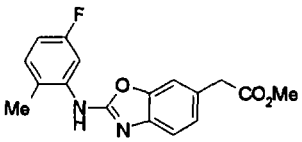
MS (FAB) m/z 516 (M^++1);

Anal. Calcd for $C_{27}H_{31}F_2N_3O_5$: C, 62.90; H, 6.06; N, 8.15. Found: C, 62.92; H, 6.25; N, 7.86.

Example 146

4-(1-((2-(5-Fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate

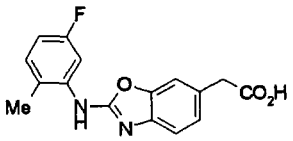


In methanol (50 ml), 5-fluoro-2-methylphenyl isothiocyanate (2.00 g, 12.0 mmol) was added to methyl 4-amino-3-hydroxyphenylacetate (2.17 g, 12.0 mmol) and the resulting mixture was stirred at room temperature for 27 hours. Mercuric oxide (yellow) (3.12 g, 14.4 mmol) was added to the reaction mixture, followed by stirring at 70°C for 4 hours. After cooling to room temperature, the reaction mixture was filtered through Celite, followed by washing with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (10/1) eluate fractions, methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate (1.73 g, 46%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.13 (s, 3H), 3.705 (s, 2H), 3.711 (s, 3H), 6.74 (dt, J=8.3,2.7Hz, 1H), 6.81 (br, 1H), 7.15 (dd, J=8.1, 1.7Hz, 2H), 7.31 (d, J=1.2Hz, 1H), 7.44 (d, J=8.1Hz, 1H), 8.09 (dd, J=11.0,2.7Hz, 1H).

MS (ESI) m/z 315 (M^++1).

(Step 2) Synthesis of (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetic acid

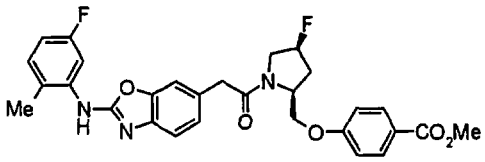


Methyl (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetate (1.73 g, 5.50 mmol) was dissolved in THF/methanol (2:1, 30 ml). To the resulting solution was added 1N NaOH (20 ml) and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetic acid (1.60 g, 97%) was obtained as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 2.49 (s, 3H), 3.64 (d, J=1.7Hz, 2H), 6.87 (dt, J=8.3,1.5Hz, 1H), 7.11 (d, J=8.1Hz, 1H), 7.25 (t, J=7.3Hz, 1H), 7.37 (d, J=8.1Hz, 1H), 7.41 (s, 1H), 7.95 and 7.98 (each s, total 1H, amide isomers), 9.80 (br, 1H).

MS (ESI) m/z 301 (M^++1).

(Step 3) Synthesis of methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate



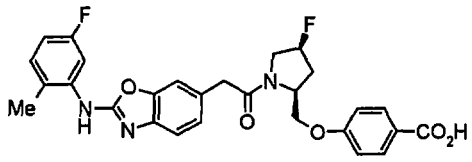
In DMF (5 ml), (2-(5-fluoro-2-methylphenylamino)-6-benzoxazoyl)acetic acid (300 mg, 1.0 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (253 mg, 1.0 mmol), EDC HCl (288 mg, 1.5 mmol), HOBt (203 mg, 1.5 mmol) and triethylamine (0.70 ml, 5.0 mmol) were stirred at room temperature for 17 hours. The reaction mixture was poured into ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1/4) eluate fractions, methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (630 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.05-2.62 (m, 5H), 3.73 (d, J=3.9Hz, 2H), 3.80 (m, 1H), 3.86 (s, 3H), 3.90-4.10 (m, 2H), 4.46-4.68 (m, 2H), 5.23-5.38 (m, 1H), 6.73 (dt, J=8.1,2.4Hz, 1H), 6.86 and 6.98 (each d, each J=8.8Hz, total 2H, amide

isomers), 7.12 (m, 3H), 7.26 (s, 1H), 7.29 (t, J=9.0Hz, 1H), 7.43 (t, J=8.1Hz, 1H), 7.95 and 7.99 (each d, each J=8.8Hz, total 2H, amide isomers), 8.05 and 8.08 (each s, total 1H, amide isomers).

MS (ESI) m/z 536 (M^++1).

(Step 4) Synthesis of 4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid



Methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (630 mg, 1.0 mmol) was dissolved in THF/methanol (20/10 ml). To the resulting solution was added 1N NaOH (20 ml). The resulting mixture was stirred at room temperature for 23 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (501 mg, 96%) as a pale pink solid.

IR (ATR) ν 2983, 1684, 1639, 1604, 1576, 1541, 1508, 1423 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.24 (m, 2H), 2.30 (s, 3H), 3.67-4.10

(m, 5H), 4.21-4.71 (m, 2H), 5.38 and 5.45 (each d, J=54.6 and 53.1Hz respectively, total 1H, amide isomers), 6.87 (dt, J=8.5,2.2Hz, 1H), 7.03-7.13 (m, 3H), 7.25 (t, J=7.6Hz, 1H), 7.36 and 7.39 (each s, total 2H, amide isomers), 7.87 (dd, J=9.0,2.2Hz, 2H), 7.95 (d, J=11.0Hz, 1H), 9.80 (br, 1H).

MS (ESI) m/z 522 (M^++1);

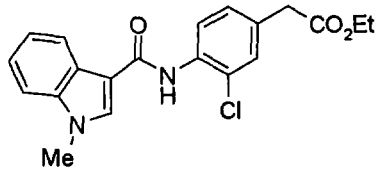
Anal. Calcd for $C_{28}H_{25}FN_3O_5 \cdot 0.7H_2O \cdot 0.4HCl$: C, 61.29; H, 4.92; N, 7.66; Cl, 2.58; F, 6.92.

Found: C, 61.13; H, 4.74; N, 7.38; Cl, 2.57; F, 6.87.

Example 147

4-(1-((3-Chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of ethyl (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetate



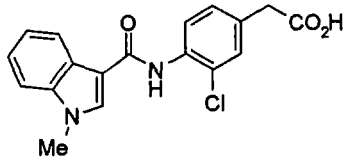
In DMF (20 ml), EDC HCl (1.44 g, 7.49 mmol) was added to 1-methyl-3-indolylcarboxylic acid (1.01 g, 5.71 mmol), ethyl 4-amino-3-chlorophenylacetate (1.22 g, 5.71 mmol), HOBt (0.86 g, 6.34 mmol), and DMAP (0.14 g, 1.15 mmol) and the resulting mixture was stirred at 70°C for 18 hours. After cooling to room temperature, the reaction mixture was

added with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (1 : 1, v/v) eluate fractions, ethyl (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (639 mg, 30%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.1Hz, 3H), 3.58 (s, 2H), 3.89 (s, 3H), 4.17 (q, J=7.1Hz, 2H), 7.24 (dd, J=8.3,2.0Hz, 1H), 7.32-7.43 (m, 4H), 7.81 (s, 1H), 8.16 (m, 1H), 8.28 (broad s, 1H), 8.59 (d, J=8.3Hz, 1H).

MS (ESI) m/z 371 (M^++1).

(Step 2) Synthesis of (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid

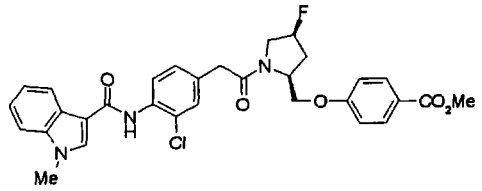


Ethyl (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (639 mg, 1.72 mmol) was dissolved in THF (17.5 ml). To the resulting solution was added 0.25N NaOH (10.3 ml, 2.58 mmol), followed by stirring at room temperature for 4 hours. The reaction mixture was poured in 1N HCl (15 ml). The crystals thus precipitated were collected by filtration under reduced

pressure, washed with water and dried under reduced pressure to give (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (549 mg, 93 %) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.61 (s, 2H), 3.89 (s, 3H), 7.17-7.28 (m, 3H), 7.43 (d, J=1.7Hz, 1H), 7.53 (d, J=8.3Hz, 1H), 7.69 (d, J=8.3Hz, 1H), 8.14 (d, J=7.8Hz, 1H), 8.26 (s, 1H), 9.26 (s, 1H).

(Step 3) Synthesis of methyl 4-(1-((3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate



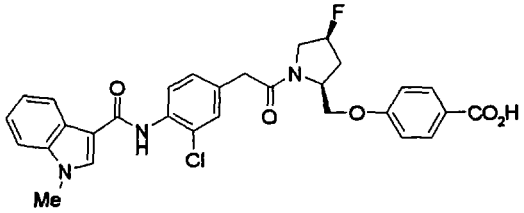
In DMF (5.0 ml), EDC HCl (161 mg, 0.84 mmol) was added to (3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (240 mg, 0.70 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (177 mg, 0.70 mmol), HOBt (114 mg, 0.84 mmol), and DMAP (17.0 mg, 0.14 mmol) and the resulting mixture was stirred at room temperature for 24 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent.

The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, methyl 4-(1-((3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (176 mg, 43%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.03-2.69 (m, 2H), 3.59 (d, J=15.2Hz, 1H), 3.64 (d, J=15.2Hz, 1H), 3.68-4.19(m, 9H, including singlet, 3H, at δ: 3.86, and singlet, 3H, at δ: 3.87), 4.47-4.63 (m, 2H), 5.36 (m, 1H), 6.98 (d, J=8.8Hz, 2H), 7.18 (d, J=8.3Hz, 1H), 7.32-7.42 (m, 4H), 7.80 (s, 1H), 7.95 (d, J=8.8Hz, 2H), 8.13 (m, 1H), 8.27 (broad s, 1H), 8.56 (m, 1H).

MS (ESI) m/z 578 (M^++1).

(Step 4) Synthesis of 4-(1-((3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoic acid



Methyl 4-(1-((3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)benzoate (176 mg, 0.30 mmol) was dissolved in THF (3.0 ml). To the resulting solution was added 0.25N NaOH (1.83 ml, 0.45 mmol). The resulting mixture was stirred at room temperature for 19 hours and at

60°C for 5 hours. The reaction mixture was poured in 1N HCl (5.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure precipitate to give the title compound (120 mg, 71 %) as a colorless solid.

IR (ATR) ν 1708, 1650, 1604, 1579, 1511, 1469 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.26-2.33 (m, 2H), 3.69 (d, J=15.9Hz, 1H), 3.75 (d, J=15.9Hz, 1H), 3.80-3.97 (m, 7H, including singlet, 3H, at δ: 3.89), 4.40-4.44 (m, 2H), 5.46 (m, 1H), 7.07 (d, J=8.8Hz, 2H), 7.18-7.28 (m, 2H), 7.39 and 7.42 (each broad s, total 1H), 7.53 (d, J=8.1Hz, 1H), 7.70 (d, J=8.1Hz, 1H), 7.87 (d, J=8.8Hz, 2H), 8.14 (d, J=7.8Hz, 1H), 8.26 (s, 1H), 9.26 (s, 1H), 12.60 (broad s, 1H).

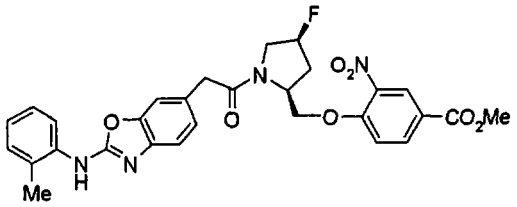
MS (ESI) m/z 564 (M^++1);

Anal. Calcd for $C_{30}H_{27}ClFN_3O_5$: C, 63.89; H, 4.83; N, 7.45. Found: C, 63.50; H, 5.01; N, 7.13.

Example 148

3-Amino-4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid

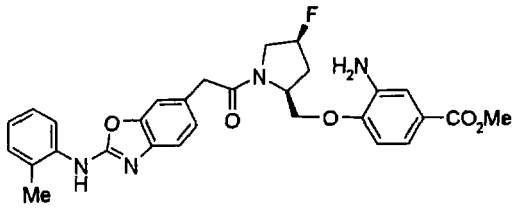
(Step 1) Synthesis of methyl 4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)-3-nitrobenzoate



In DMF (10 ml) were dissolved ((2-methylphenylamino)-6-benzoxazolyl)acetic acid (391 mg, 1.38 mmol) and methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-3-nitrobenzoate (412 mg, 1.38 mmol). To the resulting solution were added EDC HCl (405 mg, 2.11 mmol), HOBt (2.5 mg, 0.02 mmol), and DMAP (2.5 mg, 0.02 mmol), and the resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, methyl 4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy-3-nitrobenzoate (460 mg, 59%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.12 (m, 2H), 2.34 (s, 3H), 2.67 (d, J=17.2Hz, 1H), 3.73 (m, 1H), 3.82 (m, 1H), 3.92 (s, 3H), 4.03 (m, 1H), 4.11 (m, 1H), 4.58 (br, 1H), 4.72 (br, 1H), 5.31 (d, J=58.1Hz, 1H), 6.73 (m, 1H), 6.94 (m, 1H), 7.09 (m, 2H), 7.25 (m, 2H), 7.32 (m, 3H), 8.08 (m, 1H), 8.16 (m, 1H).

(Step 2) Synthesis of methyl 3-amino-4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate



In ethanol (5 ml) and THF (2 ml), methyl 4-((4S)-fluoro-1-((2-methylphenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy-3-nitrobenzoate (460 mg, 0.82 mmol) and 5% palladium-carbon (500 mg) were subjected to catalytic hydrogenation for 60 hours under normal pressure. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methyl ester (10:1, v/v) eluate fractions, methyl 3-amino-4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (192 mg, 44%) was obtained as a brown solid.

IR (KBr) ν 1708, 1639, 1573 cm^{-1};

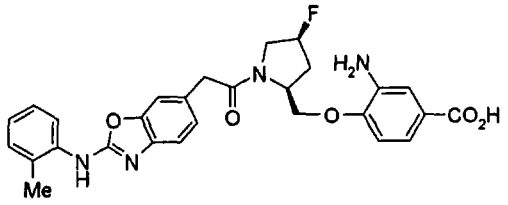
^{1}H-NMR ($CDCl_3$) δ: 2.12 (m, 2H), 2.36 (s, 3H), 2.47 (dd, J=16.0,21.5Hz, 1H), 3.73 (m, 2H), 3.84 (s, 3H), 4.11 (br, 1H), 4.16 (m, 1H), 4.40 (dd, J=4.8,8.8Hz, 1H), 4.49 (br, 1H), 4.73 (br, 1H), 5.33 (series of dt, J=4.4,52.8Hz, total 1H), 6.90 (m, 1H), 7.08 (d, J=7.2Hz, 2H), 7.23 (m, 2H), 7.30 (d, J=7.2Hz, 1H), 7.36 (dd, J=11.2,12.8Hz, 1H), 7.43 (m, 1H), 8.09 (d, J=8.0Hz, 2H).

MS (ESI) m/z 533 (M^++H);

Anal. Calced for $C_{29}H_{29}FN_4O_5$ $2.5H_2O$: C, 60.30; H, 5.93; N, 9.70.

Found: C, 60.48; 11.2, H, 5.13; N, 9.26.

(Step 3) Synthesis of 3-amino-4-((4S)-fluoro-1-((2-methylphenylamino)-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



Methyl 3-amino-4-((4S)-fluoro-1-((2-methylphenylamino-6-benzoxazolylacetyl)-(2S)-pyrrolidinylmethoxy)benzoate (191 mg, 0.36 mmol) was dissolved in THF (3 ml). To the resulting solution was added 0.25N NaOH (3 ml), and the resulting mixture was heated under reflux for 5 hours. After cooling, the reaction mixture was concentrated under reduced pressure to remove the solvent and the residue was diluted with a chloroform-methanol mixture (5:1, v/v). The solution was washed with 1N HCl, dried over anhydrous magnesium sulfate, and distilled under a reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (5:1, v/v) eluate fractions, the title compound (76 mg, 41%) was obtained as a brown solid.

IR (ATR) ν 1639, 1573 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.27 (s, 3H), 2.49 (s, 1H), 3.7-4.1

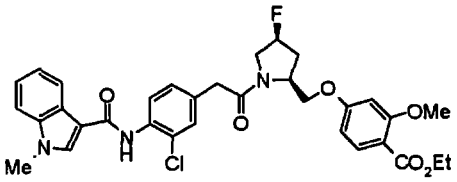
(series of m, total 4H), 4.24 (m, 2H), 4.46 (m, 2H), 5.42 (series of d, J=53.2Hz, total 1H), 6.86 (d, J=8.0Hz, 1H), 7.04 (t, J=14.4Hz, 2H), 7.05 (s, 1H), 7.14 (m, 1H), 7.22 (m, total 3H), 7.33 (d, J=5.6Hz, 1H), 7.78 (d, J=8.4Hz, 2H), 9.67 (br, 1H).

MS (ESI) 519 (M^++1).

Example 149

4-(1-(3-Chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoic acid:

(Step 1) Synthesis of ethyl 4-(1-(3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoate

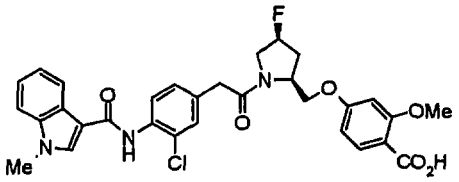


In DMF (14 ml), EDC HCl (173.2 mg, 0.904 mmol) was added to ethyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoate (179.1 mg, 0.602 mmol), 3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetic acid (206.4 mg, 0.602 mmol) and HOBt (32.6 mg, 0.241 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed successively with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and

distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (25:1, v/v) eluate fractions, ethyl 4-(1-(3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoate (100 %) was obtained as an amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, J=7.6Hz, OCH_2Me), 1.72-2.70 (total 2H, series of m), 3.52-4.18 (total 11H, series of m, including 3H, s, at δ: 3.34 and 3H, s at δ: 3.92), 4.30 (2H, q, J=7.6Hz, OCH_2Me), 4.50-4.66 (2H, m), 5.31 (1H, d, J=52.4Hz), 6.40-6.64 (total 2H, m), 7.20 (1H, m), 7.29-7.45 (4H, m), 7.75-7.88 (2H, m), 8.14 (1H, m), 8.25 (1H, m), 8.57 (1H, m).

(Step 2) Synthesis of 4-(1-(3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoic acid



Ethyl 4-(1-(3-chloro-4-((1-methyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-2-methoxybenzoate (374.6 mg, 0.602 mmol) was dissolved in THF (8.0 ml). To the resulting solution was added 0.25N NaOH (8.0 ml), followed by

stirring at room temperature for 18 hours. The reaction mixture was concentrated. The concentrate was then neutralized with 1N HCl (2.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried at 50°C under reduced pressure to give the title compound (345.8 mg, 97%) as an amorphous substance.

IR (ATR) ν 1608, 1511 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ 2.15-2.40 (2H, m), 3.40-4.78 (total 13H, m, including 3H, s at δ: 3.84 and 3H, s at δ: 3.91), 5.42, 5.49 (total 1H, br d, J=52.0Hz), 6.50-6.80 (2H, m), 7.23 (3H, m), 7.44 (1H, d, J=10.0Hz), 7.57 (1H, d, J=10.0Hz), 7.70 (2H, m), 8.16 (1H, m), 8.29 (1H, s), 9.32 (1H, m), 12.15 (1H, br s, CO_2H).

MS (ESI) m/z 594 (M^+ +1);

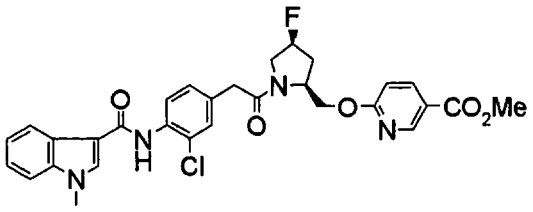
Anal. Calcd for $C_{31}H_{29}ClFN_3O_6$ H_2O: C, 60.83; H, 5.11; N, 6.87; Cl, 5.79; F, 3.10.

Found: C, 60.53; H, 5.01; N, 6.71; Cl, 5.69; F, 3.09.

Example 150

6-(1-(3-Chloro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinic acid:

(Step 1) Synthesis of methyl 6-(1-(3-chloro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinate

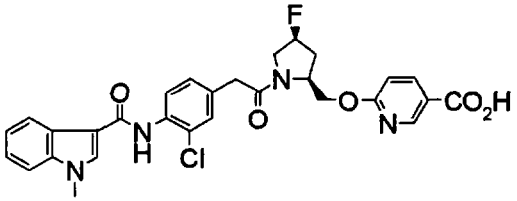


Methyl 6-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinate (197 mg, 0.50 mmol) was dissolved in methylene chloride (10 ml). Under stirring at 0°C, trifluoroacetic acid (10 ml) was added and the resulting mixture was stirred at room temperature for 30 minutes. From the reaction mixture, the solvent was distilled off under reduced pressure. To the residue was added a saturated aqueous solution of sodium bicarbonate, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was provided for the subsequent reaction without further purification. In THF (5.0 ml) and acetonitrile (5.0 ml), EDC·HCl (144 mg, 0.75 mmol) was added to the resulting compound, (3-chloro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetic acid (171 mg, 0.5 mmol), HOBt (70 mg, 0.5 mmol), and triethylamine (208 μl, 1.5 mmol) at 0°C. The resulting mixture was stirred at room temperature for 16 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate and a 2M aqueous solution of

citric acid, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC), whereby from chloroform-methanol (95:5, v/v) eluate fractions, methyl 6-(1-(3-chloro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinate (330 mg, 100 %) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 2.10-2.55 (m, 2H), 3.55-4.05 (m, 10H), 4.25-4.85 (m, 3H), 5.24-5.37 (m, 1H), 6.78 (t, J=8.8Hz, 1H), 7.25-7.44 (m, 5H), 7.80 (d, J=4.6Hz, 1H), 8.13-8.25 (m, 3H), 8.54-8.59 (m, 1H), 8.80-8.86 (m, 1H).

(Step 2) Synthesis of 6-(1-(3-chloro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinic acid



Methyl 6-(1-(3-chloro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)nicotinate (330 mg, 0.5 mmol) was dissolved in THF (10 ml) and methanol (15 ml). To the resulting solution was added 1N NaOH (1.0 ml, 1.0 mmol). The resulting mixture was stirred at 70°C for 18 hours. After cooling, the reaction mixture was acidified with

water and 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (270 mg, 96%) as a white solid.

IR (ATR) ν 2983, 1600, 1511, 1222 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.20-2.40 (m, 2H), 3.50-4.00 (m, 7H), 4.10-4.80 (m, 3H), 5.38-5.52 (m, 1H), 6.90-6.93 (m, 1H), 7.18-7.28 (m, 1H), 7.41 (s, 1H), 7.54 (d, J=8.3Hz, 1H), 7.65-7.68 (m, 1H), 8.14-8.20 (m, 2H), 8.26 (s, 1H), 8.68-8.73 (m, 1H), 9.29 (s, 1H).

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

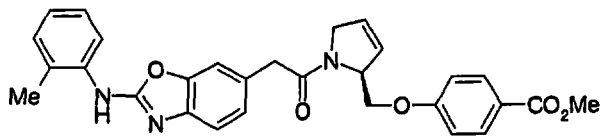
Anal. calcd for $C_{29}H_{26}ClFN_4O_5$ 0.5 H_2O: C, 60.68; H, 4.74; N, 9.76.

Found: C, 60.49; H, 4.72; N, 9.56.

Example 151

4-(3,4-Dehydro-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(3,4-dehydro-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)benzoate



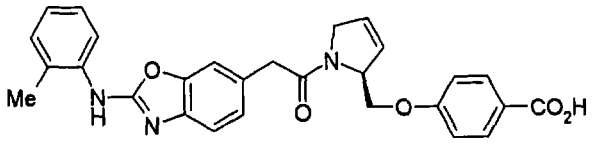
In DMF (7.5 ml) were dissolved (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid (223 mg, 0.79 mmol), methyl 4-(3,4-dehydro-(2S)-

pyrrolidinylmethoxy)benzoate (184 mg, 0.79 mmol), HOBt (21.0 mg, 0.16 mmol), and triethylamine (0.16 ml, 1.15 mmol). To the resulting solution was added EDC HCl (227 mg, 1.15 mmol) and the resulting mixture was stirred at room temperature for 12 hours. To the reaction mixture was added water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, methyl 4-(3,4-dehydro-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)benzoate (331 mg, 84 %) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.37 (s, 3H), 3.71 (s, 2H), 3.84 (s, 3H), 4.20 (m, 1H), 4.31-4.35 (m, 2H), 4.42 (dd, J=9.5,5.4Hz, 1H), 5.10 (m, 1H), 5.87-5.95 (m, 2H), 6.86 (d, J=8.8Hz, 2H), 7.05-7.09 (m, 2H), 7.16 (d, J=1.2Hz, 1H), 7.22 (d, J=8.1Hz, 1H), 7.31 (t, J=8.1Hz, 1H), 7.37 (d, J=8.1Hz, 1H), 7.93 (d, J=8.8Hz, 2H), 8.19 (d, J=7.6Hz, 1H).

MS (ESI) 498 (M^++1).

(Step 2) Synthesis of 4-(3,4-dehydro-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)benzoic acid



Methyl 4-(3,4-dehydro-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)benzoate (331 mg, 0.67 mmol) was dissolved in THF (7.0 ml). To the resulting solution was added 0.25N NaOH (4.00 ml, 1.00 mmol), followed by stirring at room temperature for 6 hours. The reaction mixture was poured in 1N HCl (10 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (241 mg, 75 %) as a pale yellow solid.

IR (ATR) ν 3060, 2921, 1681, 1639, 1604, 1573, 1509, 1423 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.29 (s, 3H), 3.71 (s, 2H), 4.23-4.25 (m, 2H), 4.33 (m, 1H), 4.22 (m, 1H), 5.18 (broad s, 1H), 5.96-6.02 (m, 2H), 6.96 (d, J=8.8Hz, 2H), 7.02-7.09 (m, 2H), 7.21-7.23 (m, 3H), 7.30 (broad s, 1H), 7.79 (d, J=8.3Hz, 1H), 7.85 (d, J=8.8Hz, 2H), 9.63 (broad s, 1H).

MS (FAB) 484 (M^++1);

Anal. Calcd for $C_{28}H_{25}N_3O_5$ 0.5H_2O: C, 68.28; H, 5.32; N, 8.53.

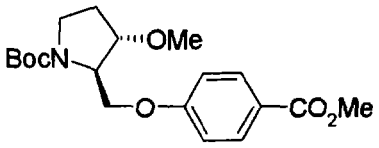
Found: C, 68.03; H, 5.35; N, 8.42.

Example 152

4-((3S)-Methoxy-1-((2-(2-methylphenylamino)-6-

benzoxazolyl)acetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid :

(Step 1) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate

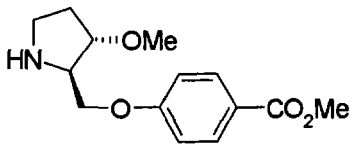


Methyl 4-((3S)-hydroxy-(2R)-pyrrolidinylmethoxy)benzoate (501 mg, 1.43 mmol) was dissolved in DMF (7.5 ml). To the resulting solution was added sodium hydride (60% in oil, 68 mg, 1.71 mmol) in portions under stirring at 0°C. After stirring at 0°C for 30 minutes, methyl iodide (0.27 ml, 4.28 mmol) was added. The resulting mixture was stirred at the same temperature for 1 hour. A saturated aqueous solution of ammonium chloride was added, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (3:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (569 mg, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (broad s, 9H), 1.95-2.19 (m, 2H), 3.34 (s. 3H), 3.38-3.54 (m, 2H), 3.89 (s, 3H), 3.93-4.30

(m, 4H), 6.96 (d, J=8.6Hz, 2H), 7.98 (d, J=8.6Hz, 2H).

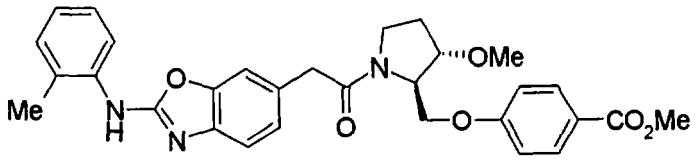
(Step 2) Synthesis of methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate



Methyl 4-(1-(tert-butoxycarbonyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (569 mg, 1.56 mmol) was dissolved in methylene chloride (10 ml). To the resulting solution was added trifluoroacetic acid (5.0 ml) under stirring at 0°C. The resulting mixture was stirred at room temperature for 3 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (356 mg, 86 %) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.86-2.01 (m, 3H), 3.02-3.15 (m, 2H), 3.35 (s. 3H), 3.45 (m, 1H), 3.81 (m, 1H), 3.88 (s, 3H), 3.95-4.02 (m, 2H), 6.92 (d, J=8.0Hz, 2H), 7.98 (d, J=8.0Hz, 2H).

(Step 3) Synthesis of methyl 4-((3S)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate

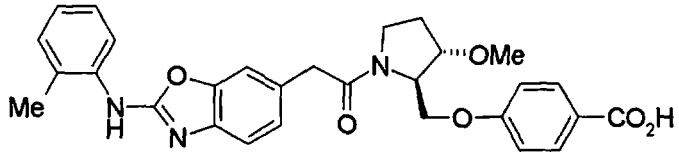


In DMF (7.0 ml), EDC HCl (193 mg, 1.01 mmol) was added to (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid (189 mg, 0.67 mmol), methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (178 mg, 0.67 mmol), HOBt (18.0 mg, 0.13 mmol), and triethylamine (0.14 ml, 1.01 mmol) and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate. The diluted mixture was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, methyl 4-((3S)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate (384 mg, 100 %) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.11 (m, 1H), 2.23 (m, 1H), 2.36 (s, 3H), 3.30 (s, 3H), 3.56-3.68 (m, 2H), 3.71 (s, 2H), 3.85 (s, 3H), 3.98 (m, 1H), 4.10 (dd, J=10.0,6.8Hz, 1H), 4.29 (dd, J=10.0,3.2Hz, 1H), 4.44 (m, 1H), 6.91 (d, J=9.0Hz, 2H), 7.04-7.08 (m, 2H), 7.19 (d, J=2.2Hz, 1H), 7.21 (m, 1H), 7.29 (m, 1H), 7.34 (d, J=7.9Hz, 1H), 7.94 (d, J=9.0Hz, 2H), 7.98 (d, J=8.1Hz, 1H), 8.01 (broad s, 1H).

MS (ESI) m/z 530 (M^++1).

(Step 4) Synthesis of 4-((3S)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(2R)-pyrrolidinylmethoxy)benzoic acid



Methyl 4-((3S)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(2R)-pyrrolidinylmethoxy)benzoate (384 mg, 0.73 mmol) was dissolved in THF (7.5 ml). To the resulting solution was added 0.25N NaOH (4.40 ml, 1.09 mmol), followed by stirring at room temperature for 5 hours. The reaction mixture was poured in 1N HCl (10 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (300 mg, 80%) as a brown solid.

IR (ATR) ν 2927, 1681, 1639, 1604, 1575, 1486, 1438 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.08 (m, 1H), 2.22 (m, 1H), 2.30 (s, 3H), 3.22 (s, 3H), 3.60 (m, 1H), 3.67 (m, 1H), 3.73 (s, 2H), 3.91 (m, 1H), 3.97 (m, 1H), 4,21-4.23 (m, 2H), 7.00-7.08 (m, 4H), 7.22-7.25 (m, 3H), 7.31 (broad s, 1H), 7.81 (d, J=8.3Hz, 1H), 7.87 (d, J=8.6Hz, 2H), 9.59 (broad s, 1H).

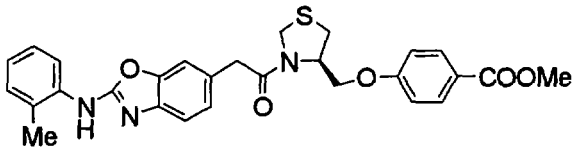
MS (FAB) m/z 516 (M^++1);

Anal. Calcd for $C_{29}H_{29}N_3O_6$ H_2O: C, 65.28; H, 5.86; N, 7.88. Found: C, 65.57; H, 5.95; N, 7.87.

Example 153

4-(1-(2-(2-Methylphenylamino)-6-benzoxazolylacetyl)-(4R)-thiazolidinylmethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4R)-thiazolidinylmethoxy)benzoate

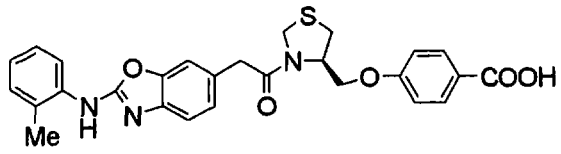


Methyl 4-((4R)-thiazolidinylmethoxy)benzoate (354 mg, 1.4 mmol), (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid (395 mg, 1.4 mmol), HOBt (189 mg, 1.4 mmol), and triethylamine (583 μl, 4.2 mmol) were dissolved in methylene chloride (15 ml). Under stirring at 0°C, EDC·HCl (403 mg, 2.1 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous solution of citric acid, and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified

by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (1:1, v/v) eluate fractions, methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4R)-thiazolidinylmethoxy)benzoate (600 mg, 83%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.34 and 2.36 (total 3H, each s), 3.05-3.18 (m, 2H), 3.80-4.94 (m, 10H), 6.81-7.41 (m, 9H), 7.97 (d, J=8.8Hz, 2H), 8.06 (d, J=8.0Hz, 1H).

(Step 2) Synthesis of 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4R)-thiazolidinylmethoxy)benzoic acid



Methyl 4-(1-(2-(2-methylphenylamino)-6-benzoxazolylacetyl)-(4R)-thiazolidinylmethoxy)benzoate (600 mg, 1.16 mmol) was dissolved in THF (5.0 ml) and ethanol (3.0 ml). To the resulting solution was added 1N NaOH (1.5 ml, 1.5 mmol). The resulting mixture was stirred at 70°C for 18 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (560 mg, 96%) as a white crystalline powder.

IR (KBr) ν 2987, 2900, 1639, 1575, 1241, 754 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 3.05-3.30 (m, 3H), 3.70-4.30 (m, 3H), 4.56-5.00 (m, 3H), 7.06-7.33 (m, 9H), 7.80-7.88 (m, 3H).

MS (FAB) m/z 504 (M^++1);

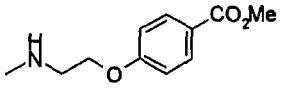
Anal. calcd for $C_{27}H_{25}N_3O_5S$: C, 64.40; H, 5.00; N, 8.34; S, 6.37.

Found: C, 63.76; H, 4.98; N, 8.18; S, 6.17.

Example 154

4-(2-((2-(2-Methylphenylamino)-6-benzoxazolyl)-N-methylacetamido)ethoxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(2-(N-methylamino)ethoxy)benzoate

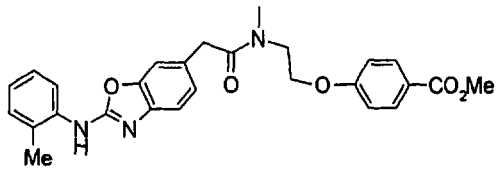


In THF (100 ml) was dissolved N-(tert-butoxycarbonyl)-2-(methylamino)ethanol (3.03 g, 17.3 mmol). To the resulting solution was added methyl 4-hydroxybenzoate (2.77 g, 18.2 mmol) and under stirring at 0°C in a nitrogen gas stream, triphenylphosphine (6.35 g, 24.2 mmol) and DIAD (3.5 ml, 24.5 mmol) were added. The resulting mixture was stirred further at room temperature for 18 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the

solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (4:1, v/v) eluate fractions, methyl 4-(2-(N-(tert-butoxycarbonyl)-N-methylamino)ethoxy)benzoate (4.09 g, 76%) was obtained as a yellow oil. The resulting compound (933 mg, 3.01 mmol) was dissolved in methylene chloride (3 ml). To the resulting solution was added trifluoroacetic acid (1 ml) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with a chloroform-methanol mixture (5:1, v/v). The extract was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl 4-(2-(N-methylamino)ethoxy)benzoate (618 mg, 98%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.54 (s, 3H), 3.02 (dd, J=5.0Hz, 2H), 3.88 (d, J=6.0Hz, 3H), 4.14 (dd, J=5.0Hz, 2H), 6.80 (d, J=8.8Hz, 1H), 6.91 (d, J=9.0Hz, 1H), 7.91 (d, J=9.0Hz, 1H), 7.98 (d, J=8.8Hz, 1H).

(Step 2) Synthesis of methyl 4-(2-((2-(2-methylphenylamino)-6-benzoxazolyl)N-methylacetamido)ethoxy)benzoate



In DMF (6 ml) were dissolved 2-(2-methylphenylamino)-6-benzoxazolylacetic acid (154 mg, 0.55 mmol) and methyl 4-(2-(N-methylamino)ethoxy)benzoate (117 mg, 0.55 mmol). To the resulting solution were added EDC HCl (157 mg, 0.81 mmol), HOBt (5 mg, 0.04 mmol), and DMAP (5 mg, 0.04 mmol). The resulting mixture was stirred at room temperature for 18 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1, v/v) eluate fractions, methyl 4-(2-((2-(2-methylphenylamino)-6-benzoxazolyl)-N-methylacetamido)ethoxy)benzoate (207 mg, 80%) was obtained as a yellow oil.

IR (ATR) ν 1710, 1631, 1573 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 2.36 (s, 3H), 3.16 (series of d, J=2.4Hz, total 2H), 3.79 (m, 3H), 3.87 (d, J=2.4Hz, 2H), 3.87 (d, J=2.4Hz, 2H), 3.92 (m, 1H), 4.23 (series of t, J=4.8Hz, total 1H), 6.87 (m, 2H), 7.07 (t, J=6.4Hz, 1H), 7.22 (m, 1H), 7.30 (m, 1H), 7.37 (d, J=8.0Hz, 1H), 7.95 (m, 2H),

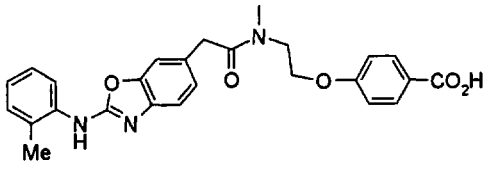
8.04 (br, 2H), 8.07(d, J=7.2Hz, 1H).

MS(ESI) m/z 474 $(M+H)^+$;

Anal. Calced for $C_{27}H_{27}FN_3O_5$ H_2O: C, 65.98; H, 5.95; N, 8.55.

Found: C, 65.98; H, 5.73; N, 7.68.

(Step 3) Synthesis of 4-(2-((2-(2-methylphenylamino)-6-benzoxazolyl)-N-methylacetamido)ethoxy)benzoic acid



Methyl 4-(2-((2-(2-methylphenylamino)-6-benzoxazolyl)-N-methylacetamido)ethoxy)benzoate (206.9 mg, 0.44 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (5 ml), and the resulting mixture was stirred at room temperature for 2 hours. To the reaction mixture was added NaOH (500 mg), followed by heating under reflux for 3 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with a chloroform-methanol mixture (5:1, v/v). The solution was washed with 1N HCl, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1, v/v) eluate fractions, the title compound (101 mg, 51%) was obtained as a pale red solid.

IR (ATR) ν 1683, 1637, 1604, 1573 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.47 (s, 2H), 3.71 (q, J=7.2Hz, 2H), 3.77 (s, 2H), 3.91 (m, 1H), 4.20 (m, 3H), 6.78 (d, J=8.0Hz, 1H), 6.83 (d, J=8.8Hz, 1H), 7.07 (m, 2H), 7.22 (m, 2H), 7.32 (m, 1H), 7.62 (m, 1H), 7.74 (d, J=8.0Hz, 1H), 8.02 (t, J=9.2Hz, 2H).

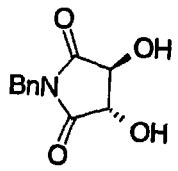
MS (ESI) m/z 460 $(M+H)^+$;

Anal. Calced for $C_{26}H_{25}FN_3O_5$ H_2O: C, 65.45; H, 5.70; N, 8.80. Found: C, 65.35; H, 5.72; N, 8.25.

Example 155

4-((4R)-Methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(3S)-pyrrolidinyloxy)benzoic acid:

(Step 1) Synthesis of 1-benzyl-(3S,4S)-dihydroxy-2,5-dioxopyrrolidine



In xylene (500 ml), D-tartaric acid (25.0 g, 0.17 mol) and benzylamine (19.6 g, 0.18 mmol) were heated under reflux for 18 hours by using a Dean-Stark water separator. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent, whereby 1-benzyl-(3S,4S)-dihydroxy-2,5-dioxopyrrolidine (33.7 g, 90 %) was obtained as a brown solid.

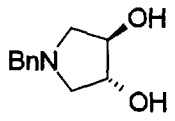
IR (KBr) ν 3291, 1710, 1434 cm^{-1};

^{1}H-NMR (CD_3OD) δ: 4.40 (s, 2H), 4.64 (s, 2H), 7.25-7.33 (m,

5H).

MS (FAB) m/z 222 (M^++1).

(Step 2) Synthesis of 1-benzyl-(3R,4R)-dihydroxypyrrolidine

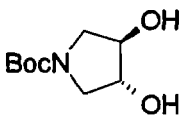


Under stirring at 0°C, 1-benzyl-(3S,4S)-dihydroxy-2,5-dioxopyrrolidine (17.3 g, 78.3 mmol) was added to a suspension of lithium aluminum hydride (8.91 g, 235 mmol) in THF (500 ml). The reaction mixture was heated under reflux for 18 hours. After the reaction mixture was cooled to 0°C, ethyl acetate (50 ml) was added thereto. The resulting mixture was stirred for 30 minutes and then, ice water was added. The reaction mixture was filtered through Celite. The filtrate was dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent to give 1-benzyl-(3R,4R)-dihydroxypyrrolidine (9.60 g, 63 %) as a red oil.

^{1}H-NMR ($CDCl_3$) δ: 2.45-2.47 (m, 2H), 2.94-2.98 (m, 2H), 3.63 (s, 2H), 4.08 (s, 2H), 7.24-7.33 (m, 5H).

MS (ESI) m/z 194 (M^++1).

(Step 3) Synthesis of 1-(tert-butoxycarbonyl)-(3R,4R)-dihydroxypyrrolidine

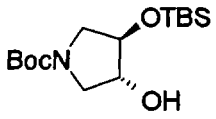


In ethyl acetate (400 ml), 5% palladium/carbon (53.1% wet, 4.20 g) was added to 1-benzyl-(3R,4R)-dihydroxypyrrolidine (9.60 g, 49.7 mmol) and di-tert-butyl dicarbonate (10.8 g, 49.7 mmol) and the resulting mixture was subjected to catalytic hydrogenation at room temperature under normal pressure for 14 hours. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent, whereby 1-(tert-butoxycarbonyl)-(3R,4R)-dihydroxypyrrolidine (5.64 g, 35 %) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 1.39 (s, 9H), 3.11 (dd, J=11.3,3.4Hz, 2H), 3.34-3.38 (m, 2H), 3.86-3.87 (m, 2H), 5.03-5.04 (m, 2H).

MS (ESI) m/z 189 (M^++1-CH_3).

(Step 4) Synthesis of 1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3R)-hydroxypyrrolidine



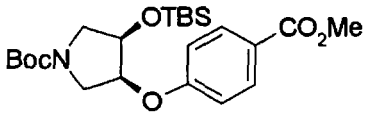
To a solution of 1-(tert-butoxycarbonyl)-(3R,4R)-dihydroxypyrrolidine (5.64 g, 27.8 mmol) in THF (50 ml) was added sodium hydride (60% in oil, 1.10 g, 27.5 mmol) in portions under stirring at 0°C. The reaction mixture was stirred at room temperature for 4 hours. To the reaction mixture was added tert-butyldimethylsilyl chloride (TBSCl) (4.15 g, 27.5 mmol), followed by stirring for 3 hours. To

the reaction mixture was added a saturated aqueous solution of ammonium chloride, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (2:1, v/v) eluate fractions, 1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3R)-hydroxypyrrolidine (5.27 g, 60%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.46 (s, 9H), 3.20-3.36 (m, 2H), 3.52-3.65 (m, 2H), 4.06-4.12 (m, 2H).

MS (ESI) m/z 318 (M^++1).

(Step 5) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3S)-pyrrolidinyloxy)benzoate



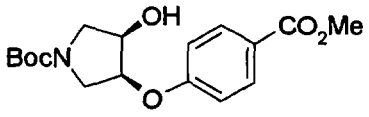
In THF (15 ml), DIAD (3.60 ml, 18.3 mmol) was added to 1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3R)-hydroxypyrrolidine (5.27 g, 16.6 mmol), methyl 4-hydroxybenzoate (2.53 g, 16.6 mmol), and triphenylphosphine (4.79 g, 18.3 mmol) and the resulting mixture was heated under reflux for 6 hours. The reaction mixture was cooled

to room temperature, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (5:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3S)-pyrrolidinyloxy)benzoate and a small amount of methyl 4-hydroxybenzoate were obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: -0.05 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 1.47 (s, 9H), 3.38 (m, 1H), 3.48-3.64 (m, 2H), 3.72 (m, 1H), 3.89 (s, 3H), 4.43 (m, 1H), 4.72 (m, 1H), 6.92 (d, J=8.8Hz, 2H), 7.97 (d, J=8.8Hz, 2H).

MS (ESI) m/z 437 (M^++1-CH_3).

(Step 6) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(4R)-hydroxy-(3S)-pyrrolidinyloxy)benzoate



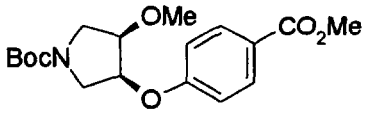
To the above-described methyl 4-(1-(tert-butoxycarbonyl)-(4R)-(tert-butyldimethylsilyloxy)-(3S)-pyrrolidinyloxy)benzoate and small amount of methyl 4-hydroxybenzoate (total 4.75 g) was added acetic acid - water - THF (3:1:1, v/v, 50 ml). The resulting mixture was stirred at room temperature for 23 hours. The reaction mixture was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with ethyl

acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (1:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4R)-hydroxy-(3S)-pyrrolidinyloxy)benzoate (3.86 g, 71% for 2 steps) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (broad s, 9H), 2.45 (m, 1H), 3.39-3.58 (m, 2H), 3.68-3.82 (m, 2H), 3.90 (s, 3H), 4.49 (m, 1H), 4.80 (m, 1H), 6.96 (d, J=8.1Hz, 2H), 8.00-8.03 (m, 2H).

MS (ESI) m/z 323 (M^++1-CH_3).

(Step 7) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate

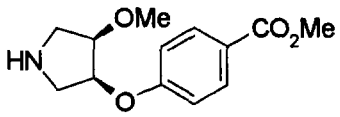


In THF (10 ml), sodium hydride (60% in oil, 72.0 mg, 1.79 mmol) was added in portions to methyl 4-(1-(tert-butoxycarbonyl)-(4R)-hydroxy-(3S)-pyrrolidinyloxy)benzoate (505 mg, 1.50 mmol) and methyl iodide (0.30 ml, 1.79 mmol) under stirring at 0°C. The resulting mixture was stirred further at the same temperature for 2 hours. To the reaction mixture was added a saturated aqueous solution of ammonium chloride, followed by extraction with ethyl

acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (3:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate (657 mg, 100 %) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (broad s, 9H), 3.41 (s, 3H), 3.44-3.72 (m, 4H), 3.89 (s, 3H), 4.04 (m, 1H), 4.87 (m, 1H), 6.96 (d, J=8.0Hz, 2H), 7.98-8.00 (m, 2H).

(Step 8) Synthesis of methyl 4-((4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate

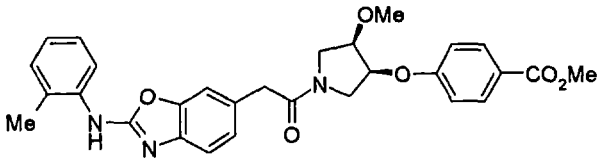


Methyl 4-(1-(tert-butoxycarbonyl)-(4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate (601 mg, 1.71 mmol) was dissolved in methylene chloride (10 ml). To the resulting solution was added trifluoroacetic acid (5 ml) under stirring at 0°C. The reaction mixture was stirred further for 2.5 hours at room temperature. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was dried over anhydrous sodium

sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 4-((4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate (339 mg, 79 %) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.11-3.20 (m, 3H), 3.28 (dd, J=12.5,5.6Hz, 1H), 3.38 (s, 3H), 3.89 (s, 3H), 3.99 (m, 1H), 4.79 (m, 1H), 6.96 (d, J=8.5Hz, 2H), 7.98 (d, J=8.5Hz, 2H).

(Step 9) Synthesis of methyl 4-((4R)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(3S)-pyrrolidinyloxy)benzoate



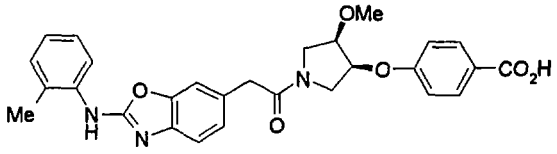
In DMF (5.0 ml), EDC HCl (192 mg, 1.00 mmol) was added to (2-(2-methylphenylamino)-6-benzoxazolyl)acetic acid (189 mg, 0.67 mmol), methyl 4-((4R)-methoxy-(3S)-pyrrolidinyloxy)benzoate (168 mg, 0.67 mmol), HOBt (18.0 mg, 0.13 mmol), and triethylamine (0.14 ml, 1.00 mmol) and the resulting mixture was stirred at room temperature for 24 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, methyl 4-((4R)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-

(3S)-pyrrolidinyloxy)benzoate (345 mg, 100 %) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.36 (s, 3H), 3.54-3.81 (m, 6H), 3.84 and 3.87 (each s, total 3H), 4.05 (m, 1H), 4.88 (m, 1H), 6.88-6.93 (m, 2H), 7.02-7.08 (m, 4H), 7.20-7.37 (m, 4H), 7.90-7.99 (m, 4H).

MS (ESI) m/z 516 (M^++1).

(Step 10) Synthesis of 4-((4R)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(3S)-pyrrolidinyloxy)benzoic acid



Methyl 4-((4R)-methoxy-1-((2-(2-methylphenylamino)-6-benzoxazolyl)acetyl)-(3S)-pyrrolidinyloxy)benzoate (345 mg, 0.67 mmol) was dissolved in THF (7.0 ml). To the resulting solution was added 0.25N NaOH (4.01 ml, 1.00 mmol). The resulting mixture was stirred at room temperature for 7 hours. The reaction mixture was poured in 1N HCl (3.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give the title compound (218 mg, 65 %) as a colorless solid.

IR (ATR) ν 2935, 1683, 1639, 1602, 1575, 1508, 1440 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H), 3.52 and 3.28 (each s,

total 3H), 3.41-3.65 (m, 2H), 3.68 and 3.71 (each s, total 2H), 3.79-3.99 (m, 2H), 4.12 and 4.19 (each m, total 1H), 5.11 and 5.17 (each m, total 1H), 7.03-7.11 (m, 4H), 7.22-7.28 (m, 3H), 7. 31 (d, J=8.8Hz, 1H), 7.79 (d, J=7.9Hz, 1H), 7.88 (d, J=8.8Hz, 2H), 9.85 (broad s, 1H).

MS (FAB) m/z 502 (M^++1);

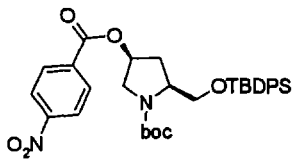
Anal. Calcd for $C_{28}H_{27}N_3O_6$ 1.5H_2O: C, 63.63; H, 5.72; N, 7.95.

Found: C, 63.69; H, 5.55; N, 8.01.

Example 156

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 1-tert-butoxycarbonyl-(2S)-tert-butyldiphenylsilyloxymethyl-(4S)-(4-nitrobenzoyloxy)pyrrolidine



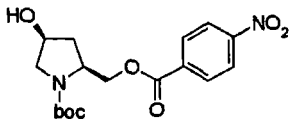
In THF (300 ml), DIAD (4.53 ml, 23.0 mmol) was added to 1-tert-butoxycarbonyl- (2S)-tert-butyldiphenylsilyloxymethyl-(4R)-hydroxypyrrolidine (10.51 g, 23.0 mmol), 4-nitrobenzoic acid (3.85 g, 23.0 mmol) and triphenylphosphine (6.03 g, 23.0 mmol) and the resulting mixture was stirred at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under

reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (5/1) eluate fractions, 1-tert-butoxycarbonyl-(2S)-tert-butyldiphenylsilyloxymethyl-(4S)-(4-nitrobenzoyloxy)pyrrolidine (15.39 g, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.02 (s, 9H), 1.36 and 1.45 (each s, total 9H, amide isomers), 2.39-2.64 (m, 2H), 3.44-3.78 (m, 2H), 3.87 (dd, J=13.0,5.4Hz, 1H), 3.98-4.24 (m, 2H), 5.56 (br, 1H), 7.26 (m, 2H), 7.28-7.41 (m, 4H), 7.51-7.65 (m, 4H), 8.01 (d, J=8.1Hz, 2H), 8.16 (d, J=7.8Hz, 2H).

MS (ESI) m/z 606 (M^++1).

(Step 2) Synthesis of 1-tert-butoxycarbonyl-(4S)-hydroxy-(2S)-(4-nitrobenzoyloxymethyl)pyrrolidine



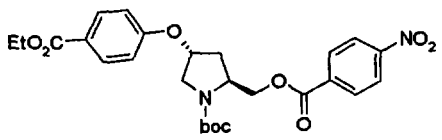
In THF (500 ml) was dissolved 1-tert-butoxycarbonyl-(2S)-tert-butyldiphenylsilyloxymethyl-(4S)-(4-nitrobenzoyloxy)pyrrolidine (15.4 g, 24.5 mmol). To the resulting solution was added a 1.0M tetrabutylammonium fluoride - THF solution (25.4 ml, 25.4 mmol) under stirring at 0°C. The temperature of the reaction mixture was gradually raised back to room temperature, at which stirring was conducted for 14 hours. Water was added to

the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2/1) and chloroform/acetone eluate fractions, 1-tert-butoxycarbonyl-(4S)-hydroxy-(2S)-(4-nitrobenzoyloxymethyl)pyrrolidine (2.53 g, 27.2%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 1.90-2.16 (m, 2H), 2.24 (m, 1H), 3.42 (d, J=12.2Hz, 1H), 3.68-3.80 (m, 1H), 4.22 and 4.36 (each br, total 1H, amide isomers), 4.51-4.72 (m, 3H), 8.23-8.29 (m, 4H).

MS (ESI) m/z 367 (M^++1).

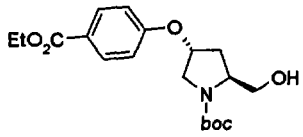
(Step 3) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(2S)-(4-nitrobenzoyloxymethyl)-(4R)-pyrrolidinyloxy)benzoate



In THF (100 ml), DIAD (1.36 ml, 6.91 mmol) was added to 1-tert-butoxycarbonyl-(4S)-hydroxy-(2S)-(4-nitrobenzoyloxymethyl)pyrrolidine (2.53 g, 6.91 mmol), ethyl 4-hydroxybenzoate (1.15 g, 6.91 mmol) and triphenylphosphine (1.81 g, 6.91 mmol) and the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was distilled under reduced pressure to

remove the solvent. The residue was purified by chromatography on a silica gel column, and chloroform/ethyl acetate (5/1) eluate fractions were collected, followed by flash chromatography on a silica gel column (ϕ 4 x 40 cm, chloroform/ethyl acetate (5/1)) to give ethyl 4-(1-tert-butoxycarbonyl-(2S)-(4-nitrobenzoyloxymethyl)-(4R)-pyrrolidinyloxy)benzoate (2.55 g, 72%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (dt, J=7.1,2.0Hz, 3H), 1.56 (s, 9H), 2.12-2.32 (m, 2H), 2.44 (m, 1H), 3.60 (dd, J=12.2,4.4Hz, 1H), 3.83 and 3.99 (each br, total 1H, amide isomers), 4.35 (dq, J=7.1,2.0Hz, 2H), 4.41-4.62 (m, 2H), 4.96 (s, 1H), 6.86 (d, J=6.8Hz, 2H), 7.99 (d, J=7.3Hz, 2H), 8.19 (d, J=7.3Hz, 2H), 8.27 (d, J=8.3Hz, 1H), 8.28 (d, J=7.3Hz, 1H). MS (ESI) m/z 515 (M^++1).

(Step 4) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate



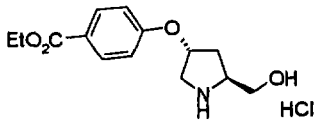
In ethanol (100 ml), potassium carbonate (685 mg, 4.96 mmol) was added to ethyl 4-(1-tert-butoxycarbonyl-(2S)-(4-nitrobenzoyloxymethyl)-(4R)-pyrrolidinyloxy)benzoate (2.55 g, 4.96 mmol) and the resulting mixture was stirred at room temperature for 24 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was

purified by chromatography on a silica gel column, whereby from chloroform/ethyl acetate (5/1) eluate fractions, ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate (1.36 g, 75%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, J=7.1Hz, 3H), 1.46 (s, 9H), 1.89 (br, 1H), 2.34 (m, 1H), 3.58-3.97 (m, 4H), 4.05-4.26 (m, 1H), 4.35 (q, J=7.1Hz, 2H), 4.69 and 4.88 (each br, total 1H, amide isomers), 6.87 (d, J=8.8Hz, 2H), 8.00 (d, J=8.5Hz, 2H).

MS (ESI) m/z 366 (M^++1).

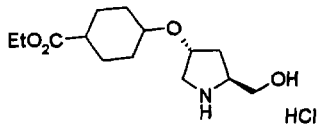
(Step 5) Synthesis of ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate hydrochloride



Ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate (1.36 g, 3.72 mmol) was dissolved in dioxane (50 ml). To the resulting solution was added a 4N HCl/dioxane solution (30 ml) and the mixture was stirred at room temperature for 3.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent, whereby ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate hydrochloride (1.21 g, 100%) was obtained as a brown oil. The resulting compound was provided for the subsequent reaction without further

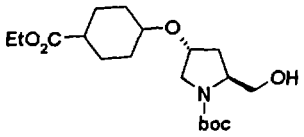
purification.

(Step 6) Synthesis of ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate hydrochloride



In ethanol (30 ml), ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)benzoate hydrochloride (1.21 g, 3.72 mmol) and rhodium/alumina (1.2 g) were subjected to catalytic hydrogenation at room temperature for 3 days under 4 kg/cm^2 of a hydrogen gas. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent, whereby ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate hydrochloride as a brown oil. The resulting compound was provided for the subsequent reaction without further purification.

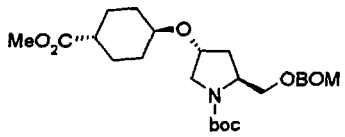
(Step 7) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate



In dioxane (30 ml), di-tert-butyl dicarbonate (812 mg, 3.72 mmol) was added to ethyl 4-((2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate hydrochloride (3.72 mmol) and a saturated aqueous solution of sodium bicarbonate (10 ml) and the resulting mixture was stirred

at room temperature for 2 days. Ethyl acetate was added to the reaction mixture. The resulting mixture was washed saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.28 g, 93% (3 steps)) as a brown oil. The resulting compound was provided for the subsequent reaction without further purification.

(Step 8) Synthesis of methyl trans-4-(1-tert-butoxycarbonyl-(2S)-benzyloxymethoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate



Ethyl 4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.28 g, 3.45 mmol) was dissolved in methylene chloride (30 ml). To the resulting solution were added N,N-diisopropylethylamine (1.20 ml, 6.90 mmol) and benzyloxycarbonyl chloride (BOMCl) (0.72 ml, 5.18 mmol). The resulting mixture was stirred at room temperature for 14 hours in a nitrogen gas stream. The reaction mixture was poured in water, followed by extraction with methylene chloride. The extract was washed with 1N HCl and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and

distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2/1) eluate fractions, ethyl 4-(1-tert-butoxycarbonyl-(2S)-benzyloxymethyloxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.02 g, 60%) was obtained as a colorless oil. The resulting compound was isomerized in the subsequent step.

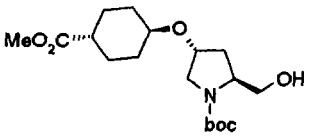
In ethanol, sodium ethoxide (1.41 g, 20.7 mmol) was added to ethyl 4-(1-tert-butoxycarbonyl-(2S)-benzyloxymethyloxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.02 g, 2.07 mmol). The resulting mixture was heated under reflux for 13 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was dissolved in methanol/toluene (1:10, 22 ml). To the resulting solution was added a 2.0M hexane solution (1.04 ml, 2.07 mmol) of trimethylsilyldiazomethane. The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by flash chromatography on a silica gel column (ϕ 3 × 30

cm, eluted in: n-hexane/ethyl acetate (10/1)) and by chromatography using a silica gel thin-layer plate (TLC) (developed in n-hexane/ethyl acetate (10/1)) to give methyl trans-4-(1-tert-butoxycarbonyl-(2S)-benzyloxymethyloxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (326 mg, 33% (2 steps) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.30 (m, 3H), 1.39-1.51 (m, 11H), 1.92-2.22 (m, 6H), 2.25 (tt, J=11.8,2.9Hz, 1H), 3.24 (tt, J=10.3,3.7Hz, 1H), 3.30-3.64 (m, 2H), 3.66 (s, 3H), 3.75 (br, 1H), 4.02 and 4.09 (each br, total 1H, amide isomers), 4.21 (br, 1H), 4.58 (s, 2H), 4.73 (d, J=4.6Hz, 2H), 7.29 (m, 1H), 7.33 (s, 2H), 7.34 (s, 2H).

MS (ESI) m/z 478 (M^++1).

(Step 9) Synthesis of methyl trans-4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate



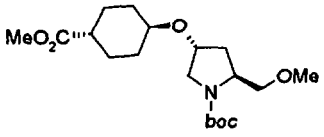
In methanol (10 ml), methyl trans-4-(1-tert-butoxycarbonyl-(2S)-benzyloxymethyloxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (326 mg, 0.683 mmol) and 5% palladium/carbon (wet.) (326 mg) were subjected to catalytic hydrogenation at room temperature for 14 hours. From the reaction mixture, the catalyst was filtered off

and the filtrate was distilled under reduced pressure to remove the solvent to give methyl trans-4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (247 mg, 100%) as a colorless oil. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.33 (m, 3H), 1.39 (m, 1H), 1.47 (s, 9H), 1.61-1.71 (m, 1H), 1.95-2.10 (m, 5H), 2.26 (m, 1H), 3.24 (m, 1H), 3.33-3.51 (m, 2H), 3.53 and 3.56 (each d, J=6.8 and 7.1Hz respectively, total 1H, amide isomers), 3.66 (s, 3H), 3.68 (m, 1H), 4.09 (br, 2H).

MS (ESI) m/z 358 (M^++1).

(Step 10) Synthesis of methyl trans-4-(1-tert-butoxycarbonyl-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate



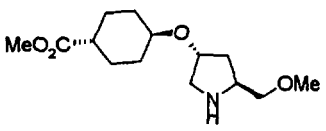
Methyl trans-4-(1-tert-butoxycarbonyl-(2S)-hydroxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (247 mg, 0.683 mmol) was dissolved in DMF (5 ml). To the resulting solution was added sodium hydride (60% in oil, 55 mg, 1.37 mmol) in portions under stirring at 0°C in a nitrogen gas stream. After the reaction mixture was stirred at the same temperature for 30 minutes, methyl iodide (85 µl, 1.37 mmol) was added thereto. Stirring was

conducted further at the same temperature for 4 hours. Sodium hydride (60% in oil, 55 mg, 1.37 mmol) and methyl iodide (85 µl, 1.37 mmol) were added and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured in water, followed by extraction with chloroform. The extract was washed with a saturated aqueous solution of sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate(2/1) eluate fractions, trans-4-(1-tert-butoxycarbonyl-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (260 mg, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.32 (m, 3H), 1.39-1.52 (m, 10H), 1.91-2.13 (m, 6H), 2.21-2.29 (m, 1H), 3.25 (m, 1H), 3.34 (s, 3H), 3.37-3.53 (m, 4H), 3.66 (s, 3H), 3.79 and 4.05 (each br, total 1H, amide isomers), 4.14 and 4.21 (each br, total 1H, amide isomers).

MS (ESI) m/z 372 (M^++1).

(Step 11) Synthesis of methyl trans-4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate



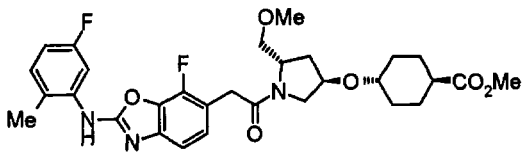
Methyl trans-4-(1-tert-butoxycarbonyl-(2S)-

methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (260 mg, 0.70 mmol) was dissolved in methylene chloride (10 ml). To the resulting solution was added trifluoroacetic acid (2 ml) and the mixture was stirred at room temperature for 14 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was basified with 1N NaOH, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (150 mg, 81%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-2.39 (m, 11H), 2.87 (dd, J=11.5,3.2Hz, 1H), 3.05 (dd, J=11.5, 4.9Hz, 1H), 3.20-3.34 (m, 2H), 3.35 (s, 3H), 3.48 (m, 2H), 3.66 (s, 3H), 4.07 and 4.14 (each br, total 1H, amide isomers).

MS (ESI) m/z 272 (M^++1).

(Step 12) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate

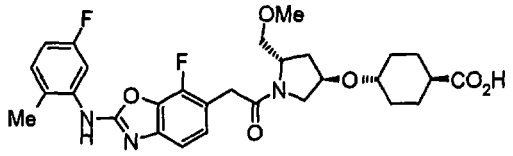


In DMF (2 ml), (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (59 mg, 0.184 mmol),

methyl trans-4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy) cyclohexanecarboxylate (50 mg, 0.184 mmol), EDC HCl (53 mg, 0.276 mmol), HOBT (37 mg, 0.276 mmol) and triethylamine (128 µl, 0.920 mmol) were stirred at room temperature for 3 days. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, and heated under reflux over anhydrous sodium sulfate. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography using a silica gel thin-layer plate (chloroform/acetone (7/1) eluent) to give methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (99 mg, 94%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.58 (m, 4H), 1.91-2.29 (m, 6H), 2.30 (s, 3H), 3.24 (m, 1H), 3.31 and 3.36 (each s, total 3H, amide isomers), 3.38-3.53 (m, 3H), 3.65 and 3.66 (s, 3H), 3.67-3.70 (m, 1H), 3.72 (s, 2H), 3.81-3.92 (m, 1H), 4.35-4.39 (m, 2H), 6.74 (dt, J=8.1,2.2Hz, 1H), 7.09-7.16 (m, 2H), 7.22 (d, J=8.1Hz, 1H), 8.06 (dd, J=11.0,2.4Hz, 1H).
MS (ESI) m/z 572 (M^++1).

(Step 13) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (99 mg, 0.173 mmol) was dissolved in THF/methanol (4/2 ml). To the resulting solution was added 1N NaOH (2 ml). After stirring at room temperature for 13 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The crude crystals were purified by column chromatography using a silica gel thin-layer plate (TLC) (chloroform/methanol (20/1) developing solution) to give the title compound (61 mg, 63%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.12-1.41 (m, 5H), 1.86-2.20 (m, 6H), 2.30 (s, 3H), 3.23 (s, 3H), 3.38-3.98 (m, 7H), 4.09 and 4.31 (each m, total 2H, amide isomers), 6.89(dt, J=8.3, 2.9Hz, 1H), 7.09 (d, J=7.8Hz, 1H), 7.19 and 7.20 (each d, each J=8.1Hz, total 1H, amide isomers), 7.26 (t, J=7.8Hz, 1H), 7.89-7.93 (m, 1H), 10.05 (br, 1H), 12.06 (br, 1H).

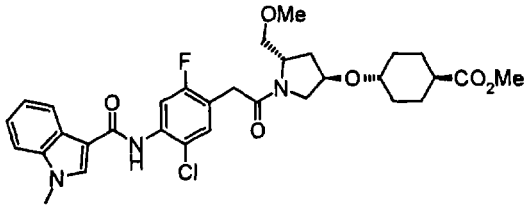
MS (ESI) m/z 558 (M^++1).

Example 157

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-

indolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate



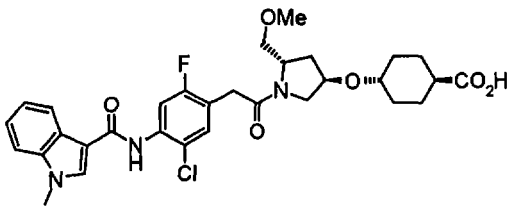
In DMF (2 ml), (5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetic acid (66 mg, 0.184 mmol), methyl trans4-((2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy) cyclohexanecarboxylate (50 mg, 0.184 mmol), EDC HCl (53 mg, 0.276 mmol), HOBt (37 mg, 0.276 mmol) and triethylamine (128 µl, 0.920 mmol) were stirred at room temperature for 3 days. The reaction mixture was poured in ice water, followed by extraction. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC) (developed with chloroform/acetone (7/1)) to give methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (99 mg,

88%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.56 (m, 4H), 1.92-2.38 (m, 6H), 3.21-3.32 (m, 1H), 3.33 and 3.35 (each s, total 3H, amide isomers), 3.37-3.49 (m, 2H), 3.61 (d, J=5.4Hz, 1H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.67-3.72 (m, 2H), 3.84 (m, 1H), 3.88 (s, 3H), 4.23-4.39 (m, 2H), 7.33-7.45 (m, 4H), 7.81 (s, 1H), 8.14 (m, 1H), 8.29 (s, 1H), 8.49 and 8.50 (each d, each J=12.0Hz, total 1H, amide isomers).

MS (ESI) m/z 614 (M^++1), 616 (M^++3).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (99 mg, 0.161 mmol) was dissolved in THF/methanol (2:1, 6 ml). To the resulting solution was added 1N NaOH (2 ml). After stirring at room temperature for 13 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The

crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The crude crystals were purified by chromatography using a silica gel thin-layer plate (TLC) (developed in chloroform/methanol (20/1)) to give the title compound (35 mg, 36%) as a colorless solid.

IR (ATR) ν 3417, 2935, 1724, 1641, 1620, 1518, 1404 cm^{-1};

^{1}H-NMR (DMSO) δ: 1.11-1.41 (m, 4H), 1.87-2.19 (m, 7H), 3.24 (s, 3H), 3.31 (s, 1H), 3.35-3.56 (m, 3H), 3.67 (s, 2H), 3.68-3.86 (m, 1H), 3.89 (s, 3H), 4.09 and 4.33 (each m, total 2H, amide isomers), 7.21 (t, J=6.9Hz, 1H), 7.27 (dt, J=8.1,1.0Hz, 1H), 7.45 (t, J=7.3Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 7.69 and 7.70 (each d, J=11.0 and 11.3Hz respectively, total 1H, amide isomers), 8.14 (d, J=7.6Hz, 1H), 8.31 (s, 1H), 9.31 (s, 1H), 12.05 (br, 1H).

MS (ESI) m/z 600 (M^++1), 602 (M^++3);

Anal. Calcd for $C_{31}H_{35}ClFN_3O_6$ $0.6H_2O$: C, 60.95; H, 5.97; Cl, 5.80;F, 3.11; N, 6.88.

Found: C, 60.79; H, 5.99; Cl, 5.83; F, 3.02; N, 6.83.

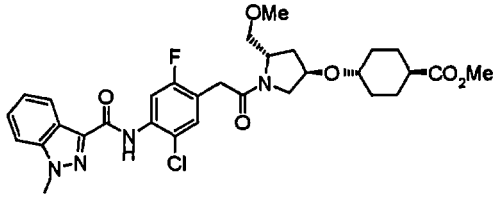
Example 158

trans-4-(1-((5-Chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-

(2S)-methoxymethyl-(4R)-

pyrrolidinylmethoxy)cyclohexanecarboxylate



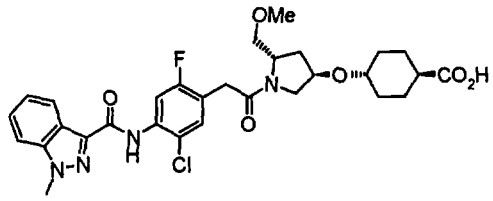
In DMF (2 ml), (5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetic acid (137 mg, 0.380 mmol), methyl trans-4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (103 mg, 0.380 mmol), EDC HCl (109 mg, 0.570 mmol), HOBt (77 mg, 0.570 mmol) and triethylamine (0.26 ml, 1.9 mmol) were stirred at room temperature for 21 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC) (chloroform/acetone (7/1) developing solution) to give methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (198 mg, 85%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.51 (m, 4H), 1.78 and 1.80 (each s, total 2H, amide isomers), 1.91-2.29 (m, 6H), 3.25 (m, 1H),

3.32 and 3.36 (each s, total 3H, amide isomers), 3.38-3.50 (m, 2H), 3.62 and 3.66 (each s, total 3H, amide isomers), 3.69 (m, 1H), 3.87 (s, 1H), 3.90 (s, 3H), 4.25-4.39 (m, 2H), 7.22 (t, J=7.3Hz, 1H), 7.35-7.46 (m, 4H), 8.01 (s, 1H), 8.43 and 8.44 (each d, each J=3.2Hz, total 1H, amide isomers).

MS (ESI) m/z 615 (M^++1), 617 (M^++3).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indazolylcarbonylamino)phenyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (198 mg, 0.322 mmol) was dissolved in THF/methanol (2:1, 12 ml). To the resulting solution was added 1N NaOH (4 ml). After stirring at room temperature for 13 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (145 mg, 75%)

as a colorless amorphous substance.

IR (ATR) ν 3361, 2939, 2864, 1724, 1685, 1620, 1529, 1408 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.43 (m, 4H), 1.84-2.21 (m, 7H), 3.25 (s, 3H), 3.34-3.57 (m, 4H), 3.68 (d, J=4.4Hz, 2H), 3.74 (q, J=18.6Hz, 1H), 4.09 and 4.35 (each m, total 2H, amide isomers), 4.22 (s, 3H), 7.38 (t, J=6.8Hz, 1H), 7.51 (t, J=7.8Hz, 1H), 7.54 (t, J=7.8Hz, 1H), 7.83 (d, J=8.5Hz, 1H), 8.07 (dd, J=11.2,1.2Hz, 1H), 8.21 (dd, J=8.1,1.2Hz, 1H), 9.72 (s, 1H), 12.07 (br, 1H).

MS (ESI) m/z 601 (M^++1), 603 (M^++3);

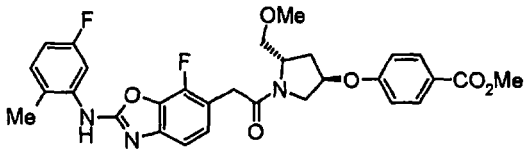
Anal. Calcd for $C_{30}H_{34}ClFN_4O_6$ 0.5H_2O 0.1HCl: C, 58.71; H, 5.76; Cl, 6.35; F, 3.10; N, 9.13.

Found: C, 58.83; H, 5.66; Cl, 6.60; F, 3.06; N, 9.14.

Example 159

4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoic acid:

(Step 1) Synthesis of methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoate



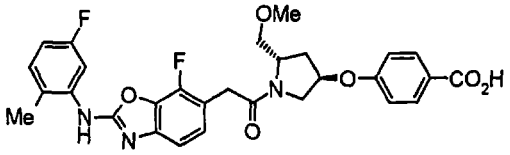
In DMF (2 ml), (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (127 mg, 0.400 mmol),

methyl 4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoate (106 mg, 0.400 mmol), EDC HCl (115 mg, 0.600 mmol), HOBt (81 mg, 0.600 mmol) and triethylamine (0.28 ml, 2.00 mmol) were stirred at room temperature for 21 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC) (chloroform/acetone (5/1) developing solution) to give methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoate (118 mg, 52%) as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 2.23-2.43 (m, 5H; including 2.32 ppm., s, 3H), 3.35 and 3.39 (each s, total 3H, amide isomers), 3.46-3.92 (m, 8H; including 3.79 ppm., s, 3H), 4.40 and 4.47 (each m, total 1H, amide isomers), 5.02 (m, 1H), 6.72-6.85 (m, 3H), 7.05 (br, 1H), 7.13 (d, J=8.3Hz, 1H), 7.15 (d, J=7.3Hz, 1H), 7.20 (d, J=8.0Hz, 1H), 7.92 (d, J=9.0Hz, 2H), 8.12 (dd, J=11.0,2.7Hz, 1H).

MS (ESI) m/z 566 (M^++1).

(Step 2) Synthesis of 4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoic acid



Methyl 4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinyloxy)benzoate (118 mg, 0.209 mmol) was dissolved in THF/methanol (2:1, 12 ml). To the resulting solution was added 1N NaOH (4 ml). After stirring at room temperature for 18 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (92 mg, 80%) as a colorless solid.

IR (ATR) ν 2939, 1684, 1639, 1604, 1577, 1506, 1452, 1244 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 2.17 (m, 1H), 2.30 (s, 3H), 2.32 (m, 1H), 3.32 and 3.35 (each s, total 3H, amide isomers), 3.48 (m, 1H), 3.51-3.58 (m, 1H), 3.73 (d, J=7.6Hz, 1H), 3.79 (d, J=10.2Hz, 1H), 3.82-4.00 (m, 2H), 4.22 and 4.50 (each m, total 1H, amide isomers), 5.13 and 5.18 (each m, total 1H, amide isomers), 6.89 (dt, J=8.5, 1.7Hz, 1H), 7.00 and 7.01 (eachd, each J=7.6Hz, total 2H, amide isomers), 7.06 and 7.09 (each d, J=7.1 and 4.4Hz respectively, total 1H, amide isomers), 7.19 (d, J=8.8Hz, 1H), 7.26 (t, J=7.8Hz, 1H),

7.88 (d, J=8.3Hz, 2H), 7.92 (d, J=11.0Hz, 1H), 10.03 (br, 1H), 12.63 (br, 1H).

MS (ESI) m/z 552 (M^++1);

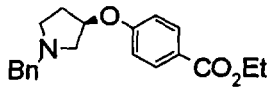
Anal. Calcd for $C_{29}H_{27}FN_3O_6$ $0.5H_2O$: C, 62.14; H, 5.03; F, 6.78; N, 7.50.

Found: C, 62.33; H, 5.01; F, 6.70; N, 7.40.

Example 160

4-(1-(2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl 4-(1-benzyl-(3R)-pyrrolidinyloxy)benzoate

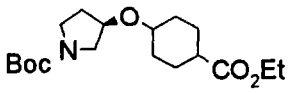


In THF (30 ml), DIAD (5.2 ml, 36.7 mmol) was added to 1-benzyl-(2S)-hydroxypyrrolidine (5.0 g, 28.2 mmol), ethyl 4-hydroxybenzoate (4.6 g, 28 mmol), and triphenylphosphine (9.6 g, 36.7 mmol) under stirring at 0°C. The reaction mixture was stirred at room temperature for 18 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (4:1 to 1:1, v/v) eluate fractions, ethyl 4-(1-benzyl-(3R)-pyrrolidinyloxy)benzoate (5.8 g, 64%) was obtained as an amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.36 (t, J=7.1Hz, 3H), 1.67 (br s, 1H),

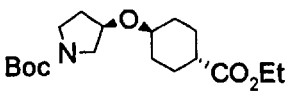
1.95-2.04 (m, 1H), 2.30-2.33 (m, 1H), 2.58-2.62 (m, 1H), 2.73-2.78 (m, 2H), 2.96-3.00 (m, 1H), 3.67 (AB q, J=7.0Hz, 2H), 4.33 (q, J=7.1Hz, 2H), 4.86-4.89 (m, 1H), 6.83 (d, J=9.0Hz, 2H), 7.25-7.32 (m, 5H), 7.96 (d, J=9.0Hz, 2H).

(Step 2) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate



In ethanol (10 ml) and acetic acid (1.0 ml), ethyl 4-(1-benzyl-(3R)-pyrrolidinyloxy)benzoate (3.8 g, 11.7 mmol) and 5% rhodium/alumina (1.9 g) were subjected to catalytic hydrogenation for 24 hours under a hydrogen gas of 5 atom. From the reaction mixture, the catalyst was filtered off, and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (5:1 to 4:1, v/v) eluate fractions, ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.9 g, 47%) was obtained as a pale yellow oil.

(Step 3) Synthesis of ethyl trans-4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate

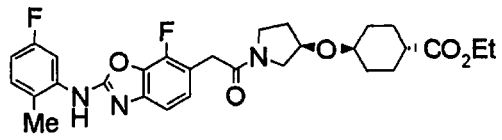


Ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (1.7 g, 4.98 mmol)

and sodium methoxide (a 20% ethanol solution) (3.5 ml) were heated under reflux for 3 hours in ethanol (15 ml). After cooling, the reaction mixture was diluted with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (4:1, v/v) eluate fractions, ethyl trans-4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (280 mg, 16%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.35 (m, 5H), 1.40-1.50 (m, 11H), 1.80-2.05 (m, 6H), 2.20-2.30 (m, 1H), 3.20-3.50 (m, 5H), 4.10-4.20 (m, 3H).

(Step 4) Synthesis of ethyl 4-(1-(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)- (3R)-pyrrolidinyloxy)cyclohexanecarboxylate



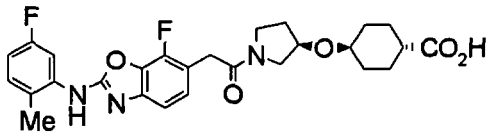
Ethyl trans-4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (280 mg, 0.82 mmol) was dissolved in methylene chloride (5.0 ml). Under stirring at 0°C, trifluoroacetic acid (5.0 ml) was added to

the resulting solution. The reaction mixture was stirred at room temperature for 0.5 hour. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent (the resulting product was used to the subsequent reaction without further purification). In THF (5.0 ml) and acetonitrile (5.0 ml), EDC·HCl (119 mg, 0.62 mmol) were added to the residue (0.41 mmol), (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (130 mg, 0.41 mmol), HOBt (84 mg, 0.41 mmol), and triethylamine (170 µl, 1.23 mmol) under ice cooling at 0°C. The reaction mixture was stirred at room temperature for 16 hours, and distilled under reduced pressure to remove the solvent. The residue was diluted with water, followed by extraction with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous solution of citric acid, and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography using a silica gel thin-layer plate (TLC) (n-hexane-ethyl acetate (1:3, v/v) developing solution) to give ethyl 4-(1-

(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (170 mg, 77%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.38 (m, 5H), 1.39-1.55 (m, 2H), 1.85-2.10 (m, 6H), 2.19-2.30 (m, 1H), 2.31 (s, 3H), 3.20-3.32 (m, 1H), 3.50-3.80 (m, 6H), 4.07-4.14 (m, 2H), 4.20-4.27 (m, 1H), 6.73-6.77 (m, 1H), 7.02 (br s, 1H), 7.12-7.26 (m, 4H), 8.08-8.11 (m, 1H).

(Step 5) Synthesis of 4-(1-(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)cyclohexanecarboxylic acid



Ethyl 4-(1-(2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolylacetyl)-(3R)-pyrrolidinyloxy)cyclohexanecarboxylate (170 mg, 0.31 mmol) was dissolved in THF (5.0 ml) and methanol (3.0 ml). To the resulting solution was added 1N NaOH (1.0 ml, 1.0 mmol). The resulting mixture was stirred at 70°C for 18 hours. The reaction mixture was cooled and distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the

title compound (140 mg, 87%) as a white solid.

IR (KBr) ν 2940, 1639, 1610, 1577, 1454, 1070 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.25 (m, 2H), 1.30-1.45 (m, 2H), 1.80-2.00 (m, 6H), 2.10-2.20 (m, 1H), 2.29 (s, 3H), 3.30-3.80 (m, 7H), 4.20-4.29 (m, 1H), 6.86-6.91 (m, 1H), 7.09 (t, J=6.8Hz, 1H), 7.20-7.27 (m, 2H), 7.92 (d, J=11.4Hz, 1H).

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

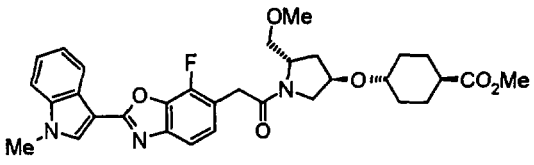
Anal. Calcd for $C_{27}H_{29}F_2N_3O_5$ $0.8H_2O$: C, 61.43; H, 5.84; N, 7.96.

Found: C, 61.64; H, 5.79; N, 7.77.

Example 161

trans-4-(1-((7-Fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate



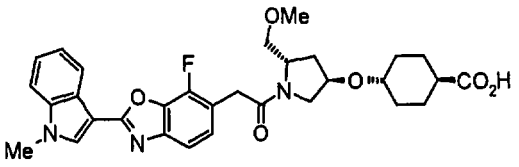
In DMF (2 ml), (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (122 mg, 0.376 mmol), methyl trans-4-((2S)-methoxymethyl-(4R)-pyrrolidinyloxy)cyclohexanecarboxylate (102 mg, 0.376

mmol), EDC HCl (108 mg, 0.564 mmol), HOBt (76 mg, 0.564 mmol) and triethylamine (0.26 ml, 1.88 mmol) were stirred at room temperature for 21 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with ice water and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC) (chloroform/acetone (10/1) developing solution) to give methyl trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6- benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (175 mg, 84%) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.53 (m, 4H), 1.82 (s, 1H), 1.93-2.31 (m, 7H), 3.25 (m, 1H), 3.33 and 3.34 (each s, total 3H, amide isomers), 3.42 (d, J=9.8Hz, 2H), 3.61 and 3.63 (each s, total 3H, amide isomers), 3.65 (s, 1H), 3.66-3.88 (m, 2H), 4.15 (s, 3H), 4.23-4.34 (m, 2H), 7.33 (t, J=6.1Hz, 1H), 7.39 (d, J=7.3Hz, 1H), 7.45 (m, 2H), 8.37 (d, J=8.1Hz, 1H), 8.49 and 8.51 (each d, each J=11.7Hz, total 1H, amide iosmers), 9.48 (s, 1H).

MS (ESI) m/z 578 (M^++1).

(Step 2) Synthesis of trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6- benzoxazolyl)acetyl)-(2S)-methoxymethyl-(4R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (175 mg, 0.324 mmol) was dissolved in THF/methanol (8/4 ml). To the resulting solution was added 1N NaOH (4 ml). After stirring at room temperature for 15 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (129 mg, 73%) as a colorless solid.

IR (ATR) ν 2937, 2864, 1724, 1626, 1583, 1502, 1442, 1369 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.41 (m, 4H), 1.83-2.19 (m, 7H), 3.24 (s, 3H), 3.7-3.38 (m, 1H), 3.42 (d, J=4.7Hz, 2H), 3.51 and 3.55 (each dd, J=10.7,4.2 and 10.7,2.9Hz respectively, total 1H, amide isomers), 3.70 (dd, J=10.5,5.4Hz, 1H), 3.81 (s, 3H), 3.91 (s, 3H), 4.10 and 4.34 (each m, total 2H, amide isomers), 7.22 (t, J=6.6Hz, 1H), 7.33 (dq, J=7.1,1.0Hz, 1H), 7.35 (dq, J=7.1,1.0Hz, 1H), 7.47 and 7.48 (each d, J=8.1 and 8.3Hz respectively, total 1H, amide isomers), 7.63 (dd, J=6.8,1.5Hz, 1H), 8.29 (dd,

J=6.3,1.5Hz, 1H), 8.44 (s, 1H), 12.05 (s, 1H).

MS (ESI) m/z 564 (M^++1);

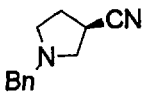
Anal. Calcd for $C_{31}H_{34}FN_3O_6$ $0.5H_2O$: C, 65.02; H, 6.16; F, 3.32; N, 7.34.

Found: C, 64.72; H, 6.15; F, 3.21; N, 7.28.

Example 162

4-(1-(5-Chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethoxy) benzoic acid:

(Step 1) Synthesis of 1-benzyl-(3R)-cyanopyrrolidine

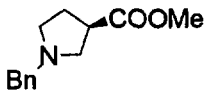


In methylene chloride (25 ml) were dissolved 1-benzyl-(3S)-hydroxypyrrolidine (4.0 g, 22.6 mmol) and triethylamine (9.1 ml, 66 mmol). Methanesulfonyl chloride (3.76 g, 33 mmol) was added dropwise under stirring at 0°C. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for hour, and then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane:ethyl acetate (1:4, v/v) eluate fractions, the resulting product was obtained as a pale yellow oil. The oil was dissolved in DMSO (25 ml), and to the resulting solution was added sodium cyanide (6.0 g, 113 mmol). The resulting mixture was stirred at 60°C

for 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane:ethyl acetate (3:1 to 1:1, v/v) eluate fractions, 1-benzyl-(3R)-cyanopyrrolidine (3.2 g, 77%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 2.05-2.30 (m, 2H), 2.58-2.70 (m, 3H), 2.80-3.05 (m, 2H), 3.64 (AB q, J=12.9Hz, 2H), 7.25-7.34 (m, 5H).

(Step 2) Synthesis of methyl 1-benzyl-(3R)-pyrrolidinylcarboxylate

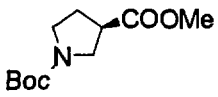


In concentrated HCl (15 ml), 1-benzyl-(3R)-cyanopyrrolidine (2.0 g, 10.75 mmol) was heated under reflux for 0.5 hour. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was dissolved in methanol (10 ml). Under stirring at -50°C, and thionyl chloride (2.6 ml) was added. The mixture was stirred further at room temperature for 18 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was

neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane:ethyl acetate (2:1 to 1:2, v/v) eluate fractions, methyl 1-benzyl-(3R)-pyrrolidinylcarboxylate (1.6 g, 70%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 2.08-2.12 (m, 2H), 2.50-2.69 (m, 3H), 2.88-3.03 (m, 2H), 3.62 (s, 3H), 3.67 (s, 3H), 7.25-7.32 (m, 5H).

(Step 3) Synthesis of methyl 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylate

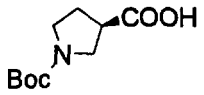


Methyl 1-benzyl-(3R)-pyrrolidinylcarboxylate (1.6 g, 7.3 mmol) and palladium hydroxide-carbon (300 mg) were subjected to catalytic hydrogenation in methanol (15 ml) under normal pressure for 18 hours. From the reaction mixture, the catalyst was filtered off, and the filtrate was distilled under reduced pressure to remove the solvent, whereby a colorless oil was obtained. The oil was dissolved in methylene chloride (20 ml). To the resulting solution were added di-tert-butyl dicarbonate (2.0 g, 9.5 mmol) and triethylamine (2.0 ml). The resulting mixture

was stirred at room temperature for 6 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane:ethyl acetate (5:1 to 1:1, v/v) eluate fractions, methyl 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylate (1.2 g, 72%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.12 (br s, 2H), 3.04-3.06 (m, 1H), 3.33-3.36 (m, 1H), 3.48-3.70 (m, 3H), 3.71 (s, 3H).

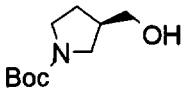
(Step 4) Synthesis of 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylic acid



Methyl 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylate (1.6 g, 6.98 mmol) was dissolved in THF (15 ml) and methanol (7 ml). To the resulting solution was added 1N NaOH (10 ml, 10 mmol). The mixture was stirred at 70°C for 18 hours. The reaction mixture was cooled and distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylic acid (1.5 g, 80%) as a white crystalline solid.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 2.10-2.20 (m, 2H), 3.08-3.11 (m, 1H), 3.36-3.62 (m, 4H).

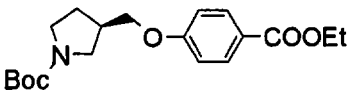
(Step 5) Synthesis of 1-tert-butoxycarbonyl-(3R)-pyrrolidinemethanol



In THF (15 ml), borane - dimethyl sulfide (a 1.0M THF solution) (8.0 ml, 8.0 mmol) was added to 1-tert-butoxycarbonyl-(3R)-pyrrolidinylcarboxylic acid (1.1 g, 5.11 mmol) under stirring at 0°C. The reaction mixture was stirred at room temperature for 3 hours and then, heated under reflux for 3 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. Water was added the residue, followed by extraction with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give 1-tert-butoxycarbonyl-(3R)-pyrrolidinemethanol (1.2 g, 100 %) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 1.80-2.00 (m, 1H), 2.30-2.45 (m, 1H), 3.05-3.15 (m, 1H), 3.20-3.70 (m, 6H).

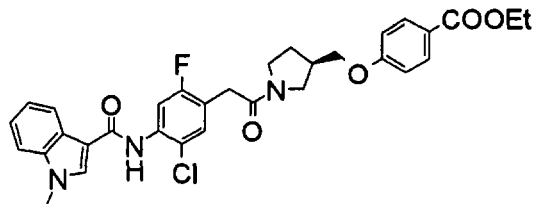
(Step 6) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)benzoate



In THF (15 ml), DIAD (1.34 g, 6.64 mmol) was added to 1-tert-butoxycarbonyl-(3R)-pyrrolidinemethanol (1.1 g, 5.11 mmol), ethyl 4-hydroxybenzoate (848 mg, 5.11 mmol), and triphenylphosphine (1.74 g, 6.64 mmol) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 18 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane:ethyl acetate (1:1, v/v) eluate fractions, ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)benzoate (800 mg, 45%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, J=7.1Hz, 3H), 1.75-1.85 (m, 1H), 2.00-2.15 (m, 1H), 2.62-2.75 (m, 1H), 3.15-3.65 (m, 4H), 3.85-4.05 (m, 2H), 4.34 (q, J=7.1Hz, 2H), 6.90 (d, J=8.5Hz, 2H), 7.99 (d, J=8.5Hz, 2H).

(Step 7) Synthesis of ethyl 4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetyl)-(3R)-pyrrolidinylmethoxy)benzoate



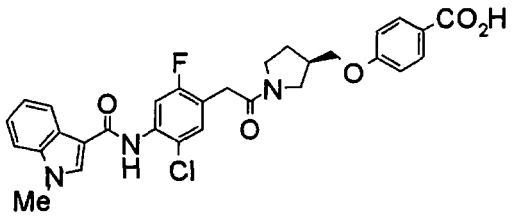
Ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)benzoate (150 mg, 0.42 mmol) was dissolved in methylene chloride (5.0 ml). To the resulting

solution was added trifluoroacetic acid (5.0 ml) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 0.5 hour. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The resulting residue was provided for the subsequent reaction without further purification. In THF (5.0 ml) and acetonitrile (5.0 ml), EDC·HCl (144 mg, 0.75 mmol) was added to the resulting oil, (5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetic acid (180 mg, 0.5 mmol), HOBt (70 mg, 0.5 mmol), and triethylamine (208 µl, 1.5 mmol) at 0°C. The resulting mixture was stirred for 16 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. Water was added to the residue, followed by extraction with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous solution of citric acid, and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC), whereby from n-hexane:ethyl

acetate (1:4, v/v) eluate fractions, methyl 4-(1-(5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethoxy)benzoate (140 mg, 55%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.32-1.39 (m, 3H), 1.80-2.30 (m, 2H), 2.62-2.88 (m, 1H), 3.35-4.10 (m, 8H), 4.20-4.40 (m, 2H), 6.88 (d, J=7.1Hz, 2H), 7.34-7.45 (m, 4H), 7.81 (d, J=7.1Hz, 1H), 7.99 (d, J=7.1Hz, 2H), 8.12-8.14 (m, 1H), 8.25-8.30 (m, 1H), 8.48-8.53 (m, 1H).

(Step 8) Synthesis of 4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethyloxy)benzoic acid



Ethyl 4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethyloxy)benzoate (140 mg, 0.24 mmol) was dissolved in THF (10 ml) and methanol (5.0 ml). To the resulting solution was added 1N NaOH (1.0 ml, 1.0 mmol). The resulting mixture was stirred at 70°C for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with water, and then acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced

pressure, washed with water and dried under reduced pressure to give the title compound (160 mg, 100%) as a white crystalline solid.

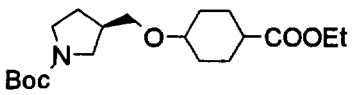
^{1}H-NMR (DMSO-d_6) δ: 1.70-2.20 (m, 2H), 2.60-2.80 (m, 1H), 3.20-3.90 (m, 9H), 4.02-4.18 (m, 2H), 7.03-7.06 (m, 2H), 7.20-7.29 (m, 2H), 7.47 (dd, J=2.7,7.5, 1H), 7.56 (d, J=8.0Hz, 1H), 7.70 (dd, J=2.9,11.2Hz, 1H), 7.88-7.91 (m, 1H), 8.15 (d, J=7.5Hz, 1H), 8.31 (s, 1H), 9.31 (d, J=2.9Hz, 1H).

MS (ESI) m/z 564 $(M + H)^+$.

Example 163

trans-4-(1-(5-Chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethyloxy)cyclohexanecarboxylic acid:

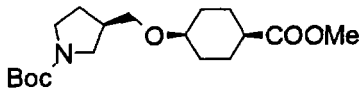
(Step 1) Synthesis of ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylate

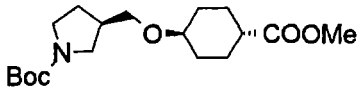


Ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)benzoate (650 mg, 1.86 mmol) and 5% rhodium-alumina (300 mg) were subjected to catalytic hydrogenation in ethanol (10 ml) and acetic acid (1.0 ml) under a hydrogen gas of 5 atm for 24 hours. From the reaction mixture, the catalyst was filtered off, and the filtrate was distilled under reduced pressure to remove the solvent, whereby ethyl 4-(1-tert-butoxycarbonyl-3R-

pyrrolidinylmethoxy)cyclohexanecarboxylate (660 mg, 100 %) was obtained as a colorless oil. The resulting compound was provided for the subsequent reaction without further purification.

(Step 2) Synthesis of methyl cis- and trans-4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylates





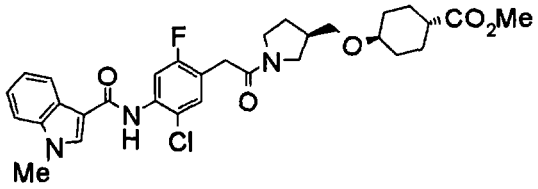
Ethyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (640 mg, 1.91 mmol) and a sodium ethoxide ethanol solution (4.0 mmol) were heated under reflux for 3 hours in ethanol (20 ml). After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with ethyl acetate. The ethyl acetate solution was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give 4-(1-tert-butoxycarbonyl-3R-pyrrolidinylmethoxy)cyclohexanecarboxylic acid. The resulting product was dissolved in toluene (16 ml) and methanol (4.0 ml). Trimethylsilyldiazomethane (a 2.0M hexane solution) (1.4 ml) was added dropwise to the resulting solution. After stirring at room temperature for 1 hour, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified

by flash column chromatography using a silica gel, whereby from n-hexane:ethyl acetate (4:1, v/v) eluate fractions, methyl 4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (270 mg, 41% for cis-isomer, 120 mg, 18% for trans-isomer) was obtained as a colorless oil.

Cis isomer; ^{1}H-NMR ($CDCl_3$) δ: 1.39-2.00 (m, 19H), 2.30-2.50 (m, 2H), 3.00-3.10 (m, 1H), 3.22-3.55 (m, 6H), 3.66 (s, 3H).

Trans isomer; ^{1}H-NMR ($CDCl_3$) δ: 1.18-1.28 (m, 2H), 1.40-1.55 (m, 11H), 1.90-2.10 (m, 6H), 2.20-2.50 (m, 2H), 3.00-3.55 (m, 7H), 3.66 (s, 3H).

(Step 3) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetyl)-(3R)-pyrrolidinylmethyloxy)cyclohexanecarboxylate



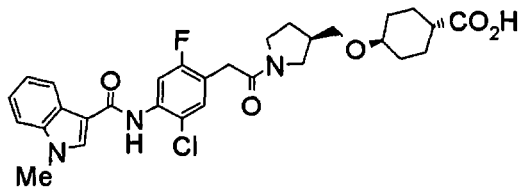
Methyl trans-4-(1-tert-butoxycarbonyl-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (120 mg, 0.35 mmol) was dissolved in methylene chloride (5.0 ml). To the resulting solution was added trifluoroacetic acid (5.0 ml) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 0.5 hour. From the reaction mixture, the solvent was distilled off under

reduced pressure. A saturated aqueous solution of sodium bicarbonate was added to the residue, followed by extraction with methylene chloride. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The crude product thus obtained was provided for the subsequent reaction without further purification. In THF (5.0 ml) and acetonitrile (5.0 ml), EDC·HCl (100 mg, 0.52 mmol) was added to the crude product, (5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetic acid (126 mg, 0.35 mmol), HOBt (48 mg, 0.35 mmol), and triethylamine (139 µl, 1.0 mmol) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 16 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was diluted with water, followed by extraction with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous solution of citric acid, and a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC), whereby from n-hexane:ethyl acetate (1:7, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetyl)-(3R)-

pyrrolidinylmethyloxy)cyclohexanecarboxylate (110 mg, 54%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.31 (m, 2H), 1.35-1.50 (m, 2H), 1.52-1.85 (m, 2H), 1.90-2.10 (m, 6H), 2.15-2.30 (m, 1H), 2.40-2.60 (m, 1H), 3.20-3.80 (m, 10H), 3.89 (s, 3H), 7.33-7.44 (s, 4H), 7.80 (s, 1H), 8.12-8.14 (m, 1H), 8.29 (s, 1H), 8.48-8.52 (m, 1H).

(Step 4) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetyl)-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(3R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (110 mg, 0.2mmol) was dissolved in THF (10 ml) and methanol (5.0 ml). To the resulting solution was added 1N NaOH (1.0 ml, 1.0 mmol). The resulting mixture was stirred at 70°C for 18 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (100 mg, 100%) as a

white crystalline solid.

IR (ATR) ν 1614, 1517, 1403, 1099 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.21 (m, 2H), 1.30-1.40 (m, 2H), 1.50-1.75 (m, 1H), 1.80-2.05 (m, 5H), 2.10-2.40 (m, 2H), 3.05-3.80 (m, 9H), 3.89 (s, 3H), 7.19-7.29 (m, 2H), 7.45 (d, J=7.3Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 7.69 (d, J=11.0Hz, 1H), 8.15 (d, J=7.8Hz, 1H), 8.30 (s, 1H), 9.31 (s, 1H).

MS (FAB) m/z 570 $(M+H)^+$;

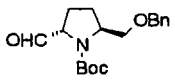
Anal. calcd for $C_{30}H_{33}ClFN_3O_5$: C, 63.21; H, 5.83; N, 7.37; Cl, 6.22; F, 3.33.

Found: C, 62.86; H, 5.71; N, 7.15; Cl, 5.99; F, 3.19.

Example 164

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of (5S)-benzyloxymethyl-N-tert-butoxycarbonyl-(2S)-pyrrolidinecarbaldehyde

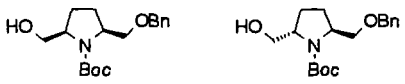


To a solution of oxalyl chloride (1.58 ml, 18.1 mmol) in methylene chloride (30 ml) was added dropwise DMSO (1.93 ml, 27.2 mmol) under stirring at -78°C. To the reaction mixture, a solution of (5S)-benzyloxymethyl-N-tert-butoxycarbonyl-(2S)-pyrrolidinemethanol (2.91 g, 9.05 mmol) in methylene chloride (20 ml) was added at the same

temperature. At a reaction temperature raised from -78°C to -40°C, stirring was conducted for 3 hours. Triethylamine (6.31 ml, 45.3 mmol) was added to the reaction mixture, and the mixture was stirred at 40°C for 2 hours. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (4:1, v/v) eluate fractions, (5S)-benzyloxymethyl-N-tert-butoxycarbonyl-(2S)-pyrrolidinecarbaldehyde (2.90 g, 100%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.42 and 1.43 (each s, total 9H), 1.85-2.04 (m, 3H), 2.16-2.35 (m, 1H), 3.41-3.45 and 3.55-3.59 (each m, total 1H), 3.61-3.63 (m, 1H), 4.07-4.30 (m, 2H), 4.48-4.57 (m, 2H), 7.27-7.35 (m, 5H), 9.52 and 9.58 (each s, total 1H).

(Step 2) Synthesis of (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-hydroxymethylpyrrolidine and (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-hydroxymethylpyrrolidine



In methanol (30 ml) was dissolved (5S)-

benzyloxymethyl-N-tert-butoxycarbonyl-(2S)-pyrrolidinecarbaldehyde (2.90 g, 9.08 mmol). To the resulting solution was added potassium carbonate (1.50 g, 10.9 mmol) and the mixture was heated under reflux for 10 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. Water was added to the residue, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby (5S)-benzyloxymethyl-N-tert-butoxycarbonylpyrrolidinecarbaldehyde (2.52 g) was obtained. In methanol (20 ml), sodium borohydride (0.60 g, 15.9 mmol) was added to (5S)-benzyloxymethyl-N-tert-butoxycarbonylpyrrolidinecarbaldehyde (2.52 g, 7.89 mmol) under stirring at 0°C, while adding thereto . The reaction mixture was stirred at room temperature for 20 hours. The mixture was concentrated under reduced pressure to remove the solvent. Water was added to the residue, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (3:1, v/v) eluate fractions, (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-hydroxymethylpyrrolidine (1.42 g, 56%)

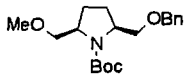
was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) (2S,5R) δ: 1.43 (s, 9H), 1.87-2.01 (m, 4H), 3.44-3.52 (m, 2H), 3.74-3.78 (m, 1H), 3.92-4.01 (m, 2H), 4.50-4.57 (m, 1H), 4.70 (m, 1H), 7.27-7.37 (m, 5H).

In addition, (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5S)-hydroxymethylpyrrolidine (0.65 g, 26%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) (2S,5S) δ: 1.41 (s, 9H), 1.93-2.16 (m, 4H), 3.33-3.38 (m, 1H), 3.52-3.60 (m, 2H), 3.66-3.72 (m, 1H), 3.95-4.02 (m, 2H), 4.29 (m, 1H), 4.48-4.54 (m, 2H), 7.28-7.36 (m, 5H).

(Step 3) Synthesis of (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-methoxymethylpyrrolidine

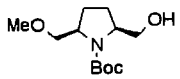


In DMF (5 ml) were suspended (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-hydroxymethylpyrrolidine (190 mg, 0.59 mmol) and sodium hydride (28 mg, 1.17 mmol). To the resulting suspension was added methyl iodide (44 µl, 0.71 mmol) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 2 days. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue

was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (5:1, v/v) eluate fractions, (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-methoxymethylpyrrolidine (183 mg, 92%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H), 1.87-1.99 (m, 4H), 3.28-3.34 (m, total 5 H, including s, 3H, at δ: 3.31), 3.49 (m, 1H), 3.51-3.61 (m, 1H), 3.96 (m, 2H), 4.52 (s, 2H), 7.25-7.33 (m, 5H).

(Step 4) Synthesis of N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinemethanol

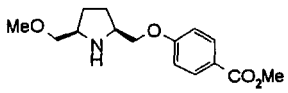


In methanol (10 ml) was dissolved (2S)-benzyloxymethyl-N-tert-butoxycarbonyl-(5R)-methoxymethylpyrrolidine (183 mg, 0.55 mmol). In the presence of 10% palladium-carbon (40 mg, ca. 20 wt%), the resulting solution was subjected to catalytic hydrogenation for 15 hours. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2:1, v/v) eluate fractions, N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinemethanol (116 mg, 87%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.48 (s, 9H), 1.87-2.01 (m, 4H), 3.36 (s,

3H), 3.38-3.39 (m, 1H), 3.45-3.51 (m, 1H), 3.78-3.99 (m, 3H), 4.66-4.69 (m, 1H).

(Step 5) Synthesis of methyl 4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate



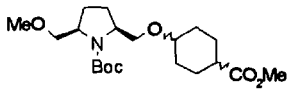
In THF (20 ml), DIAD (1.14 ml, 5.79 mmol) was added to N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinemethanol (950 mg, 3.87 mmol), methyl 4-hydroxybenzoate (648 mg, 4.26 mmol) and triphenylphosphine (1.22 g, 4.65 mmol) and the resulting mixture was heated under reflux for 10 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (6:1, v/v) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.62 g) was obtained.

The resulting product (1.62 g) was dissolved in methylene chloride (15 ml). To the resulting solution was added trifluoroacetic acid (15 ml). The reaction mixture was stirred at room temperature for 17 hours. The reaction mixture was made basic with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced

pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (20:1, v/v) eluate fractions, methyl 4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.03 g, 95% for 2 steps) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.49-2.01 (m, 5H), 3.27-3.33 (m, 1H), 3.37-3.44 (m, total 5H, including s, 3H, at δ: 3.37), 3.53-3.59 (m, 1H), 3.87-4.00 (m, total 5H, including s, 3H, at δ: 3.88), 6.09 (d, J=8.8Hz, 2H), 7.97 (d, J=8.8Hz, 2H).

(Step 6) Synthesis of methyl 4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



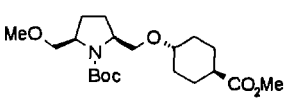
Methyl 4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)benzoate (1.03 g, 3.69 mmol) was dissolved in methanol/trifluoroacetic acid (21 ml, 20:1, v/v). To the resulting solution was added rhodium-alumina (0.50 g) and the resulting mixture was subjected to catalytic hydrogenation for 1 day under a hydrogen gas of 10 atm. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent, whereby methyl 4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate trifluoroacetate

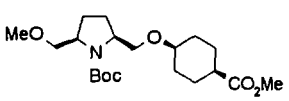
(1.15 g) was obtained.

To the resulting product (1.15 g) were added dioxane/a saturated aqueous solution of sodium bicarbonate (30 ml, 1:1, v/v) and di-tert-butyl dicarbonate (0.81 g, 3.71 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (5:1, v/v) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.32 g, 93% for 2 steps) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.64-1.67 (m, 2H), 1.80-1.98 (m, 6H), 2.10-2.34 (m, 5H), 3.32-3.39 (m, total 5 H, including s, 3H, at δ: 3.35), 3.46-3.63 (m, 3H), 3.67 (s, 3H), 3.91 (m, 2H).

(Step 7) Synthesis of methyl trans-4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate and methyl cis-4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate





Methyl 4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.32 g, 3.42 mmol) was dissolved in methanol (10 ml). To the resulting solution was added sodium methoxide (0.55 g, 10.2 mmol) and the mixture was heated under reflux for 20 hours. After cooling to the room temperature, the reaction mixture was concentrated under reduced pressure to remove the solvent. The residue was added with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby a crude product was obtained. The crude product was dissolved in methanol/benzene (10 ml, 1:4, v/v). To the resulting solution was added trimethylsilyldiazomethane (a 2.0M hexane solution, 680 µl, 1.36 mmol) and the mixture was stirred further at room temperature for 3 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by flash column chromatography using a silica gel, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, methyl trans-4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (321 mg, 24%) was obtained as a pale yellow oil.

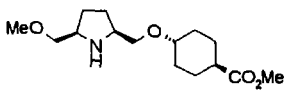
^{1}H-NMR ($CDCl_3$) (1,4-trans): δ: 1.22-1.33 (m, 2H), 1.41-1.51 (m, total 11 H, including s, 9H, at δ: 1.46), 1.87-2.07 (m,

8H), 2.24-2.29 (m, 1H), 3.17-3.63 (m, total 8H, including s, 3H, at δ: 3.35), 3.66 (s, 3H), 3.87-3.97 (m, 2H).

In addition, methyl cis-4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (349 mg, 26%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): (1,4-cis): δ: 1.43-1.52 (m, total 11H, including s, 9H, at δ: 1.46), 1.64-1.67 (m, 2H), 1.79-1.97 (m, 8H), 2.32-2.36 (m, 1H), 3.29-3.52 (m, total 8H, including s, 3H, at δ: 3.35), 3.66 (s, 3H), 3.88-3.94 (m, 2H).

(Step 8) Synthesis of methyl trans-4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

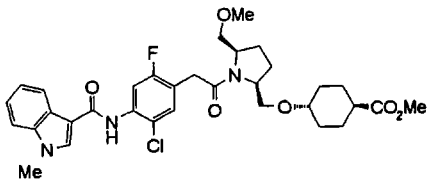


Methyl trans-4-(N-tert-butoxycarbonyl-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (321 mg, 0.83 mmol) was dissolved in methylene chloride (3 ml). To the resulting solution was added trifluoroacetic acid (3 ml) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was made basic with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and

distilled under reduced pressure to remove the solvent to give methyl trans-4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (240 mg, 100%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.33 (m, 2H), 1.41-1.50 (m, 2H), 1.80-1.86 (m, 3H), 1.99-2.09 (m, 5H), 2.23-2.30 (m, 1H), 3.18-3.26 (m, 1H), 3.29-3.44 (m, total 8H, including s, 3H, at δ: 3.36), 3.49-3.52 (m, 1H), 3.66 (s, 3H).

(Step 9) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



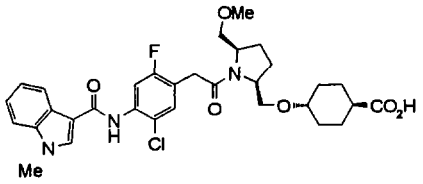
In DMF (5 ml), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (168 mg, 0.47 mmol), methyl trans-4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (133 mg, 0.47 mmol), EDC HCl (134 mg, 0.70 mmol), HOBt (94 mg, 0.70 mmol), and triethylamine (100 μl, 0.71 mmol) were stirred at room temperature for 20 hours. The reaction mixture was diluted with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under

reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1:1 to 4:5, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (251 mg, 86%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.14-1.32 (m, 2H), 1.40-1.53 (m, 2H), 1.85-2.10 (m, 8H), 2.23-2.32 (m, 1H), 3.20-3.25 (m, 1H), 3.39-3.84 (m, 12H), 3.87 (s, 3H), 4.11-4.24 (m, 2H), 7.30-7.42 (m, 4H), 7.79 (s, 1H), 8.11-8.15 (m, 1H), 8.28 (s, 1H), 8.49 (dd, J=1.5,12.0Hz, 1H).

MS (ESI) m/z 628.5 (M^++1).

(Step 10) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (251 mg, 0.40 mmol) was dissolved in THF (3 ml). To the resulting

solution was added 0.5N NaOH (3.0 ml, 1.50 mmol) and the resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were purified by chromatography on a silica gel column, whereby from chloroform/methanol (50:1 to 20:1, v/v) eluate fractions, the title compound (160 mg, 65%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.40 (m, 4H), 1.74-1.90 (m, 8H), 2.06-2.17 (m, 1H), 3.16-3.55 (m, 8H), 3.79-3.84 (m, 2H), 3.88 (s, 3H), 3.99-4.06 (m, 1H), 4.18-4.25 (m, 1H), 7.18-7.28 (m, 2H), 7.40-7.43 (m, 1H), 7.55 (d, J=8.1Hz, 1H), 7.66-7.69 (m, 1H), 8.14 (d, J=8.1Hz, 1H), 8.30 (s, 1H), 9.30 (s, 1H), 12.02 (broad s, 1H).

MS (ESI) m/z 614 (M^++1).

Anal. Calcd for $C_{32}H_{37}ClFN_3O_6$: C, 62.59; H, 6.07; N, 6.84; F, 3.09; Cl, 5.77.

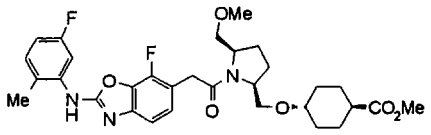
Found: C, 62.43; H, 6.20; N, 6.59; F, 2.93; Cl, 5.47.

Example 165

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5R)-methoxymethyl-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate

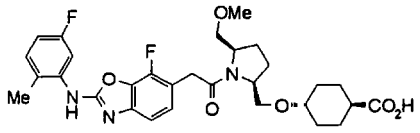


In DMF (5 ml), (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (123 mg, 0.39 mmol), methyl trans-4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (110 mg, 0.39 mmol), EDC HCl (110 mg, 0.57 mmol), HOBt (78 mg, 0.58 mmol), and triethylamine (80 μl, 0.57 mmol) were stirred at room temperature for 20 hours. The reaction mixture was diluted with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1:1, v/v) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (223 mg, 99%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.33 (m, 2H), 1.40-1.53 (m, 2H), 1.86-2.11 (m, 8H), 2.23-2.27 (m, 1H), 2.30 (s, 3H), 3.19-3.28 (m, 1H), 3.34-3.71 (m, total 10H), 3.83-3.97 (m, 2H), 4.19-4.25 (m, 2H), 6.72-6.76 (m, 1H), 7.05-7.35 (m, 4H), 8.04-8.07 (dd, J=2.4,10.7Hz, 1H).

MS (ESI) m/z 586.4 (M^++1).

(Step 2) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (223 mg, 0.38 mmol) was dissolved in THF (3 ml). To the resulting solution was added 0.5N NaOH (3.0 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture poured in ice-1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The crude crystals were recrystallized from n-hexane/ethyl acetate to give the title compound (169 mg, 78%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.36 (m, 4H), 1.75-1.94 (m, 8H), 2.14 (m, 1H), 2.28 (s, 3H), 3.15-3.53 (m, 8H), 3.86-3.88 (m, 2H), 3.90-4.02 (m, 1H), 4.21-4.23 (m, 1H), 6.86-6.89 (m, 1H), 7.02-7.04 (m, 1H), 7.18-7.26 (m, 2H), 7.90-7.93 (m, 1H).

MS (ESI) m/z 572 (M^++1).

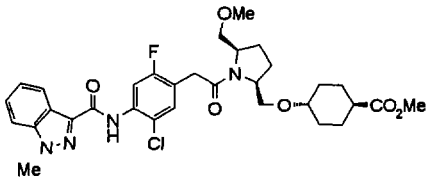
Anal. Calcd for $C_{30}H_{35}F_2N_3O_6$: C, 63.04; H, 6.17; N, 7.35; F, 6.65.

Found: C, 63.01; H, 6.35; N, 6.96; F, 6.28.

Example 166

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

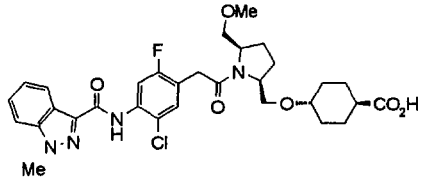


In DMF (3 ml), (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (56 mg, 0.15 mmol), methyl trans-4-((5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (60 mg, 0.15 mmol), EDC HCl (45 mg, 0.23 mmol), HOBt (32 mg, 0.24 mmol), and triethylamine (33 μl, 0.24 mmol) were stirred at room temperature for 2 days. The reaction mixture was diluted with water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced

pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (40:1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (101 mg, 100%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.32 (m, 2H), 1.41-1.53 (m, 2H), 1.85-2.05 (m, 8H), 2.23-2.32 (m, 1H), 3.20-3.25 (m, 1H), 3.35-3.84 (m, 12H), 4.13-4.26 (m, total 5H, including s, 3H at δ: 4.16), 7.31-7.39 (m, 2H), 7.44-7.49 (m, 2H), 8.39 (d, J=8.3Hz, 1H), 8.51 (d, J=11.7Hz, 1H), 9.49 (s, 1H).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(5R)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (101 mg, 0.16 mmol) was dissolved in THF (2 ml). To the resulting solution was added 0.5N NaOH (1.0 ml, 0.50 mmol) and the mixture was stirred at room temperature for 15 hours. The

reaction mixture was poured in ice-1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (40:1, v/v) eluate fractions, the title compound (78 mg, 79%) was obtained as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 1.11-1.48 (m, 4H), 1.74-2.01 (m, 8H), 2.14-2.17 (m, 1H), 3.16-3.55 (m, 8H), 3.80-3.89 (m, 2H), 3.97-4.07 (m, 1H), 4.17-4.26 (m, total 4H, including s, 3H at δ: 4.21), 7.34-7.38 (m, 1H), 7.45-7.48 (m, 1H), 7.51-7.55 (m, 1H), 7.81 (d, J=8.6Hz, 1H), 8.03-8.07 (m, 1H), 8.20 (d, J=8.3Hz, 1H), 9.71 (s, 1H), 12.06 (broad s, 1H).

MS (LC) m/z 614.8 (M^++1), 613.6 (M^+-1).

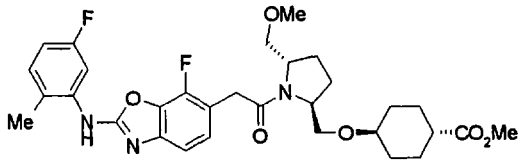
Anal. Calcd for $C_{31}H_{36}ClFN_4O_6$: C, 60.53; H, 5.90; N, 9.11; F, 3.09; Cl, 5.76.

Found: C, 60.56; H, 5.97; N, 8.71; F, 3.07; Cl, 5.70.

Example 167

trans-4-(1-((2-(5-Fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

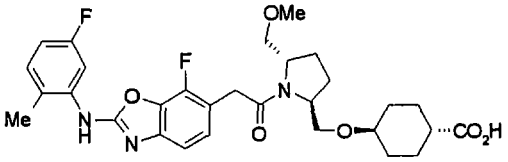


In DMF (10 ml) were dissolved (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (228 mg, 0.71 mmol), methyl trans-4-((5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (186 mg, 0.65 mmol) and EDC-HCl(163 mg, 0.85 mmol). To the resulting solution was added HOBt (26.0 mg, 0.20 mmol), and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in water, followed by extraction with ethyl acetate. The extract was washed with water (three times), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by column chromatography using a silica gel thin-layer plate (TLC), whereby from hexane-ethyl acetate (1/3) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (331 mg, 87%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.12-2.32 (series of m, 12H), 2.31 and 2.32 (s, total 3H), 3.11-4.25 (series of m, 10H), 3.30, 3.31 and 3.39 (s, total 3H), 3.63 and 3.67 (s, total 3H), 6.73-6.78 (m, 1H), 7.11-7.16 (m, 2H), 7.23-7.27 (m, 2H), 8.07-8.12 (m, 1H).

MS (ESI) m/z 586 (M^++1).

(Step 2) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (313 mg, 0.53 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added aqueous 0.25N NaOH (12.8 ml, 3.20 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction with a chloroform/methanol mixture (10/1). The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (288 mg, 94%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.10-2.26 (series of m, 12H), 2.29 and 2.31 (s, total 3H), 3.07-4.28 (series of m, 11H), 2.29 and 3.31 (s, total 3H), 7.30-7.35 (m, 2H),

6.76 (dt, J=2.0,8.0Hz, 1H), 7.11-7.21 (series of m, 3H), 7.11-7.21 (series of m, 3H), 7.82 and 7.90 (d, J=6.4Hz, total 1H).

MS (ESI) m/z 571 (M^++1);

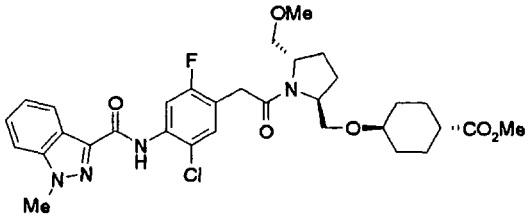
Anal. calcd for $C_{30}H_{35}F2N_3O_6$: C, 63.04; H, 6.17; N, 7.35.

Found : C, 63.29; H, 6.32; N, 7.35.

Example 168

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indazolyl) carbonyl)aminophenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolyl)carbonyl)aminophenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



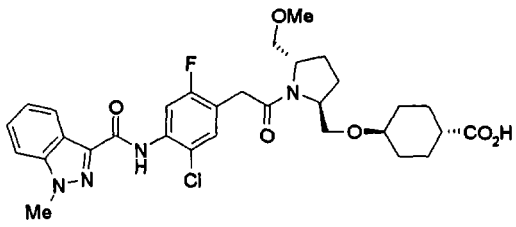
In DMF (10 ml), HOBt (29.0 mg, 0.21 mmol) was added to (5-chloro-2-fluoro-4-((1-methyl-3-indazolyl)carbonyl)aminophenyl)acetic acid (280 mg, 0.78 mmol), methyl trans-4-((5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (201 mg, 0.70 mmol) and EDC-HCl (175 mg, 0.92 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in water, followed by

extraction with ethyl acetate. The extract was washed with water (three times), dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography using a silica gel thin-layer plate (TLC), whereby from hexane/ethyl acetate (1/5) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolyl)carbonyl)aminophenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (322 mg, 73%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.10-2.30 (series of m, 12H), 3.13-4.25 (series of m, 10H), 3.33 and 3.37 (s, total 3H), 3.61 and 3.67 (s, total 3H), 4.18 (s, 3H), 7.33-7.37 (m, 1H), 7.43-7.51 (m, 3H), 8.40 (d, J=8.0Hz, 1H), 8.50 and 8.53 (d, J=12.0Hz, total 1H), 9.50 (s, 1H).

MS (ESI) m/z 629 (M^++1).

(Step 2) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolyl)carbonyl)aminophenyl)acetyl)-(5S)-methoxymethyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolyl)carbonyl)aminophenyl)acetyl)-(5S)-methoxymethyl-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (305 mg, 0.49 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (11.6 ml, 2.91 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction with a chloroform/methanol mixture (10/1). The extract was dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (311 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.10-2.35 (series of m, 12H), 3.14-4.26 (series of m, 12H), 3.32 and 3.37 (s, total 3H), 8.37-8.40 (m, 1H), 8.49 and 8.52 (s, total 1H), 9.50 (s, 1H).

MS (ESI) m/z 615 (M^++1);

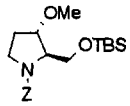
Anal. calcd for $C_{31}H_{36}ClFN_4O_6$: C, 60.53; H, 5.90; N, 9.11.

Found : C, 60.67; H, 6.07; N, 8.80.

Example 169

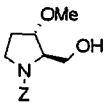
trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of N-benzyloxycarbonyl-(2R)-tert-butyldimethylsilyloxymethyl-(3S)-methoxypyrrolidine



In DMF (10 ml), methyl iodide (0.53 ml, 8.51 mmol) was added to N-benzyloxycarbonyl-(2R)-tert-butyldimethylsilyloxymethyl-(3S)-hydroxypyrrolidine (2.60 g, 7.11 mmol) and sodium hydride (0.34 g, 14.2 mmol) under stirring at 0°C. The reaction mixture was stirred further at the same temperature for 13 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (6:1, v/v) eluate fractions, N-benzyloxycarbonyl-(2R)-tert-butyldimethylsilyloxymethyl-(3S)-methoxypyrrolidine (2.73 g, 100%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.05 (s, 6H), 0.90 and 0.93 (each s, total 9H), 2.02-2.08 (m, 2H), 3.35-3.37 (each s, total 3H), 3.41-3.64 (m, 3H), 3.75-3.98 (m, 3H), 5.08-5.27 (m, 2H), 7.32-7.40 (m, 5H).

(Step 2) Synthesis of N-benzyloxycarbonyl-(3S)-methoxy-(2R)-pyrrolidinemethanol



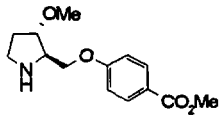
In THF (15 ml) was dissolved N-benzyloxycarbonyl-(2R)-

tert-butyldimethylsilyloxymethyl-(3S)-methoxypyrrolidine (2.73 g, 7.19 mmol). To the resulting solution was added tetrabutylammonium fluoride (TBAF) (a 1M THF solution, 14.4 ml, 14.4 mmol) under stirring at 0°C. The reaction mixture was stirred further at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. To the residue was added 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (20:1, v/v) eluate fractions, N-benzyloxycarbonyl-(3S)-methoxy-(2R)-pyrrolidinemethanol (2.01 g, 100%) was obtained as a colorless oil..

^{1}H-NMR ($CDCl_3$) δ: 1.98 (m, 2H), 3.34 (s, 3H), 3.41-3.74 (m, 5H), 3.88 and 4.01 (each m, total 1H), 5.14 (s, 2H), 7.30-7.36 (m, 5H).

MS (ESI) m/z 265.9 (M^++1).

(Step 3) Synthesis of methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate



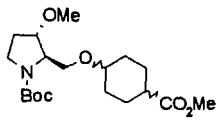
In THF (20 ml), DIAD (1.69 ml, 8.58 mmol) was added to N-benzyloxycarbonyl-(3S)-methoxy-(2R)-

pyrrolidinemethanol (1.90 g, 7.16 mmol), methyl 4-hydroxybenzoate (1.20 g, 7.89 mmol) and triphenylphosphine (2.25 g, 8.58 mmol) and the resulting mixture was heated under reflux for 12 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1:1, v/v) eluate fractions, methyl 4-(N-benzyloxycarbonyl-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate was obtained. The resulting compound was dissolved in methanol (50 ml), followed by the addition of 10% palladium-carbon (1.50 g). The mixture was subjected to catalytic hydrogenation for 20 hours under normal pressure. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (30:1, v/v) eluate fractions, methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (1.39 g, 73% for 2 steps) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.87-2.01 (m, 2H), 3.03-3.18 (m, 2H), 3.35 (s, 3H), 3.43-3.47 (m, 1H), 3.79-3.82 (m, 1H), 3.89 (s, 3H), 3.95-4.02 (m, 2H), 6.91-6.93 (m, 2H), 7.97-8.00 (m, 2H).

(Step 4) Synthesis of methyl 4-(N-tert-butoxycarbonyl-(3S)-methoxy-(2R)-

pyrrolidinylmethoxy)cyclohexanecarboxylate

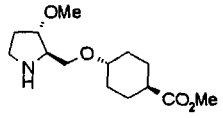


Methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)benzoate (1.39 g, 5.24 mmol) was dissolved in methanol/acetic acid (22 ml, 10:1, v/v). To the resulting solution was added rhodium/alumina (0.55 g) and the mixture was subjected to catalytic hydrogenation for 2 days under a hydrogen gas of 10 atom. From the reaction mixture, the catalyst was filtered off and the filtrate was distilled under reduced pressure to remove the solvent. The residue was dissolved into chloroform. The resulting solution was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give methyl 4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.42 g). The resulting product (1.42 g), di-tert-butyl dicarbonate (1.26 g, 5.77 mmol), and DMAP (0.06 g, 0.49 mmol) were stirred at room temperature for 20 hours in acetonitrile (20 ml). From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (4:1 to 3:1, v/v) eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.67 g, 86% for

2 steps) was obtained as a pale yellow oil.

MS (ESI) m/z 372 (M^++1).

(Step 5) Synthesis of methyl trans-4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate

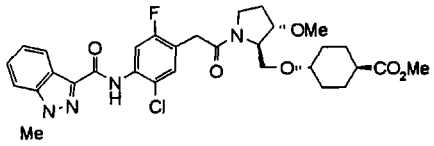


Methyl 4-(N-tert-butoxycarbonyl-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (1.67 g, 4.50 mmol) was dissolved in methanol (15 ml). To the resulting solution was added sodium methoxide (0.73 g, 13.5 mmol). The resulting mixture was heated under reflux for 24 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was acidified with 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was dissolved in methanol/benzene (20 ml, 1:4, v/v), followed by the addition of trimethylsilyldiazomethane (a 2.0M hexane solution, 1.10 ml, 1.10 mmol). The resulting mixture was stirred further at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (2:1, v/v) eluate fractions, methyl trans-4-(N-tert-butoxycarbonyl-(3S)-methoxy-(2R)-

pyrrolidinylmethoxy)cyclohexanecarboxylate was obtained as a colorless oil. The resulting compound (60 g) was dissolved in methylene chloride (3 ml). To the resulting solution was added trifluoroacetic acid (3 ml). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was made basic with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (40 mg, 3% for 3 steps) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.29 (m, 2H), 1.42-1.52 (m, 2H), 1.72-2.08 (m, 6H), 2.23-2.31 (m, 1H), 2.99-3.02 (m, 2H), 3.15-3.51 (m, total 8H, including s, 3H, at δ: 3.31), 3.64-3.66 (m, total 4H, including s, 3H, at δ: 3.66).

(Step 6) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate



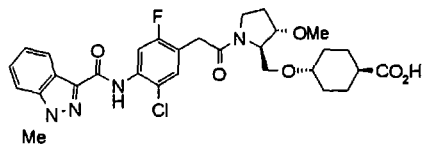
In DMF (3 ml), (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (53 mg, 0.15

mmol), methyl trans-4-((3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (40 mg, 0.15 mmol), EDC HCl (42 mg, 0.22 mmol), HOBt (30 mg, 0.22 mmol), and triethylamine (31 µl, 0.22 mmol) were stirred at room temperature for 3 hours. The reaction mixture was poured into water. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were purified by chromatography on a silica gel column, whereby from chloroform/methanol (60:1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (70 mg, 77%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.26 (m, 2H), 1.38-1.52 (m, 2H), 1.94-2.07 (m, 5H), 2.16-2.28 (m, 2H), 3.17-3.24 (m, 1H), 3.33 (s, 3H), 3.44-3.74 (m, total 9H, including s, 3H, at δ: 3.62), 3.84-3.89 (m, 1H), 4.17 (s, 3H), 4.22-4.25 (m, 1H), 7.31-7.49 (m, 4H), 8.38 (d, J=8.1Hz, 1H), 8.51 (d, J=11.8Hz, 1H), 9.49 (s, 1H).

MS (ESI) m/z 614.8 (M^++1).

(Step 7) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(3S)-methoxy-(2R)-pyrrolidinylmethoxy)cyclohexanecarboxylate (70 mg, 0.11 mmol) was dissolved in THF (1.5 ml). To the resulting solution was added 0.25N NaOH (1.4 ml, 0.35 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (57 mg, 83%) as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.13-1.37 (m, 4H), 1.85-2.18 (m, 7H), 3.15-3.84 (m, 11H), 3.95-3.96 and 4.11-4.14 (each m, total 1H), 4.22 (s, 3H), 7.35-7.39 (m, 1H), 7.50-7.56 (m, 2H), 7.82 (d, J=8.6Hz, 1H), 8.07 (d, J=11.3Hz, 1H), 8.21 (d, J=8.3Hz, 1H), 9.72 (s, 1H), 12.10 (broad s, 1H).

MS (LC) m/z 600.8 (M^++1), 599.4 (M^+-1);

Anal. Calcd for $C_{30}H_{34}ClFN_4O_6$: C, 59.95; H, 5.70; N, 9.32; F, 3.16; Cl, 5.90.

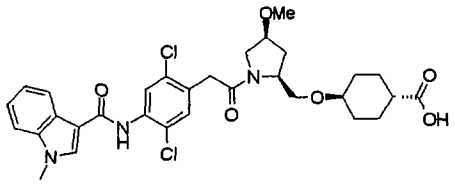
Found: C, 59.71; H, 5.85; N, 8.89; F, 3.00; Cl, 5.88.

Example 170

trans-4-(1-(2,5-Dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(2,5-dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-

methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (2 ml) was dissolved methyl trans-4-(N-tert-butoxycarbonyl-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (100 mg, 0.37 mmol). To the resulting solution were added (2,5-dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (140 mg, 0.37 mmol), HOBt (95 mg, 0.70 mmol), DMAP (catalytic amount) and EDC·HCl salt (107 mg, 0.56 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate three times. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform/methanol 10:0 to 97:3, 20 ml/min, ϕ 50 mm x 150 mm). The purified ester was dissolved in THF (4 ml) and to the resulting solution was added 0.25M NaOH (2.4 ml, 0.61 mmol). The resulting mixture was stirred for 18 hours at room temperature. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was crystallized by the addition of 1M HCl. The

crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (150 mg, 66%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (m, 4H), 1.80-2.20 (m, 8H), 3.15-4.30 (m, 8H), 3.28 (s, 3H), 3.90 (s, 3H), 7.21 (t, J=7.5Hz, 1H), 7.28 (t, J=7.5Hz, 1H), 7.50 (d, J=15.2Hz, 1H), 7.56 (d, J=8.3Hz, 1H), 7.88 (d, J=4.1Hz, 1H), 8.15 (d, J=8.0Hz, 1H), 8.31 (s, 1H), 9.39 (s, 1H).

MS (ESI) m/z 617 $(M+1)^+$;

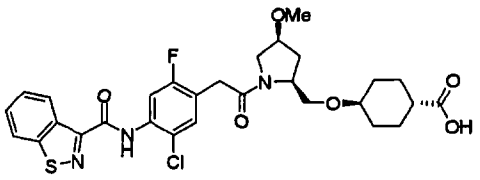
Anal. Calcd for $C_{31}H_{35}Cl_2N_3O_6 \cdot 0.5H_2O$: C, 59.52; H, 5.80; N, 6.72.

Found: C, 59.36; H, 5.72; N, 6.68.

Example 171

trans-4-(1-(5-Chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (2 ml) was dissolved methyl trans-4-(N-tert-butoxycarbonyl-(4S)-methoxy-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (100 mg, 0.37 mmol). To the resulting solution were added (3-benzo(d)isothiazolylcarbonyl)amino)phenylacetic acid (135 mg, 0.37 mmol), HOBt (95 mg, 0.70 mmol), DMAP (catalytic amount) and EDC·HCl salt (107 mg, 0.56 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate three times. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform/methanol 10:0 to 97:3, 20 ml/min, ϕ 50 mm x 150 mm). The purified ester was dissolved in THF (4 ml) and to the resulting solution was added 0.25M NaOH (2.4 ml, 0.61 mmol). After stirring for 18 hours at room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was crystallized by the addition of 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (150 mg, 67%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (m, 4H), 1.80-2.20 (m, 8H), 3.15-4.30 (m, 8H), 3.28 (s, 3H), 7.51 (dd, J=7.0Hz, 1H), 7.66 (t, J=7.5Hz, 1H), 7.73 (t, J=7.5Hz, 1H), 7.95 (dd, J=6.0,10.6Hz, 1H), 8.38 (d, J=8.1Hz, 1H), 8.81 (d, J=8.3Hz,

1H), 10.30 (s, 1H), 12.05 (s, 1H).

MS (ESI) m/z 605 $(M+1)^+$;

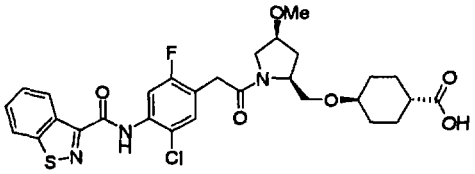
Anal. Calcd for $C_{29}H_{31}ClFN_3O_6S \cdot 0.5H_2O$: C,56.81; H, 5.26; N, 6.85.

Found: C, 56.78; H, 5.15; N, 6.86

Example 171

trans-4-(1-(5-Chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (2 ml) was dissolved methyl trans-4-(N-tert-butoxycarbonyl-(4S)-methoxy-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (100 mg, 0.37 mmol). To the resulting solution were added ((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetic acid (135 mg, 0.37 mmol), HOBt (95 mg, 0.70 mmol), DMAP (catalytic amount) and EDC·HCl salt (107 mg, 0.56 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl, followed by extraction with ethyl acetate three times. The extract

was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, chloroform/methanol 10:0 to 97:3, 20 ml/min, ϕ 50 mm x 150 mm). The purified ester was dissolved in THF (4 ml) and to the resulting solution was added 0.25M NaOH (2.4 ml, 0.61 mmol). After stirring for 18 hours at room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was crystallized by the addition of 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (150 mg, 67%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (m, 4H), 1.80-2.20 (m, 8H), 3.15-4.30 (m, 8H), 3.28 (s, 3H), 7.51 (dd, J=7.0Hz, 1H), 7.66 (t, J=7.5Hz, 1H), 7.73 (t, J=7.5Hz, 1H), 7.95 (dd, J=6.0,10.6Hz, 1H), 8.38 (d, J=8.1Hz, 1H), 8.81 (d, J=8.3Hz, 1H), 10.30 (s, 1H), 12.05 (s, 1H).

MS (ESI) m/z 605 $(M+1)^+$;

Anal. Calcd for $C_{29}H_{31}ClFN_3O_6S \cdot 0.5H_2O$: C,56.81; H, 5.26; N, 6.85.

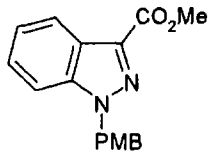
Found: C, 56.78; H, 5.15; N, 6.86

Example 172

trans-4-(1-((5-Chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 1-(4-methoxybenzyl)-3-indazolylcarboxylate

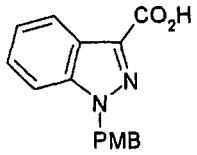


Methyl 3-indazolylcarboxylate (2.0 g, 11.4 mmol) was dissolved in DMF (20 ml). To the resulting solution were added 4-methoxybenzyl chloride (1.7 ml, 12.5 mmol) and potassium carbonate (2.35 g, 17.0 mmol). The resulting mixture was stirred at 80°C for 15 hours. After cooling, the reaction mixture was poured in water (50 ml), followed by extraction with ethyl acetate (200 ml). The extract was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, methyl 1-(4-methoxybenzyl)-3-indazolylcarboxylate (polar fractions, 838 mg, 25%) was obtained as a pale yellow oil and 2(4-methoxybenzyl) isomer (non-polar fractions, 500 mg, 15%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.76 (s, 3H), 4.05 (s, 3H), 5.64 (s, 2H), 6.82 (d, J=8.5Hz, 2H), 7.20 (d, J=8.5Hz, 2H), 7.30 (dd, J=8.1,4.2Hz, 1H), 7.36-7.37 (m, 2H), 8.23 (dd, J=8.1,1.0Hz, 1H).

MS (ESI) m/z 297 (M^++1).

(Step 2) Synthesis of 1-(4-methoxybenzyl)-3-indazolylcarboxylic acid

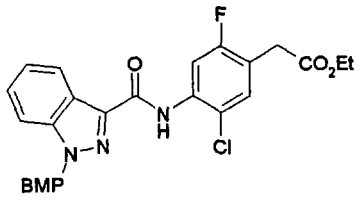


Methyl 1-(4-methoxybenzyl)-3-indazolylcarboxylate (830 mg, 2.80 mmol) was dissolved in THF (22 ml). To the resulting solution was added 0.25N NaOH (22 ml, 5.60 mmol). The resulting mixture was stirred for 15 hours at room temperature. The reaction mixture was poured in 1N HCl (50 ml), followed by extraction with chloroform (2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform and hexane was added to the resulting solution until precipitation appeared. The crystals thus precipitated were collected by filtration under reduced pressure and dried for 12 hours under reduced pressure to give 1-(4-methoxybenzyl)-3-indazolylcarboxylic acid (630 mg, 80%) as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 3.70 (s, 3H), 5.69 (s, 2H), 6.88 (d, J=8.8Hz, 2H), 7.26 (d, J=8.8Hz, 2H), 7.29-7.32 (m, 1H), 7.43-7.48 (m, 1H), 7.84 (d, J=8.6Hz, 1H), 8.08 (d, J=8.6Hz, 1H), 13.06 (br s, 1H).

MS (ESI) m/z 283 (M^++1).

(Step 3) Synthesis of ethyl (5-chloro-2-fluoro-4-(1-(4-methoxybenzyl)-3-indazolylcarbonylamino)phenyl)acetate



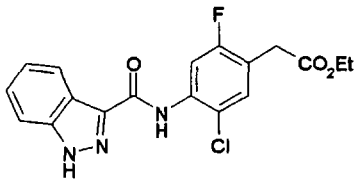
In methylene chloride (10 ml) was dissolved 1-(4-methoxybenzyl)-3-indazolylcarboxylic acid (630 mg, 2.23 mmol). To the resulting solution were added oxalyl chloride (292 μl, 3.53 mmol) and DMF (1 drop). The resulting mixture was stirred until the mixture became uniform. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride (20 ml). Ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (517 mg, 2.23 mmol) and triethylamine (621 μl, 4.46 mmol) were added to the resulting solution. The resulting mixture was heated under reflux for 15 hours. After cooling, the reaction mixture was added with water (50 ml), followed by extraction with chloroform (200 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane-ethyl acetate (4:1) eluate fractions, ethyl (5-chloro-2-fluoro-4-(1-(4-methoxybenzyl)-3-indazolylcarbonylamino)phenyl)acetate (881 mg, 80%) was

obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.1Hz, 3H), 3.62 (s, 2H), 3.77 (s, 3H), 4.19 (q, J=7.1H, 2H), 5.59 (s, 2H), 6.85 (d, J=8.8Hz, 2H), 7.22 (d, J=8.8Hz, 2H), 7.24-7.42 (m, 4H), 8.39 (d, J=8.1Hz, 1H), 8.54 (d, J=11.7Hz, 1H), 9.56 (s, 1H).

MS (ESI) m/z 496 (M^++1).

(Step 4) Synthesis of ethyl (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetate

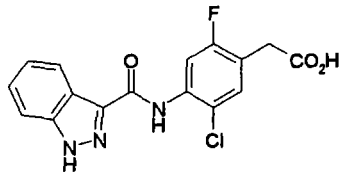


A mixture of anisole (288 μl, 2.66 mmol), trifluoroacetic acid (10 ml), and ethyl (5-chloro-2-fluoro-4-(1-(4-methoxybenzyl)-3-indazolylcarbonylamino)phenyl)acetate (880 mg, 1.77 mmol) was heated under reflux for 15 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. Water (50 ml) was added to the residue. The crystals thus precipitated were collected by filtration under reduced pressure and washed with water. The crude crystals thus obtained were recrystallized from chloroform-methanol, whereby ethyl (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetate (531 mg, 80%) was obtained as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 1.20 (t, J=7.1Hz, 3H), 3.75 (s, 2H), 4.12 (q, J=7.1Hz, 2H), 7.34 (t, J=7.8Hz, 1H), 7.49 (dt, J=8.1,1.0Hz, 1H), 7.63 (d, J=7.8Hz, 1H), 7.71 (d, J=8.1Hz, 1H), 8.16 (d, J=11.5Hz, 1H), 8.21 (d, J=8.1Hz, 1H), 9.79 (s, 1H).

MS (ESI) m/z 376 (M^++1).

(Step 5) Synthesis of (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetic acid

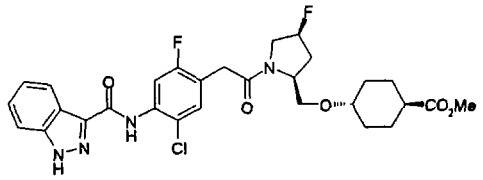


Ethyl (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetate (531 mg, 1.41 mmol) was dissolved in methanol (50 ml). To the resulting solution was added 0.25N NaOH (12 ml, 3 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure for 15 hours to give (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetic acid (480 mg, 98%) as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.63 (s, 2H), 7.34 (t, J=7.6Hz, 1H), 7.49 (t, J=7.6Hz, 1H), 7.62 (m, 1H), 7.72 (d, J=8.3Hz, 1H), 8.13 (d, J=11.2Hz, 1H), 8.21 (d, J=8.1Hz, 1H), 9.79 (s,

1H), 13.96 (br s, 1H).

(Step 6) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

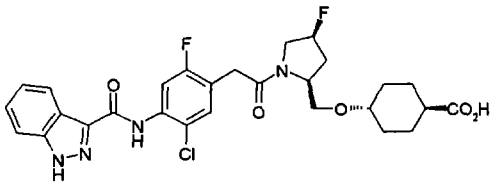


In DMF (10 ml) were dissolved (5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetic acid (300 mg, 0.863 mmol) and methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (224 mg, 0.863 mmol). To the resulting solution were added EDC HCl (248 mg, 1.29 mmol), HOBt (catalytic amount), and DMAP (catalytic amount). The resulting mixture was stirred at room temperature for 15 hours. To the reaction mixture were added ethyl acetate (200 m) and water (200 ml). The ethyl acetate layer was washed with saturated brine (2 × 100 ml), dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (20:1) eluate fractions, trans-4-(1-((5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (223 mg, 44%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.35 (m, 2H), 1.36-1.54 (m, 2H), 1.96-2.12 (m, 4H), 2.20-2.58 (m, 3H), 3.24-4.12 (series of m, 10H), 4.36 and 4.47 (m, each, total 1H, due to double bond character of the C(O)-N bond in amide), 5.25 and 5.38 (m, each, total 1H, due to double bond character of the C(O)-N bond in amide), 7.26 (m, 1H), 7.36-7.40 (m, 1H), 7.47-7.49 (m, 1H), 8.20 (t, J=13.4Hz, 1H), 8.33 (d, J=8.1Hz, 1H), 9.50 (d, J=8.1Hz, 1H), 11.7 (s, 1H).

MS (ESI) m/z 589 (M^++1).

(Step 7) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((5-chloro-2-fluoro-4-(3-indazolylcarbonylamino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (223 mg, 0.379 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.25N NaOH (4 ml, 1 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in 1N HCl (100 ml), followed by extraction with a chloroform-methanol mixture (5:1, 2 × 100 ml). The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to

remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (10:1 to 5:1) eluate fractions, the title compound (125 mg, 57%) was obtained as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.17-1.38 (m, 4H), 1.86-2.23 (series of m, 7H), 3.17-4.37 (series of m, 8H), 5.26-5.49 (m, 1H), 7.34 (t, J=7.6Hz, 1H), 7.48-7.53 (m, 2H), 7.72 (d, J=8.3Hz, 1H), 8.12 (dd, J=11.5,4.9Hz, 1H), 8.22 (d, J=8.3Hz, 1H), 9.79 (s, 1H), 13.90 (br s, 1H).

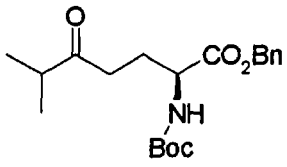
MS (ESI) m/z 575 (M^++1);

Anal. Calcd for $C_{28}H_{29}ClF_2N_4O_5$: C, 58.49; H, 5.08; N, 9.74. Found: C, 58.32; H, 5.28; N, 9.22.

Example 173

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of benzyl (2S)-(N-(tert-butoxycarbonyl)amino-6-methyl-5-oxo)heptanoate



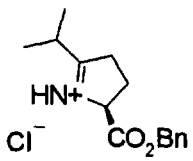
In THF (60 ml), isopropylmagnesium chloride (a 2.0M ether solution, 15.0 ml, 30.0 mmol) was added to benzyl 1-(tert-butoxycarbonyl)-L-pyroglutamate (8.02 g, 25.1 mmol) under stirring at -78°C. After stirring at the same

temperature for 2.5 hours, the reaction mixture was acidified with a saturated aqueous solution of ammonium chloride and 1N HCl at the same temperature. The resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by Biotage's flash column chromatography on silica gel, whereby from n-hexane/ethyl acetate (6:1, v/v) eluate fractions, benzyl (2S)-((tert-butoxycarbonyl)amino-6-methyl-5-oxo)heptanoate (1.79 g, 20%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.05 (d, J=7.0Hz, 6H), 1.43 (s, 9H), 1.92 (m, 1H), 2.10 (m, 1H), 2.42-2.58 (m, 3H), 4.31 (m, 1H), 5.09 (m, 1H), 5.13 and 5.20 (AB q, J=12.2Hz, 2H), 7.35 (m, 5H);

MS (ESI) m/z 364 (M^++1).

(Step 2) Synthesis of (5S)-benzyloxycarbonyl-2-isopropyl-1-pyrrolidine hydrochloride

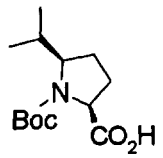


To benzyl (2S)-((tert-butoxycarbonyl)amino-6-methyl-5-oxo)heptanoate (3.83 g, 10.5 mmol) was added 4.0N HCl (a

dioxane solution, 6 ml). The resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent to give (5S)-benzyloxycarbonyl-2-isopropyl-1-pyrrolidine hydrochloride (3.05 g, 100 %) as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (d, J=7.2Hz, 6H), 3.48 (m, 1H), 2.72 (m, 1H), 2.42-2.58 (m, 3H), 3.56 (m, 1H), 5.21 and 5.25 (AB q, J=7.7Hz, 2H), 7.33-7.41 (m, 5H).

(Step 3) Synthesis of 1-(tert-butoxycarbonyl)-(5R)-isopropyl-L-proline



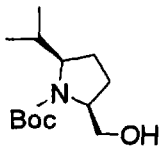
In ethanol (20 ml) was dissolved (5S)-benzyloxycarbonyl-2-isopropyl-1-pyrrolidine hydrochloride (3.05 g, 10.5 mmol). To the resulting solution was added 10% palladium-carbon (750 mg) and the mixture was subjected to catalytic hydrogenation at room temperature under normal pressure for 18 hours. After removal of the catalyst by filtration, the filtrate was distilled under reduced pressure to remove the solvent, whereby a brown solid was obtained. The resulting product was dissolved in acetonitrile-water (1:1, v/v, 50 ml). To the resulting solution were added di-tert-butyl dicarbonate (2.29 g, 10.5 mmol) and triethylamine (2.93 ml, 21.0 mmol) and the mixture was stirred at room temperature for 2 hours. The

reaction mixture was concentrated under reduced pressure to remove the solvent. To the residue was added 1N HCl, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1:1, v/v) eluate fractions, 1-(tert-butoxycarbonyl)-(5R)-isopropyl-L-proline (2.18 g, 81%) was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 0.91 (m, 6H), 1.48 (s, 9H), 1.80-1.86 (m, 2H), 1.95-2.35 (series of m, total 4H), 3.73 (m, 1H), 4.34 (br s, 1H).

MS (ESI) m/z 258 (M^++1).

(Step 4) Synthesis of 1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethanol



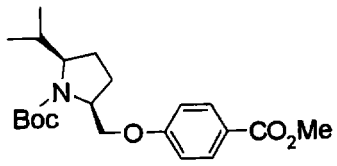
In THF (40 ml) was dissolved 1-(tert-butoxycarbonyl)-(5R)-isopropyl-L-proline (2.18 g, 8.48 mmol). To the resulting solution was added borane·dimethyl sulfide (1.70 ml, 17.0 mmol). The resulting mixture was stirred at 60°C for 2 hours. The reaction mixture was added with water at 0°C and then, distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl, followed by

extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (3:1, v/v) eluate fractions, 1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethanol (530 mg, 96%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 0.86 (d, J=6.8Hz, 3H), 0.92 (d, J=6.8Hz, 3H), 1.47 (s, 9H), 1.65 and 1.67 (s, total, 1H), 1.74 (m, 3H), 1.99 (m, 1H), 3.52 (t, J=9.6Hz, 1H), 3.66 (m, 2H), 4.00 (m, 1H), 5.06 (m, 1H).

MS (ESI) m/z 244 (M^++1).

(Step 5) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)benzoate



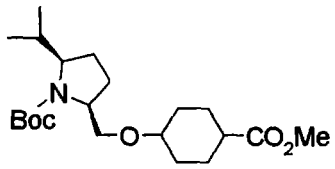
In THF (30 ml), DIAD (1.85 ml, 9.39 mmol) was added dropwise to 1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethanol (1.90 g, 7.81 mmol), triphenylphosphine (2.46 ml, 9.38 mmol), and methyl 4-hydroxybenzoate (1.19 g, 7.82 mmol). After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 14 hours. From the reaction mixture,

the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (4:1, v/v) eluate fractions, methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)benzoate (2.97 g, 100 %) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 0.86 and 0.90 (d, J=6.8Hz, total 6H, due to double bond character of C(O)-N bond in amide), 1.26-1.44 (m, 1H), 1.47 (s, 9H), 1.79 (m, 2H), 1.98 (m, 3H), 3.63 (m, 1H), 3.88 (s, 3H), 4.16 (m, 1H), 4.23 (m, 1H), 6.94 (d, J=8.8Hz, 2H), 7.97 (d, J=8.8Hz, 2H).

MS (ESI) m/z 378 (M^++1).

(Step 6) Synthesis of methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



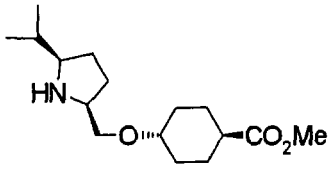
Methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)benzoate (2.97 g, 7.81 mmol) was dissolved in methylene chloride (15 ml). To the resulting solution was added trifluoroacetic acid (3.5 ml). After stirring for 3 hours at room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent, whereby a yellow oil was obtained. The resulting

yellow oil was dissolved in ethanol (35 ml). To the resulting solution was added rhodium-alumina (1.40 g) and catalytic hydrogenation was effected for 14 hours under a hydrogen gas of 12 atm. After removal of the catalyst by filtration, the filtrate was distilled under reduced pressure to remove the solvent, whereby a pale brown solid (1.60 g) was obtained. The resulting compound was dissolved in acetonitrile-water (1:1, v/v, 40 ml). To the resulting solution were added di-tert-butyl dicarbonate (1.23 g, 5.63 mmol) and triethylamine (786 µl, 5.64 mmol) and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent. To the residue was added 1N HCl, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (a pale yellow oil, 2.18 g, 100 %) was obtained as a mixture of cis-trans isomers (ca 4:1, determined from ^{1}H-NMR spectrum).

^{1}H-NMR ($CDCl_3$) δ: 0.81 and 0.88 (d, J=6.8Hz, total 6H, due to double bond character of C(O)-N bond in amide), 1.45 (s, 9H), 1.47-1.74 (series of m, total 4H), 1.79-1.92 (series of m, total 6H), 2.04 (s, 3H), 2.34 (m, 1H), 3.23 (m, 1H),

3.47 (m, 1H), 3.56 (m, 2H), 3.67 (s, 3H), 3.91 (m, 1H).

(Step 7) Synthesis of methyl trans-4-((5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



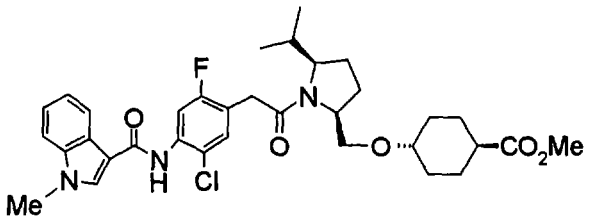
Methyl 4-(1-(tert-butoxycarbonyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (2.18 g, 5.54 mmol) and sodium methoxide (914 mg, 16.9 mmol) were heated under reflux for 14 hours in methanol (50 ml). After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. To the residue was added 1N HCl, followed by extraction with ethyl acetate. The extract was washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent, whereby a yellow oil was obtained. The resulting oil was dissolved in benzene (40 ml) and methanol (10 ml). To the resulting solution was added a 2M hexane solution (1.4 ml, 2.8 mmol) of trimethylsilyldiazomethane and the resulting mixture was stirred at room temperature for 2 hours. After addition of acetic acid (500 µl, 0.30 mmol), the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (6:1) eluate fractions, a trans

isomer was obtained as a pale yellow oil (740 mg). The resulting product was dissolved in methylene chloride (12 ml). To the resulting solution was added trifluoroacetic acid (3 ml), and the mixture was stirred at room temperature for 2 hours. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was neutralized with a saturated aqueous solution of sodium bicarbonate, followed by extraction with chloroform-methanol (5:1, v/v). The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent, whereby methyl trans-4-((5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (567 mg, 35%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 0.97 (d, J=6.4Hz, 3H), 1.11 (d, J=6.4Hz, 3H), 1.25 (m, 2H), 1.47 (m, 2H), 1.72 (m, 1H), 1.81 (m, 1H), 1.89-2.11 (series of m, total 7H), 2.26 (tt, J=11.6,3.6Hz, 1H), 3.17 (m, 1H), 3.33 (tt, J=10.4,3.6Hz, 1H), 3.64 (m, 1H), 3.66 (s, 3H), 3.76 (m, 2H).

MS (ESI) m/z 284 (M^++1).

(Step 8) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (5 ml), EDC HCl (151 mg, 0.81 mmol), HOBt (2.5 mg, 0.02 mmol), and DMAP (2.5 mg, 0.02 mmol) were addedto (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (171 mg, 0.54 mmol) and methyl trans-4-((5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (152 mg, 0.54 mmol) and the resulting mixture was stirred at room temperature for 14 hours. Water was added to the reaction mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from chloroform-methanol (40:1, v/v) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (159 mg, 50%) was obtained as a pale yellow oil.

IR (ATR) ν 2945, 1730, 1637, 1514, 1400 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ: 0.73 and 0.87 (d, J=6.8Hz, total 3H, due to double bond character of C(O)-N bond in amide), 0.81 and

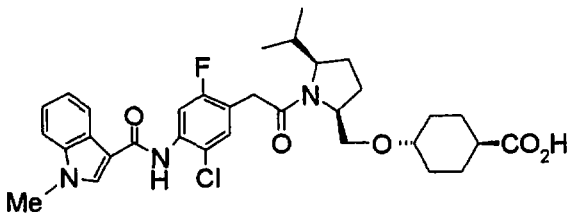
0.94 (d, J=6.8Hz, total 3H, due to double bond character of C(O)-N bond in amide), 1.19 (m, 2H), 1.39 (m, 2H), 1.64 (m, 1H), 1.84-2.00 (series of m, total 6H), 1.96 (s, 3H), 2.21 (m, 1H), 2.28 (m, 1H), 3.16 (m, 1H), 3.34 (m, 2H), 3.45 (m, 1H), 3.58 (s, 3H), 3.71 (m, 1H), 3.96 (m, 1H), 4.08 (m, 2H), 7.25 (m, 2H), 7.30 (m, 2H), 7.69 (m, 1H), 8.05 (dd, J=6.0, 2.8Hz, 1H), 8.18 (s, 1H), 8.39 and 8.41 (d, J=12.0Hz, total 1H, due to double bond character of C(O)-N bond in amide).

MS (ESI) m/z 626 (M^++1);

Anal. Calcd for $C_{34}H_{41}ClFN_3O_5$ 0.75 H_2O: C, 63.84; H, 6.70; N, 6.57.

Found: C, 63.66; H, 6.59; N, 6.54.

(Step 9) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (2 ml) and methanol (1 ml) was dissolved methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(5R)-isopropyl-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (100 mg, 0.16 mmol). To the resulting solution was added 0.25N NaOH (2

ml), and the resulting mixture was heated under reflux for 2 hours at room temperature. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to remove the solvent. The concentrate was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (81 mg, 83%) as a white solid.

IR (ATR) ν 2937, 1724, 1620, 1514, 1402 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 0.75 and 0.90 (d, J=6.4Hz, total 3H, due to double bond character of C(O)-N bond in amide), 0.80 and 0.96 (d, J=6.4Hz, total 3H, due to double bond character of C(O)-N bond in amide), 1.13-1.23 (m, 3H), 1.33 (m, 2H), 1.71 (m, 2H), 1.88 (m, 4H), 1.98 (m, 2H), 2.11 (m, 1H), 2.21 (m, 1H), 3.21 (m, 3H), 3.72 (m, 2H), 4.16 (m, 1H), 7.18 (t, J=7.2Hz, 1H), 7.32 (d, J=7.2Hz, 1H), 7.47 (d, J=8.0Hz, 1H), 7.75 (d, J=11.2Hz, 1H), 8.12 (d, J=7.6Hz, 1H), 8.24 (s, 1H), 9.07 (s, 1H).

MS (ESI) m/z 612 (M^++1);

Anal. Calcd for $C_{33}H_{39}ClF_2N_3O_5$: C, 64.75; H, 6.42; N, 6.86. Found: C, 64.54; H, 6.50; N, 6.73.

Test 1: In vitro evaluation of test compounds

In vitro evaluation test (1)

CHO cells forcedly expressed by the transduction of integrins haα_4 and β_1 were seeded in a Coster 3599 plate (3

$\times 10^4$ cells/100 µl/well) and they were cultured for 2 days. After the medium was washed with buffer A* twice, 50 µl/well of Eu^{3+}-hVCAM-1 D1D7-IgG diluted to 2 nM with an assay buffer ** was added. To the resulting well was added 50 µl/well of a test compound diluted with 2% DMSO-assay buffer (in the presence or absence of 6% human serum albumin) (to a well subjected to Scatchard analysis was added a solution diluted in another manner). After stirring for 5 minutes on a plate mixer, the plate was allowed to stand at room temperature for 1 hour. Then, the plate was washed four times with the buffer A and added with 100 µl/well of an enhancement reagent (DELFIA). The plate was shaken for 5 minutes on a plate mixer, followed by measurement of fluorescence intensity by a time-resolved fluorometer (DELFIA Wallac). From the binding ratio available by the following calculation formula: $((F_T-F_{NS})-(F_I-F_{NS})) / (F_T-F_{NS}) \times 100$, the IC_{50} (concentration inhibiting 50% of binding of CHO cells with hVCAM-1 D1D7-IgG) of the test compound was determined. In the above formula, F_T means the fluorescence intensity of the well free of the test compound, F_{NS} means the fluorescence intensity of the well free of the test compound and anti-hα_4 antibody (SG/73), and F_I means the fluorescence intensity of the well containing the test compound. The Kd indicating the binding strength and Bmax (maximum binding) were estimated

within a range of 0.06 to 20 nM in accordance with the Scatchard analysis method. The results are shown in Table 1.

The value Ki was calculated based on:

$$Ki = \frac{IC_{50}}{1 + \frac{[L]}{Kd}}$$

((L) means a ligand concentration).

(* buffer A: 25 mM HEPES (pH 7.5), 150 mM NaCl, 1 mM Ca^{2+}, 1 mM Mg^{2+}, 4 mM Mn^{2+}; ** assay buffer: 25 mM HEPES (pH 7.5), 150 mM NaCl, 1 mM Ca^{2+}, 1 mM Mg^{2+}, 4 mM Mn^{2+}, 0.1% BSA, 20 μM DTPA, with/without 6% ALBUMIN, HUMAN SERUM (C/N A-1653, SIGMA))

In vitro Evaluation Test (2)

In a 96-well microplate, hVCAM-1 D1D7-IgG (600 ng/ml in TSM) was immobilized at 4°C (50 μl/well). After blocking by the addition of 100 μl/well of a 2% BSA-TSM solution, 150 μl/well (2.1×10^5/well) of Jurkat cells labeled with BCECF-AM and 50 μl/well of a test compound were added and the plate was allowed to stand at 37°C for 1 hour. The test compound was adjusted to have a final concentration of 0.1 ng/ml to 100 ng/ml (0.5% DMSO). The well was filled with the below-described medium and sealed with a plate seal (product of Sumitomo Bakelite). The

plate was then turned inside out and allowed to stand at room temperature for 30 minutes. Then, unbound cells were removed. After suction of the medium, the cells were solubilized with a 0.1% NP-40 solution and fluorescence intensity was measured by a fluorescence reader (excited at 485 nm/measured at 550 nM). From the binding ratio available by the following formula: $((F_T-F_{NS})-(F_I-F_{NS}))$ / $(F_T-F_{NS}) \times 100$, the IC_{50} (concentration inhibiting 50% of the binding of hVCAM-1 D1D7-IgG with Jarkat cells) of the test compound was determined. In the above equation, F_T means the fluorescence intensity of the well free of the test compound, F_{NS} means the fluorescence intensity of the well free of the test compound and hVCAM-1 D1D7-IgG, and F_I means the fluorescence intensity of the well containing the test compound.

(TSM: 25 mM Tris-HCl (pH 8.0)-150 mM NaCl-2 mM $MgCl_2$; medium: RPMI (FACS-free); BCECF-AM (Dojin Kagaku))

Table 1

Example	Ki (nM)
1	30
2	17
3	40
6	14
7	7.1
8	24
15	2.2
18	7.8
20	3.9
21 (Isomer G)	382
21 (Isomer H)	2.5
22 (Isomer B)	3.5
24 (Isomer A)	14

25 (Isomer A)	18
26 (Isomer A)	2
30	40
31	16
33	31
34	26
36	1.5
37	6.9
38	0.43
39	2.1
40	1.9
41	3.8
43	6
44	2
45	8.8
46	37
47	5.8
49	4.4
50	13
52	10
53	32
54	5.6
55	8.5
56	2.1
57	7.3
59	7.2
60	6.3
61	2.3
62	3.4
63	3.1
64	0.31
65	4
69	34
70	7.2
71	18
72	4.4
73	51
74	7.7
75	21
76	1.6
78	14
79	4.5
80	12
81	25
82	18
83	1.9
85	6.4
87	9.1
89	3.6

91	2
92	2.7
95	34
96	20
98	3.6
99	17
100	5.5
101	8.1
102	47
104	20
105	42
107	11
108	21
109	25
110	7
111	2.6
112	6.5
114	4.8
115	30
116	2.5
117	5.1
118	6.9
119	5.9
120	1.9
121	3.9
122	29
123	5.8
124	1.4
125	6.5
126	2
127	9.7
128	2.7
129	1.5
130	8.8
131	17
133	22
134	3.1
135	19
136	5.4
137	5.6
138	15
139	9.1
140	1.8
141	21
142	18
143	17
144	48
145	18
146	21

147	40
150	10
151	37
155	20
156	43
159	47
160	61
163	39
164	6.4
165	2.9
166	7.9
167	0.87
168	59
169	16
170	4.3
171	5
172	6.8
173	10

Test 2: In vivo evaluation of test compounds

Transmigration test of eosinophils in the mice actively sensitized with ascaris (Ascaris suum antigen in pigs):

It has been reported that eosinophil transmigration was induced by active sensitization with ascaris (Int. Arch. Immunol., 108, 11-18(1995)). Test compounds were evaluated in accordance with the method described in this literature. Test compounds were each orally or subcutaneously administered two or three times a day. The total cell count and eosinophil count in BALF 48 hours after sensitization were calculated and effects were compared between the test-compound-administered group and a test-compound-free group.

Inhibitory action against pleurisy of rat sensitized with Compound 48/80:

By intrapleurally inoculating 7-week-old male CD/IGS

rats (Charles River Japan) with 50 μg of Compound 48/80 (Sigma), pleurisy was caused. The pleural exudate for 24 hours was collected together with the buffer and the number of eosophils in the exudate was counted. The test compound was orally or subcutaneously administered once or twice by using a proper solvent such as 0.5% MC (aqueous solution of methyl cellulose). Effects of it were compared with those of a test-compound-free group.

Test 3: Evaluation of oral bioavailability by mouse bioassay

A test compound was suspended or dissolved in a proper administration medium to give a concentration of 1 mg/ml. To 7 to 9 week old female Balb/C mice, 10 mg/kg of the resulting suspension or solution was orally administered. Fifteen minutes after the administration, blood was collected from the postcava under anesthesia with ether and the serum was separated from it. The concentration of each test compound was determined by estimating the serum level from a calibration curve obtained with VCAM-1/VLA-4 inhibitory activity as an index or measuring the concentration by using LC/MS/MS. The results are shown in Table 2.

Table 2

Mouse Bioassay Evaluation Results

Example No.	Dose / kg	Blood level (ng/ml)
25 (Isomer A)	10	1094

24 (Isomer A)	10	2179
36	10	1099
37	10	3687
39	10	5157
43	10	1194
44	10	912
49	10	508
55	10	2029
61	10	3316
62	10	3196
63	10	8551
65	10	11473
70	10	2803
71	10	7339
72	10	1878
74	10	14058
79	10	9372
83	10	1536
87	10	15144
89	10	10871
91	10	2957
92	10	1987
98	10	2211
100	10	533
101	10	3144
114	10	3450
115	10	888
116	10	9405
117	10	2927
118	10	5733
121	10	4406
123	10	705
125	10	2570
130	10	3591
136	10	2504
138	10	1264
139	10	2428
141	10	8824
155	10	571
164	10	2301
165	10	816
166	10	3068
169	10	21769
170	10	3363
171	10	2732
172	10	848
173	10	3473

Evaluation Example 4: Tests on pharmacokinetics and oral bioavailability

The pharmacokinetic parameter of the test compound orally administered to rats or dogs are described below. The results are shown in Table 3.

Table 3

Evaluation of pharmacokinetics and oral bioavailability

Tested	Example	Dose/kg	AUC[1] (ng · h/ml)	F[2] (%)	CLtot[3] (mL/min/kg)
Rat	20 (Isomer A)	2.0	152	35	73
	21 (Isomer H)	5.0	14931	52	3.3
Dog	20 (Isomer A)	2.0	776	44	19.1
	21 (Isomer H)	2.0	759.9	40	17.9

[1]AUC (ng · h/ml): total area under the plasma concentration (measured by LC/MS/MS method) versus time curve;

[2]F (%): oral bioavailability;

[3]CLtot (mL/min/kg): apparent plasma clearance

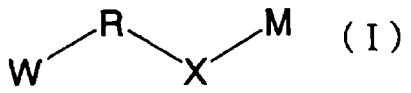
Industrial Applicability

The invention compounds or salts thereof selectively inhibit the binding of cell adhesion molecules to VLA-4 and exhibit high oral bioavailability so that they are usable as a preventive or remedy for various diseases mediated by migration and adhesion of leukocytes such as inflammatory diseases, autoimmune diseases, metastasis, bronchial asthma, rhinostenosis, diabetes, arthritis, psoriasis, multiple sclerosis, inflammatory intestinal diseases, and

rejection upon transplantation. They are highly effective when orally administered and can be administered for a long period of time so that they are of high clinical utility.

Claims

1. A compound represented by the following formula (I):



(I)

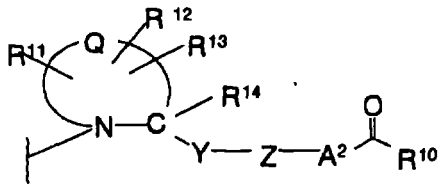
(wherein, W represents W^A-A^1-W^B-

(in which, W^A represents a substituted or unsubstituted aryl group or a substituted or unsubstituted monovalent heterocyclic group, A^1 represents -NR^1-, a single bond, -C(O)-, -C(O)NR^1-, a substituted or unsubstituted vinylene group, an ethynylene group, -$CR^{1a}R^{1b}$-O-, -CR^{1a}=CR^{1b}-C(O)NR^1- or -CR^{1a}=CR^{1b}-C(O)- (in which, R^1 represents a hydrogen atom or a lower alkyl group, and R^{1a} and R^{1b} each independently represents a hydrogen atom or a lower alkyl group), and W^B represents a substituted or unsubstituted arylene group or a substituted or unsubstituted divalent heterocyclic group);

R represents a single bond, -NH-, -OCH_2-, an alkenylene group or -$(CH_2)_n$- (in which, n stands for 1 or 2);

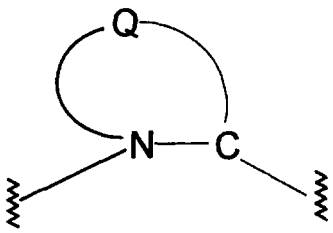
X represents -C(O)-, -CH_2- or -$S(O)_2$-, and

M represents the following formula (iii), (iv) or (v):



(iii)

(in which,

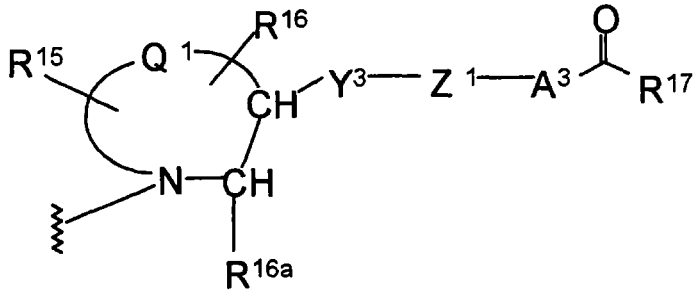


(iii - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group (in which the nitrogen atom is bonded to X and Q represents a carbon, sulfur, oxygen or nitrogen atom), R^{11}, R^{12} and R^{13} each independently represents a hydrogen atom, a hydroxyl group, an amino group, a halogen atom, a cyano group, a carboxyl group, an alkoxycarbonyl group, a carbamoyl group, a substituted or unsubstituted mono- or dialkylaminocarbonyl group, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted mono- or dialkylamino group, a substituted or unsubstituted cycloalkylamino group, a substituted or unsubstituted alkylsulfonylamino group, a substituted or unsubstituted arylsulfonylamino group, a substituted or unsubstituted aryloxy group, a substituted or unsubstituted

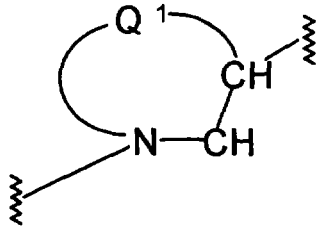
heteroaryloxy group, a substituted or unsubstituted benzyloxy group, a substituted or unsubstituted alkylthio group, a substituted or unsubstituted cycloalkylthio group, a substituted or unsubstituted arylthio group, a substituted or unsubstituted alkylsulfonyl group, a substituted or unsubstituted cycloalkylsulfonyl group, or a substituted or unsubstituted arylsulfonyl group, or R^{11} and R^{12} or R^{12} and R^{13} may be coupled to form, together with the atom constituting the heterocyclic group to which R^{11} to R^{13} are bonded, a 3 to 7-membered cyclic hydrocarbon or heterocycle (which may have, on the ring thereof, 1 to 3 substituents selected from a hydroxyl group, halogen atoms, an amino group, alkyl groups, alkoxy groups, aryl groups, aryloxy groups, alkylamino groups, a benzyloxy group and heteroaryl groups), R^{14} represents a hydrogen atom or a substituted or unsubstituted lower alkyl group, Y represents a single bond, -C(O)-, -C(O)NH-, or a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring or may have one or more carbon atoms substituted with -O-, -S-, $-S(O)_2-$, -C(O)- or $-NY^1-$ (in which, Y^1 represents a hydrogen atom or a lower alkyl group), Z represents a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, A^2 represents a single bond, an alkenylene group, an alkynylene group, $-(CH_2)_t-$ or $-O(CH_2)_v-$ (in which, t stands

for 1, 2 or 3 and v stands for 0, 1, 2 or 3), and R^{10} represents a hydroxyl or a lower alkoxy group),



(iv)

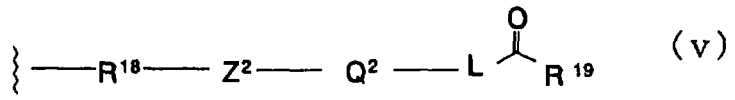
(in which,



(iv - a)

represents a divalent 4-, 5-, 6- or 7-membered heterocyclic group (in which the nitrogen atom is bonded to X, and Q^1 represents a carbon, sulfur, oxygen or nitrogen atom), R^{15} and R^{16} each independently represents a hydrogen atom, a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group or an alkoxy group, R^{16a} represents a hydrogen atom or a substituted or unsubstituted alkyl group, Y^3 represents -O-, -S-, $-S(O)_2-$, $-(CH_2)_fO-$ or $-NY^4-$ (in which f stands for 1, 2 or 3 and Y^4 represents a hydrogen atom or a lower alkyl group), Z^1 represents a substituted or unsubstituted arylene group, a

substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, A^3 represents a single bond, an alkenylene group, an alkynylene group or $-(CH_2)_e-$ (in which e stands for 1, 2 or 3), and R^{17} represents a hydroxyl group or a lower alkoxy group),



(v)

(in which, R^{18} represents $-NR^{20}-$ (in which R^{20} represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted benzyl group, a substituted or unsubstituted lower alkenyl group or a substituted or unsubstituted alkynyl group), Z^2 represents a linear or branched divalent aliphatic C_{1-12} hydrocarbon group which may have a C_{3-6} spiro ring, may have one or more carbon atoms substituted with a divalent C_{3-8} cycloalkylene group or may have one or more carbon atoms substituted with -O-, -S-, $-S(O)_2-$, -C(O)- or $-NR^{21}-$ (in which, R^{21} represents a hydrogen atom or a substituted or unsubstituted lower alkyl group), Q^2 represents a single bond, a substituted or unsubstituted arylene group, a substituted or unsubstituted heteroarylene group or a substituted or unsubstituted cycloalkylene group, L stands for a single bond, a substituted or

unsubstituted lower alkylene group or a substituted or unsubstituted lower alkenylene group, or R^{19} represents a hydroxyl or a lower alkoxy group)); or salt thereof.

2. A compound or salt according to Claim 1, wherein W represents the following formula (i) or (ii):

W^1-A^1-W^2- (i)

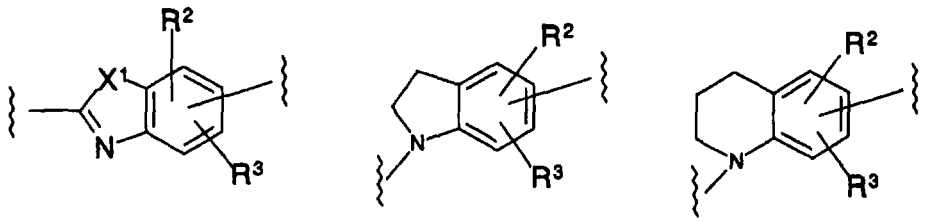
(wherein, W^1 represents a substituted or unsubstituted aryl group or a substituted or unsubstituted monovalent heterocyclic group, A^1 represents -NR^1-, a single bond, -C(O)-, -C(O)NR^1-, a substituted or unsubstituted vinylene group, an ethynylene group, -$CR^{1a}R^{1b}$-O-, -CR^{1a}=R^{1b}-C(O)NR^1- or -CR^{1a}=R^{1b}-C(O)- (in which, R^1 represents a hydrogen atom or a lower alkyl group, and R^{1a} and R^{1b} each independently represents a hydrogen atom or a lower alkyl group), and W^2 represents a substituted or unsubstituted divalent bicyclic heterocyclic group),

W^3-A^1-W^4- (ii)

(wherein, W^3 represents a substituted or unsubstituted monovalent bicyclic heterocyclic group, A^1 represents -NR^1-, a single bond, -C(O)-, -C(O)NR^1-, a substituted or unsubstituted vinylene group, an ethynylene group, -$CR^{1a}R^{1b}$-O-, -CR^{1a}=CR^{1b}-C(O)NR^1- or -CR^{1a}=CR^{1b}-C(O)- (in which, R^1 represents a hydrogen atom or a lower alkyl group, and R^{1a} and R^{1b} each independently represents a hydrogen atom or a lower alkyl group), and W^4 represents a substituted or unsubstituted arylene group or a substituted or

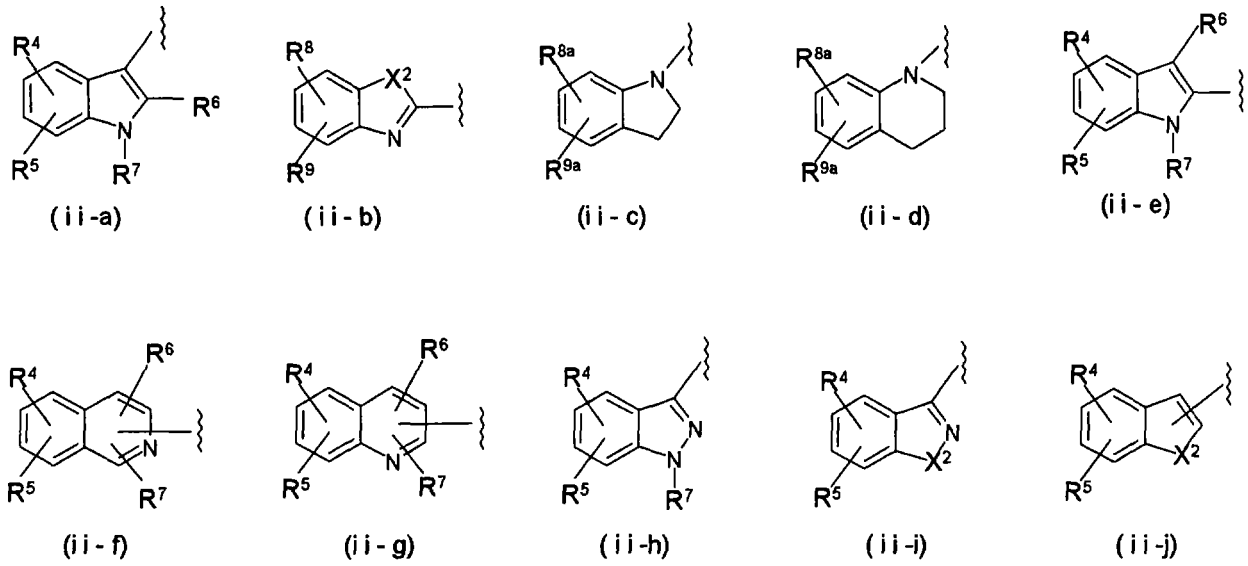
unsubstituted divalent monocyclic heterocyclic group).

3. A compound or salt according to Claim 2, wherein W^2 represents the following formula (i-a), (i-b) or (i-c):



(wherein, the bonding on the left side is to A^1, the bonding on the right side is to R, X^1 represents an oxygen or sulfur atom, and R^2 and R^3 each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group or an amino group, with the proviso that A^1 is not $-NR^1-$ when W^2 is (i-b) or (i-c)).

4. A compound or salt according to Claim 2 or 3, wherein W^3 represents any one of the following formulas (ii-a) to (ii-j):



(in which, X^2 represents an oxygen or sulfur atom, R^4 and R^5 each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group or an amino group, R^6 and R^7 each independently represents a hydrogen atom or a lower alkyl group, and R^8, R^9, R^{8a} and R^{9a} each independently represents a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxyl group, a lower alkoxy group or an amino group, with the proviso that when W^3 represents (ii-c) or (ii-d), A^1 does not represents $-NR^1-$).

5. A compound or salt according to Claim 1, wherein W represents the formula (i).

6. A compound or salt according to any one of Claims 1 to 5, wherein A^1 represents a single bond, a group -NH or -C(O)NH-.

7. A compound or salt according to any one of Claims 1 to 6, wherein M represents the formula (iii).

8. A compound or salt according to Claim 7, wherein the formula (iii-a) represents a pyrrolidine ring.

9. A compound or salt according to Claim 7 or 8, wherein Y represents $-CH_2O-$, $-CH_2S-$, $-CH_2S(O)_2-$, $-(CH_2)_2-$, $-CH=CH-$, $-C\equiv C-$ or $-CH_2NY^1-$.

10. A compound or salt according to Claim 7 or 8, wherein Y represents $-CH_2O-$.

11. A compound or salt according to any one of Claims 7 to 10, wherein A^2 represents a single bond and R^{10} represents a hydroxyl or lower alkoxy group.

12. A compound or salt according to Claim 3, wherein in the formula (i-a), X^1 represents an oxygen atom and the bonding on the right side is to R at the 6-position of benzoxazole.

13. A medicament comprising a compound or salt as claimed in any one of Claims 1 to 12.

14. A medicament according to Claim 13, which is a preventive and/or remedy of a disease caused by cell adhesion.

15. A medicament according to Claim 14, wherein the disease caused by cell adhesion is selected from inflammatory diseases, autoimmune diseases, metastasis, bronchial asthma, rhinostenosis, diabetes, arthritis, psoriasis, multiple sclerosis, inflammatory intestinal diseases and rejection upon transplantation.

16. A pharmaceutical composition comprising a

pharmaceutically acceptable carrier and a compound or salt as claimed in any one of Claims 1 to 12.

17. Use of a compound or salt of Claim 1 for the preparation of a medicament.

18. A treating method of a disease caused by cell adhesion, which comprises administering a compound or salt as claimed in Claim 1.