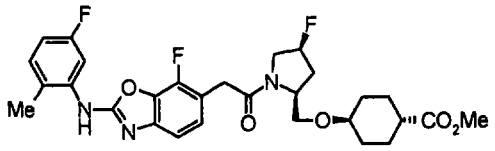
MS (ESI) m/z 319 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

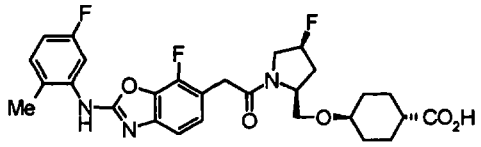


In DMF (4 ml) were dissolved (2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (159 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol). The resulting solution was stirred at room temperature for 19 hours. The 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 thin plate, whereby from chloroform/acetone (5/1) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (243 mg, 87%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.62 (m, 4H), 1.97-2.29 (m, 6H), 2.31 (s, 3H), 2.51 (m, 1H), 3.22-3.61 (m, 2H), 3.65 (s, 1H), 3.67 (s, 3H), 3.70 (s, 1H), 3.71-4.09 (m, 3H), 4.31-4.44 (m, 1H), 5.18-5.41 (m, 1H), 6.75 (t, J=6.3Hz, 1H), 7.09-7.18 (m, 3H), 7.21 (d, J=9.5Hz, 1H), 8.07 (dd, J=10.7, 2.2Hz, 1H).

MS (ESI) m/z 560 (M^++1).

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



In THF/methanol (8/4 ml) was dissolved methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (243 mg, 0.434 mmol). To the resulting solution was added 1N NaOH (4 ml). After stirring 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. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (184 mg, 78%) as a colorless solid.

IR (ATR) ν 3224, 2937, 1720, 1703, 1639, 1610, 1579, 1452 cm^{-1};

^1H-NMR (DMSO-d_6) δ: 1.12-1.43 (m, 4H), 1.82-2.22 (m, 7H), 2.30 (s, 3H), 3.20 (t, J=10.0Hz, 1H), 3.40-4.08 (m, 6H), 4.13 and 4.36 (m and q, J=7.1Hz, total 1H, amide isomers), 5.32 and 5.40 (dt and d, J=54.4, 4.4 and 53.5Hz respectively, total 1H, amide isomers), 6.89 (dt, J=8.3,2.0Hz, 1H), 7.05 and 7.08 (each t, J=7.1 and 7.3Hz respectively, total 1H, amide isomers), 7.21 (dd, J=8.1, 2.4Hz, 1H), 7.26 (t, J=7.8Hz, 1H), 7.92 (d, J=11.5Hz, 1H), 10.04 (br, 1H).

MS (ESI) m/z 546 (M^++1);

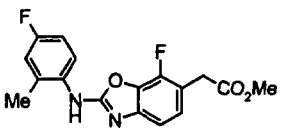
Anal. Calcd for $C_{28}H_{30}F_3N_3O_5$ $0.4H_2O$: C, 60.84; H, 5.62; N, 7.60; F, 10.31.

Found: C, 60.91; H, 5.49; N, 7.41; F, 10.32.

Example 45

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

(Step 1) Synthesis of methyl (2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate



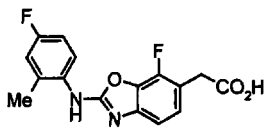
In methanol (30 ml) was dissolved methyl (4-amino-2-

fluoro-3-hydroxyphenyl)acetate (1.0 g, 5.02 mmol). To the resulting solution was added 4-fluoro-2-methylphenyl isothiocyanate (0.74 ml, 5.23 mmol). After the mixture was stirred at room temperature for 5 days, mercuric oxide (yellow) (1.14 g, 4.36 mmol) was added thereto. The mixture was stirred at 70°C for 6 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and washed 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 (30/1) eluate fractions, methyl (2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.32 g, 91%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.72 (s, 3H), 3.75 (s, 2H), 6.71 (br, 1H), 6.92-7.01 (m, 2H), 7.09 (t, J=8.1Hz, 1H), 7.18 (d, J=8.1Hz, 1H), 7.93 (dd, J=8.8,5.4Hz, 1H).

MS (ESI) m/z 333 (M^++1).

(Step 2) Synthesis of (2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid



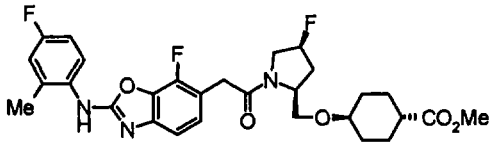
In THF/methanol (2:1, v/v, 120 ml) was dissolved methyl (2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-

benzoxazolyl)acetate (1.32 g, 3.97 mmol). To the resulting solution was added 1N NaOH (40 ml). After stirring at room temperature for 12 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-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (1.38 g, 100%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 2.26 (s, 3H), 3.68 (s, 2H), 7.06-7.14 (m, 4H), 7.75 (m, 1H), 9.91 (s, 1H).

MS (ESI) m/z 319 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



To a mixture of methyl (2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (159 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol),

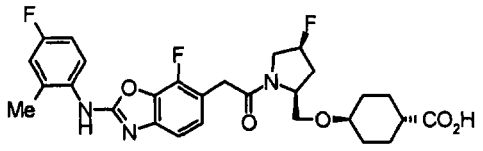
EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) was added DMF (4 ml). The resulting mixture was stirred at room temperature for 19 hours. The reaction mixture was poured in ice water, followed by extraction with ethyl acetate. The extract was washed with saturated 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), whereby from chloroform/acetone (5/1) eluate fractions, methyl trans-4-(1-((2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (245 mg, 88%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.27-1.57 (m, 5H), 1.96-2.28 (m, 7H), 2.32 (s, 3H), 2.45 and 2.51 (each d, J=15.7 and 14.9Hz respectively, total 1H, amide isomers), 3.24-3.41 (m, 1H), 3.55 (m, 1H), 3.65 and 3.67 (each s, total 3H, amide isomers), 3.72-4.06 (m, 3H), 4.31-4.43 (m, 1H), 5.27 and 5.31 (each dt, J=54.0, 4.7 and 53.2, 4.3Hz respectively, total 1H, amide isomers), 6.92-7.08 (m, 3H), 7.13 (t, J=8.1Hz, 1H), 7.80 (m, 1H).

MS (ESI) m/z 560 (M^++1).

(Step 4) Synthesis of trans-4-(1-((2-(4-fluoro-2-

methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (2:1, 12 ml) was dissolved methyl trans-4-(1-((2-(4-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (245 mg, 0.438 mmol). To the resulting solution was added 1N NaOH (4 ml). After stirring 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. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (199 mg, 83%) as a colorless solid.

IR (ATR) ν 3165, 2941, 1699, 1635, 1581, 1496, 1454 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.27 (m, 2H), 1.34 (t, J=12.4Hz, 2H), 1.82-2.22 (m, 7H), 2.30 (s, 3H), 3.19 (t, J=8.8Hz, 1H), 3.40-4.03 (m, 6H), 4.13 and 4.35 (m and q, J=7.1Hz, total 1H, amide isomers), 5.32 and 5.40 (d and dt, J=54.9, 4.6 and 53.7Hz respectively, total 1H, amide isomers), 6.99-7.16 (m, 4H), 7.76 (dd, J=8.8,5.6Hz, 1H), 9.89(br, 1H),

12.04(br, 1H).

MS (ESI) m/z 546 (M^++1);

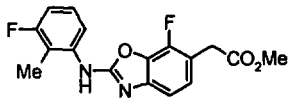
Anal. Calcd for $C_{28}H_{30}F_3N_3O_5 \cdot 0.4H_2O$: C, 60.84; H, 5.62; N, 7.60; F, 10.31.

Found: C, 61.15; H, 5.71; N, 7.15; F, 9.97.

Example 46

trans-4-(1-((2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid

(Step 1) Synthesis of methyl (2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate



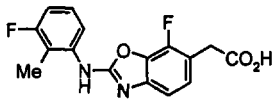
In THF (20 ml) was dissolved 3-fluoro-2-methylaniline (0.57 ml, 5.0 mmol). To the resulting solution was added thiophosgene (990 mg, 5.0 mmol) under stirring at room temperature. After the reaction mixture was stirred for 4 hours at room temperature, methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (996 mg, 5.0 mmol) was added thereto. The resulting mixture was stirred further at room temperature for 2 days. Mercuric oxide (yellow) (1.08 g, 5.0 mmol) was added and the mixture was stirred at 70°C for 4.5 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and washed 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 n-hexane/ethyl acetate (4/1) eluate fractions, methyl (2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.21 g, 73%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, 3H), 3.72 (s, 3H), 3.76 (s, 2H), 6.87 (t, J=8.8Hz, 1H), 7.09 (t, J=6.6Hz, 1H), 7.22 (d, J=7.8Hz, 1H), 7.27 (m, 1H), 7.93 (d, J=7.8Hz, 1H).

MS (ESI) m/z 333 (M^++1).

(Step 2) Synthesis of (2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid



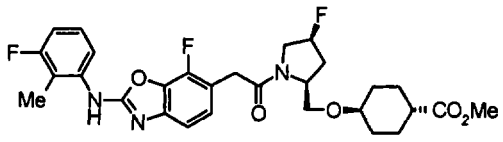
In THF/methanol (2:1, 60 ml) was dissolved methyl (2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetate (1.21 g, 3.64 mmol). To the resulting solution was added 1N NaOH (20 ml). After stirring at room temperature for 17 hours, the reaction mixture was distilled under reduced pressure to remove 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-(3-fluoro-2-methylphenylamino)-7-

fluoro-6-benzoxazolyl)acetic acid (1.10 g, 15%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 2.21 (d, J=2.0Hz, 3H), 3.66 (s, 2H), 7.00 (t, J=8.8Hz, 1H), 7.10-7.16 (m, 2H), 7.26 and 7.30 (each d, J=7.8 and 8.1Hz respectively, total 1H, amide isomers), 7.72 (d, J=7.1Hz, 1H), 10.10 (br, 1H).

MS (ESI) m/z 319 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



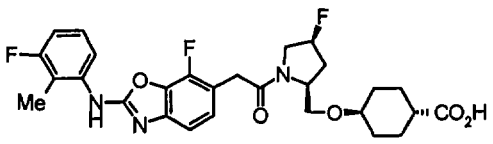
To a mixture of (2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetic acid (159 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) was added DMF (4 ml). The resulting mixture was stirred at room temperature for 18 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 thin-layer plate (TLC), whereby from chloroform/acetone (5/1) eluate fractions, methyl trans-4-(1-((2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (264 mg, 94%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.91-1.58 (m, 4H), 1.96-2.21 (m, 5H), 2.25 (d, J=1.7Hz, 3H), 2.27 and 2.48 (each m, total 1H, amide isomers), 3.22-3.33 (m, 1H), 3.35 and 3.56 (t and tt, J=8.5 and 9.3, 6.1Hz respectively, total 1H, amide isomers), 3.65 and 3.67 (each s, total 3H, amide isomers), 3.69 (s, 1H), 3.70-4.02 (m, 5H), 4.33 and 4.39 (q and dt, J=7.6 and 7.8, 4.4Hz, total 1H, amide isomers), 5.27 and 5.31 (each dt, = 54.0, 4.1 and 53.0, 3.9Hz, total 1H, amide isomers), 6.86 (t, J=8.3Hz, 1H), 7.06 and 7.08 (each t, J=7.8 and 11.7Hz respectively, total 1H, amide isomers), 7.16-7.29 (m, 2H), 7.88 (dd, J=8.1, 2.6Hz, 1H).

MS (ESI) m/z 560 (M^++1).

(Step 4) Synthesis of trans-4-(1-((2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF/methanol (2:1, 63 ml) was dissolved methyl

trans-4-(1-((2-(3-fluoro-2-methylphenylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (264 mg, 0.472 mmol). To the resulting solution was added 1N NaOH (10 ml). After stirring at room temperature for 17 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 (199 mg, 83%) as a colorless solid.

IR (ATR) ν 3167, 2939, 1701, 1641, 1581, 1452 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.39 (m, 5H), 1.83-2.03 (m, 5H), 2.08-2.17 (m, 2H), 2.50 (d, J=2.0Hz, 3H), 3.19 (t, J=8.8Hz, 2H), 3.41-4.06 (m, 4H), 4.12 and 4.36 (m and q, J=6.8Hz, total 1H, amide isomers), 5.32 and 5.40 (dt and d, J=54.5, 5.4 and 54.8Hz respectively, total 1H, amide isomers), 7.00 (t, J=8.8Hz, 1H), 7.05 (m, 1H), 7.13 and 7.15 (each d, J=2.7 and 2.9Hz respectively, total 1H, amide isomers), 7/28 (dd, J=14.9, 8.1Hz, 1H), 7.72 (d, J=8.1Hz, 1H).

MS (ESI) m/z 546 (M^++1);

Anal. Calcd for $C_{28}H_{30}F_3N_3O_5$ 0.1HCl·1.4H_2O: C, 58.55; H, 5.77; N, 7.32; F, 9.92.

Found: C, 58.24; H, 5.38; N, 7.09; F, 9.63.

Example 47

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

(Step 1) Synthesis of 4,6-difluoro-2-hydroxynitrobenzene



Under stirring at room temperature, 10N NaOH (18 ml, 180 mmol) was added dropwise to a solution of 2,4,6-trifluoronitrobenzne (15.0 g, 84.7 mmol) in DMSO (75 ml). After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl to neutralize therewith, followed by extraction 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 ethyl acetate/chloroform (1/10) eluate fractions, 4,6-difluoro-2-hydroxynitrobenzene (12.5 g, 84%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 6.55-6.60 (m, 1H), 6.68-6.71 (m, 1H), 10.90 (s, 1H).

(Step 2) Synthesis of 2-benzyloxy-4,6-

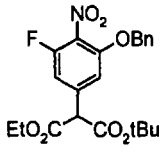
difluoronitrobenzene



To a solution of 4,6-difluoro-2-hydroxynitrobenzene (12.5 g, 71.1 mmol) in DMF (150 ml) was added sodium hydride (60% in oil, 3.70 g, 92.4 mmol) under stirring at 0°C, and the reaction mixture was stirred for 15 minutes. Benzyl bromide (11.0 ml, 92.4 mmol) was added dropwise at 0°C. After completion of the dropwise addition, the reaction mixture was stirred at 80°C for 18 hours. After cooling to room temperature, the mixture was poured in ice-1N HCl to neutralize therewith, followed by extraction 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 ethyl acetate/hexane (1/5) eluate fractions, 2-benzyloxy-4,6-difluoronitrobenzene (13.7 g, 73%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 5.18 (s, 2H), 6.55-6.63 (m, 2H), 7.32-7.46 (m, 5H).

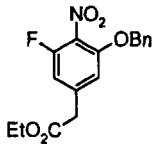
(Step 3) Synthesis of tert-butyl ethyl 5-benzyloxy-3-fluoro-4-nitrophenylmalonate



To a solution of tert-butyl ethyl malonate (10.0 g, 51.0 mmol) in DMF (200 ml) was added sodium hydride (60% in oil, 2.04 g, 51.0 mmol) at 0°C under stirring. The reaction mixture was stirred at the same temperature for 30 minutes. A solution of 2-benzyloxy-4,6-difluoronitrobenzene (9.02 g, 34.0 mmol) in DMF (60 ml) was added dropwise to the reaction mixture at 0°C. The reaction mixture was then stirred at 80°C for 18 hours. After cooling to room temperature, the reaction mixture was poured in ice-1N HCl to neutralize therewith, followed by extraction with ether. The extract was washed with saturated brine, dried over anhydrous sodium sulfate, then distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from with ethyl acetate/hexane (1/5) eluate fractions, tert-butyl ethyl 5-benzyloxy-3-fluoro-4-nitrophenylmalonate (2.91 g, 17%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.30 (m, 3H), 1.47 (s, 9 H), 4.11-4.28 (m, 2H), 4.47 (s, 1H), 5.20 (s, 2H), 6.91 (d, J=9.6Hz, 1H), 7.00 (s, 1H), 7.32-7.39 (m, 5 H).

(Step 4) Synthesis of ethyl 5-benzyloxy-3-fluoro-4-nitrophenylacetate

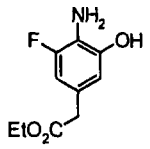


In methylene chloride (30 ml) was dissolved tert-butyl ethyl 5-benzyloxy-3-fluoro-4-nitrophenylmalonate (2.89 g, 6.67 mmol). To the resulting solution was added trifluoroacetic acid (30 ml). The resulting mixture was stirred at room temperature for 3.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was neutralized with an aqueous saturated 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 ethyl acetate/hexane (1/5) eluate fractions, ethyl 5-benzyloxy-3-fluoro-4-nitrophenylacetate (1.57 g, 70%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.2Hz, 3H), 3.60 (s, 2H), 4.17 (q, J=7.2, 14.4Hz, 2H), 5.20 (s, 2H), 6.80 (d, J=10.0Hz, 1H), 6.84 (s, 1H), 7.27-7.40 (m, 5 H).

(Step 5) Synthesis of ethyl 4-amino-3-fluoro-5-

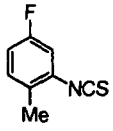
hydroxyphenylacetate



Ethyl 3-fluoro-4-nitro-5-benzyloxyphenylacetate (1.54 g, 4.62 mmol) and 10% palladium-carbon (122 mg) were subjected to catalytic hydrogenation for 20 hours under normal pressure while stirring at room temperature in EtOH (20 ml). From the reaction mixture, the catalyst was 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 ethyl acetate/hexane (1/2) eluate fractions, ethyl 4-amino-3-fluoro-5-hydroxyphenylacetate (639 mg, 65%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7.2Hz, 3H), 3.43 (s, 2H), 4.15 (q, J=7.2, 14.4Hz, 2H), 6.48 (s, 1H), 6.54 (d, J=10.4Hz, 1H).

(Step 6) Synthesis of 5-fluoro-2-methylphenyl isothiocyanate

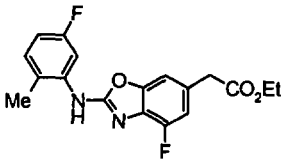


Under stirring at 0°C, a solution of 5-fluoro-2-methylaniline (1.23 g, 9.84 mmol) in methylene chloride (10

ml) was added dropwise to a mixture of calcium carbonate (2.46 g, 24.6 mmol) and thiophosgene (750 µl, 9.84 mmol) in a methylene chloride/water (1/1, 40 ml) mixture. After completion of the dropwise addition, the reaction mixture was stirred further at 0°C for 35 minutes. The reaction mixture was poured in ice-1N HCl, 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 5-fluoro-2-methylphenyl isothiocyanate (1.45 g, 88%) as a brown oil.

MS (ESI) m/z 167 (M^+).

(Step 7) Synthesis of ethyl (2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetate



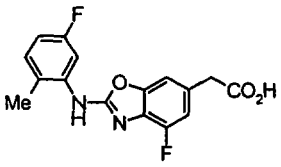
Under stirring at room temperature, ethyl 4-amino-3-fluoro-5-hydroxyphenylacetate (233 mg, 1.10 mmol) was added to a solution of 5-fluoro-2-methylphenyl isothiocyanate (184 mg, 1.10 mmol) in methanol (20 ml). The resulting mixture was stirred at 70°C for 1 hour. To the reaction mixture was added mercuric oxide (yellow) (262 mg, 1.21 mmol), followed by stirring for further 30 minutes. After

cooling to room temperature, the reaction mixture was filtered through Celite. The filtrate was washed with methanol and then, 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, ethyl (2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetate (216 mg, 57%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.2Hz, 3H), 2.32 (s, 3H), 3.67 (s, 2H), 4.18 (q, J=6.8, 14.4Hz, 2H), 6.74-6.79 (m, 1H), 6.92-6.97 (m, 2H), 7.14-7.17 (m, 2H), 8.05-8.09 (m, 1H).

MS (ESI) m/z 347 (M^++1).

(Step 8) Synthesis of (2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetic acid



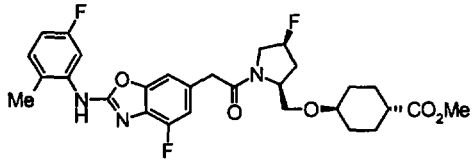
Ethyl (2-(5-fluoro- 2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetate (215 mg, 0.62 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (12.4 ml, 3.10 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured in 1N HCl to acidify the mixture, 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 (2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetic acid (165 mg, 83%) as a pale brown solid.

^{1}H-NMR ($CDCl_3$) δ: 2.28 (s, 3H), 3.66 (s, 2H), 6.87-6.91 (m, 1H), 7.03 (d, J=11.6Hz, 1H), 7.23-7.29 (m, 3H), 7.84-7.87 (m, 1H), 9.98 (brs, 1H).

MS (ESI) m/z 319 (M^++1).

(Step 9) Synthesis of methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



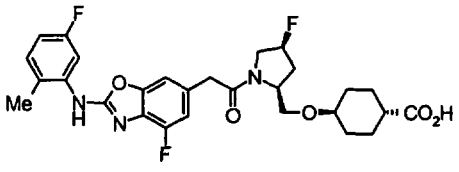
To a solution of (2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetic acid (165 mg, 0.52 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (134 mg, 0.52 mmol) and EDC-HCl (119 mg, 0.62 mmol) in DMF (10 ml) was added HOBt (14.0 mg, 0.10 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 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)-4-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (251 mg, 87%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of amide-isomers, δ: 1.24-1.32 (m, 2H), 1.40-1.53 (m, 2H), 1.96-2.52 (series of m, 7H), 2.31 (s, 3H), 3.22-4.41 (series of m, 8H), 3.65 and 3.67 (s, total 3H), 4.28-4.42 (m, 1H), 5.17-5.36 (m, 1H), 6.73-6.77 (m, 1H), 6.89-6.92 (m, 1H), 7.12-7.16 (m, 3H), 8.01-8.05 (m, 1H).

MS (ESI) m/z 561 (M^++2).

(Step 10) Synthesis of trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((2-(5-fluoro-2-methylphenylamino)-4-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (239 mg, 0.43 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added aqueous 0.25N NaOH (8.50 ml, 2.14 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was acidified with 1N HCl, 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. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (15/1) eluate fractions, the title compound (233 mg, 100 %) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of amide-isomers, δ: 1.22-1.33 (m, 2H), 1.42-1.52 (m, 2H), 2.02-2.62 (series of m, 7H), 2.31 (s, 3H), 3.23-4.42 (series of m, 8H), 4.28-4.42 (m, 1H), 5.17-5.36 (m, 1H), 6.74-6.78 (m, 1H), 6.89-6.92 (m, 1H), 7.11-7.15 (m, 3H), 7.75 (d, J=10.5Hz, 1H).

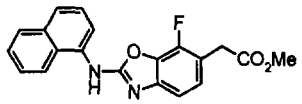
MS (ESI) m/z 547 (M^++2).

Example 48

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

(Step 1) Synthesis of methyl (2-(1-naphthylamino)-7-

fluoro-6-benzoxazolyl)acetate



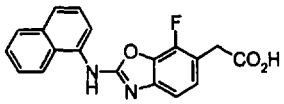
Methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (996 mg, 5.00 mmol) was dissolved in methanol (50 ml). To the resulting solution was added 1-naphthyl isothiocyanate (926 mg, 5.00 mmol). After the resulting mixture was stirred at room temperature for 2 days, mercuric oxide (yellow) (1.08 g, 5.00 mmol) was added thereto. The mixture was stirred at 70°C for 3.5 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The crude crystals thus obtained were recrystallized from chloroform/n-hexane to give methyl (2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetate (1.41 g, 81%) as a pale gray crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 3.717 and 3.723 (each s, total 3H, amide isomers), 3.75 (d, J=1.2Hz, 2H), 7.05 and 7.07 (each d, J=6.6 and 6.3Hz respectively, total 1H, amide isomers), 7.53-7.59 (m, 3H), 7.73 (d, J=8.3Hz, 1H), 7.92 (dd, J=7.1,2.4Hz, 1H), 8.14 (dd, J=7.8,1.0Hz, 1H).

MS (ESI) m/z 351 (M^++1).

(Step 2) Synthesis of (2-(1-naphthylamino)-7-fluoro-6-

benzoxazolyl)acetic acid

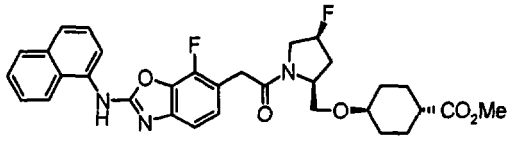


Methyl (2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetate (1.41 g, 4.02 mmol) was dissolved in THF/methanol (21, 30 ml). To the resulting solution was added 1N NaOH (10 ml). After stirring at room temperature for 12 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. 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-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetic acid (1.44 g, 100%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.70 (s, 2H), 7.15 (q, J=6.3Hz, 1H), 7.16 (s, 1H), 7.55-7.61 (m, 3H), 7.78 (d, J=7.8Hz, 1H), 7.97 and 7.98 (d and m, J=5.9Hz, total 1H, amide isomers), 8.10 (d, J=7.6Hz, 1H), 8.25-8.30 (m, 1H), 10.64 (br, 1H).

MS (ESI) m/z 337 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



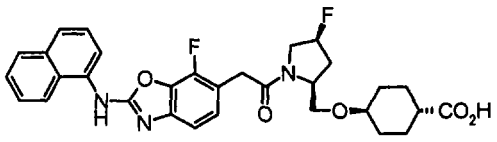
To a mixture of methyl (2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetate (168 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) was added DMF (5 ml). The resulting mixture was stirred at room temperature for 3 days. 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 thin-layer plate (TLC), whereby from chloroform/acetone (10/1) eluate fractions, methyl trans-4-(1-((2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (280 mg, 97%) was obtained as a pale brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.57 (m, 5H), 1.95-2.53 (m, 8H), 3.19-3.58 (m, 2H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.71-4.06 (m, 3H), 4.29-.45 (m, 1H), 5.17-5.39 (m, 1H), 6.95-7.11 (m, 2H), 7.51-7.56 (m, 3H), 7.69 (d, J=7.3Hz,

1H), 7.89 (m, 1H), 8.07-8.13 (m, 2H), 8.56 (br, 1H).

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

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



Methyl trans-4-(1-((2-(1-naphthylamino)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (280 mg, 0.485 mmol) was dissolved in THF/methanol (2:1, v/v, 15 ml). To the resulting solution was added 1N NaOH (5 ml). After stirring at room temperature for 3 days, 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 (204 mg, 74.6%) as a pale pink solid.

IR (ATR) ν 3278, 2935, 2864, 1701, 1637, 1572, 1452 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.41 (m, 4H), 1.82-2.36 (m, 7H), 3.19 (m, 2H), 3.36-4.39 (m, 6H), 5.25-5.50 (m, 1H), 7.01-7.09 (m, 1H), 7.15 and 7.16 (each d, J=2.9 and 3.2Hz

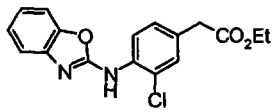
respectively, total 1H, amide isomers), 7.55-7.60 (m, 3H), 7.77 (d, J=8.3Hz, 1H), 7.97 and 7.98 (each d, J=3.2 and 2.2Hz respectively, total 1H, amide isomers), 8.11 (d, J=7.8Hz, 1H), 8.28 and 8.29 (each d, J=5.1 and 4.2Hz respectively, total 1H, amide isomers), 10.64 (br, 1H), 12.04 (br, 1H).

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

Example 49

trans-4-(1-(4-(2-Benzoxazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetate



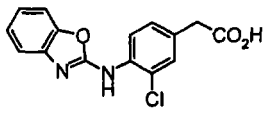
In xylene (10 ml), 2-chlorobenzoxazole (743 µl, 6.51 mmol) and ethyl 4-amino-3-chlorophenylacetate (1.30 g, 6.51 mmol) were heated under reflux for 2 hours. After cooling to room temperature, the reaction mixture was diluted with chloroform (50 ml). The mixture was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (9:1, v/v) eluate fractions,

ethyl (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetate (1.70 g, 79%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.25-1.28 (m, 3H), 3.58 (s, 2H), 4.14-4.19 (m, 2H), 7.15-7.19 (m, 1H), 7.24-7.30 (m, 3H), 7.36-7.38 (m, 2H), 7.52-7.54 (m, 1H), 8.51-8.53 (m, 1H).

MS (ESI) m/z 331 (M^++1).

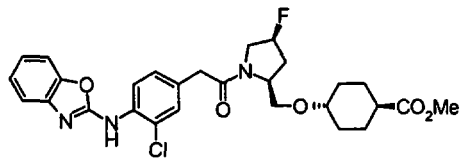
(Step 2) Synthesis of (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetic acid



Ethyl (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetate (1.70 g, 5.14 mmol) was dissolved in THF (30 ml). To the resulting solution was added 0.5N NaOH (30 ml, 15.0 mmol) under stirring. The resulting mixture was stirred at room temperature for 20 hours. The mixture was concentrated and the residue was acidified with ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetic acid (1.24 g, 80%) as a pale yellow crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 7.10-7.19 (m, 1H), 7.21-7.28 (m, 1H), 7.30-7.31 (m, 1H), 7.38-7.40 (m, 1H), 7.45-7.49 (m, 3H), 7.94-7.96 (m, 1H).

(Step 3) Synthesis of methyl trans-4-(1-(4-(2-benzoxazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



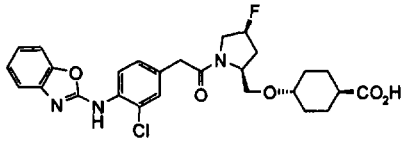
In DMF (5 ml), (4-(2-benzoxazolyl)amino-3-chlorophenyl)acetic acid (247 mg, 0.82 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (225 mg, 0.87 mmol), EDC·HCl (235 mg, 1.23 mmol), HOBt (166 mg, 1.23 mmol), and triethylamine (171 μl, 1.23 mmol) were stirred at room temperature for 5 hours. To the reaction mixture was added water (20 ml), 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 (60:1, v/v) eluate fractions, trans-4-(1-(4-(2-benzoxazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (454 mg, 100%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.53 (m, 4H), 1.97-2.51 (m, 7H),

3.23-3.36 and 3.49-3.59 (each m, total 2H), 3.63-4.01 (m, 8H), 4.19-4.24 and 4.35-4.41 (each m, total 1H), 5.17-5.20 and 5.30-5.33 (each m, total 1H), 7.15-7.19 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.38 (m, 2H), 7.52-7.54 (m, 1H), 8.47-8.53 (m, 1H).

MS (ESI) m/z 544 (M^++1).

(Step 4) Synthesis of trans-4-(1-(4-(2-benzoxazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-(4-(2-benzoxazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (454 mg, 0.83 mmol) were added THF (5 ml) and 0.5N NaOH (5.0 ml, 2.50 mmol), followed by stirring at room temperature for 15 hours. The reaction mixture was poured in ice-1N HCl to acidify the 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 chloroform/methanol (50:1, v/v) eluate fractions, the title compound (359 mg, 81%) was obtained as a colorless

amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.34 (m, 2H), 1.43-1.55 (m, 2H), 2.02-2.51 (m, 7H), 3.24-3.37 and 3.47-3.52 (each m, total 2H), 3.58-4.01 (m, 5 H), 4.19-4.25 and 4.35-4.41 (each m, total 1H), 5.16-5.19 and 5.30-5.32 (each m, total 1H), 7.12-7.16 (m, 1H), 7.22-7.25 (m, 2H), 7.33-7.36 (m, 2H), 7.47-7.49 (m, 1H), 8.27-8.32 (m, 1H).

MS (ESI) m/z 530 (M^++1);

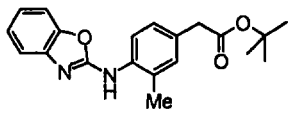
Anal. Calcd for $C_{27}H_{29}ClFN_3O_5 \cdot 5/4H_2O$: C, 58.69; H, 5.75; N, 7.61.

Found: C, 58.74; H, 5.17; N, 7.38.

Example 50

trans-4-(1-(4-(2-Benzoxazolyl)amino-3-methylphenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of tert-butyl (4-(2-benzoxazolyl)amino-3-methylphenyl)acetate

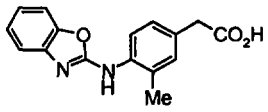


In xylene (20 ml), 2-chlorobenzoxazole (845 µl, 7.40 mmol) and tert-butyl 4-amino-3-methylphenylacetate (1.26 g, 5.69 mmol) were heated under reflux for 2 hours under stirring. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the

solvent. The residue was dissolved in chloroform/methanol (9:1, v/v, 100 ml). The resulting solution 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 n-hexane/ethyl acetate (4:1, v/v) eluate fractions, tert-butyl (4-(2-benzoxazolyl)amino-3-methylphenyl)acetate (1.17 g, 61%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9 H), 2.30 (s, 3H), 3.49 (s, 2H), 7.05-7.24 (m, 4H), 7.27-7.29 (m, 1H), 7.38-7.40 (m, 1H), 7.86-7.88 (m, 2H).

(Step 2) Synthesis of (4-(2-benzoxazolyl)amino-3-methylphenyl)acetic acid



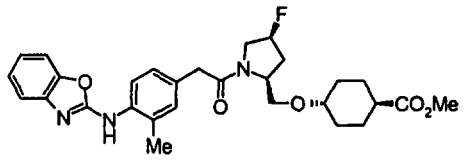
In methylene chloride (10 ml) was dissolved tert-butyl (4-(2-benzoxazolyl)amino-3-methylphenyl)acetate (1.17 g, 3.46 mmol). To the resulting solution was added trifluoroacetic acid (10 ml). The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was poured in ice water, 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 on a silica gel column, whereby from chloroform/methanol (60:1 to 50:1, v/v) eluate fractions, (4-(2-benzoxazolyl)amino-3-methylphenyl)acetic acid (924 mg, 95%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.38 (s, 3H), 3.68 (s, 2H), 7.22-7.29 (m, 4H), 7.36-7.42 (m, 3H), 7.48-7.52 (m, 1H).

MS (ESI) m/z 283 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(4-(2-benzoxazolyl)amino-3-methylphenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



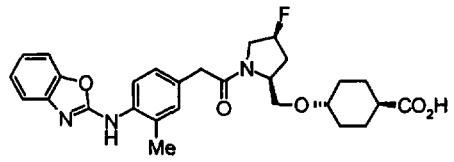
To a mixture of (4-(2-benzoxazolyl)amino-3-methylphenyl)acetic acid (220 mg, 0.78 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (210 mg, 0.80 mmol), EDC·HCl (224 mg, 1.17 mmol), HOBt (158 mg, 1.17 mmol), and triethylamine (163 μl, 1.17 mmol) was added DMF (5 ml). The resulting mixture was stirred at room temperature for 15 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 (60:1, v/v) eluate fractions, methyl trans-4-(1-(4-(2-benzoxazolyl)amino-3-methylphenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (380 mg, 93%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.26-1.46 (m, 4H), 1.99-2.46 (m, 10H), 3.25-3.89 (m, 10H), 4.23-4.25 and 4.38 (each m, total 1H), 5.19 and 5.32 (each m, total 1H), 7.08-7.21 (m, 4H), 7.28-7.29 (m, 1H), 7.41-7.43 (m, 1H), 7.67 (broad s, 1H), 7.87-7.93 (m, 1H).

MS (ESI) m/z 524 (M^++1).

(Step 4) Synthesis of trans-4-(1-(4-(2-benzoxazolyl)amino-3-methylphenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (5 ml) was dissolved methyl trans-4-(1-(4-(2-benzoxazolyl)amino-3-methylphenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (380 mg, 0.73 mmol). To the resulting solution was added 0.5N NaOH (5.0

ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 3 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 (60:1 to 50:1, v/v) eluate fractions, the title compound (155 mg, 42%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.35 (m, 2H), 1.43-1.54 (m, 2H), 1.99-2.15 (m, 4H), 2.24-2.52 (m, total 6H), 3.25-4.02 (m, 7H), 4.21-4.27 and 4.37-4.43 (each m, total 1H), 5.17-5.21 and 5.30-5.34 (each m, total 1H), 7.07-7.23 (m, 4H), 7.30-7.40 (m, 2H), 7.69-7.74 (m, 1H).

MS (ESI) m/z 510 (M^++1);

Anal. Calcd for $C_{28}H_{32}FN_3O_5 \cdot 1/2H_2O$: C, 64.85; H, 6.41; N, 8.10.

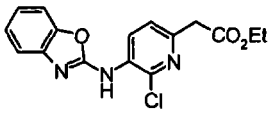
Found: C, 64.75; H, 6.56; N, 7.65.

Example 51

trans-4-(1-(3-(2-Benzoxazolyl)amino-2-chloro-6-pyridylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (3-(2-benzoxazolyl)amino-2-

chloro-6-pyridyl)acetate

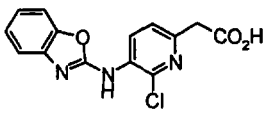


In xylene (100 ml), 2-chlorobenzoxazole (326 μl, 2.86 mmol) and ethyl (3-amino-2-chloro-6-pyridyl)acetate (557 mg, 2.59 mmol) were heated under reflux for 4 hours under stirring. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (3:1, v/v) eluate fractions, ethyl (3-(2-benzoxazolyl)amino-2-chloro-6-pyridyl)acetate (460 mg, 53%) was obtained as a colorless gum.

^{1}H-NMR ($CDCl_3$) δ: 1.25-1.28 (m, 3H), 3.79 (s, 2H), 4.16-4.21 (m, 2H), 7.14-7.18 (m, 1H), 7.22-7.26 (m, 1H), 7.31-7.36 (m, 3H) 7.49-7.51 (m, 1H), 8.86-8.89 (m, 1H).

MS (ESI) m/z 332 (M^++1).

(Step 2) Synthesis of (3-(2-benzoxazolyl)amino-2-chloro-6-pyridyl)acetic acid

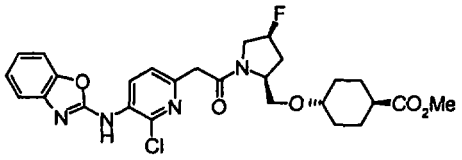


In THF (8 ml) was dissolved ethyl (3-(2-benzoxazolyl)amino-2-chloro-6-pyridyl)acetate (460 mg, 1.39 mmol). To the resulting solution was added 0.5N NaOH (8.0

ml, 4.00 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (3-(2-benzoxazolyl)amino-2-chloro-6-pyridyl)acetic acid (332 mg, 79%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 3.30 (s, 2H), 6.68-6.72 (m, 1H), 6.76-6.80 (m, 1H), 6.96-7.06 (m, 3H), 8.00-8.02 (m, 1H).

(Step 3) Synthesis of methyl trans-4-(1-(3-(2-benzoxazolyl)amino-2-chloro-6-pyridylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



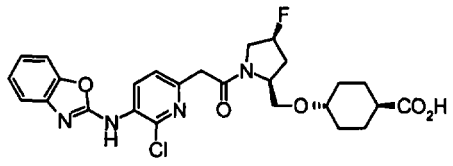
To a mixture of (3-(2-benzoxazolyl)amino-2-chloro-6-pyridyl)acetic acid (153 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (131 mg, 0.51 mmol), EDC·HCl (145 mg, 0.76 mmol), HOBt (102 mg, 0.75 mmol), and triethylamine (105 µl, 0.75 mmol) was added DMF (5 ml). The resulting mixture was stirred at room temperature for 2 days. 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 n-hexane-ethyl acetate (1:2, v/v) eluate fractions, methyl trans-4-(1-(3-(2-benzoxazolyl)amino-2-chloro-6-pyridylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (270 mg, 98%) was obtained as a colorless thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.29 (m, 2H), 1.39-1.53 (m, 2H), 1.96-2.52 (m, 7H), 3.22-3.36 and 3.50-3.54 (each m, total 2H), 3.64-4.14 (m, 8H), 4.38 and 4.45-4.47 (each m, total 1H), 5.20-5.23 and 5.34 (each m, total 1H), 7.15-7.27 (m, 2H), 7.35-7.39 (m, 2H), 7.50-7.52 (m, 1H), 7.72 (broad s, 1H), 8.83-8.89 (m, 1H).

MS (ESI) m/z 545 (M^++1).

(Step 4) Synthesis of trans-4-(1-(3-(2-benzoxazolyl)amino-2-chloro-6-pyridylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (3.0 ml) was dissolved methyl trans-4-(1-(3-(2-benzoxazolyl)amino-2-chloro-6-pyridylacetyl)-(4S)-

fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (270 mg, 0.50 mmol). To the resulting solution was added 0.5N NaOH (3.0 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with n-hexane, and dried under reduced pressure to give the title compound (192 mg, 73%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.21-1.36 (m, 4H), 1.83-2.23 (m, 7H), 3.18-4.07 (m, 7H), 4.12 and 4.38 (each m, total 1H), 5.25-5.31 and 5.39-5.45 (each m, total 1H), 7.11-7.15 (m, 1H), 7.19-7.23 (m, 1H), 7.36-7.40 (m, 2H), 7.47-7.49 (m, 1H), 8.42 (m, 1H).

MS (ESI) m/z 531 (M^++1);

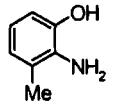
Anal. Calcd for $C_{26}H_{28}ClFN_4O_5 \cdot 1/2H_2O$: C, 57.83; H, 5.41; N, 10.38.

Found: C, 58.03; H, 5.70; N, 9.62.

Example 52

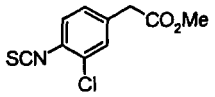
trans-4-(1-(3-Chloro-4-(2-(4-methylbenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-amino-3-methylphenol



In methanol (20 ml), 10% palladium-carbon (0.30 g, 20 wt%) was added to 3-methyl-2-nitrophenol (1.50 g, 9.80 mmol) and they were subjected to catalytic hydrogenation for 4 days. From the reaction mixture, an insoluble matter was filtered off through Celite. The filtrate was distilled under reduced pressure to remove the solvent to give 2-amino-3-methylphenol (1.19 g, 99%) as a brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (s, 3H), 6.60-6.62 (m, 2H), 6.68-6.71 (m, 1H).

(Step 2) Synthesis of methyl 3-chloro-4-isothiocyanatophenylacetate

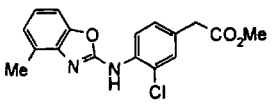


Calcium carbonate (626 mg, 6.25 mmol) and thiophosgene (191 μl, 2.51 mmol) were suspended in methylene chloride-water (10 ml, 1:1, v/v). To the resulting suspension was added a solution of methyl 4-amino-3-chlorophenylacetate (500 mg, 2.50 mmol) in methylene chloride (5 ml) under stirring at 0°C. The temperature of the reaction mixture was raised from 0°C to room temperature over 1.5 hours. The reaction mixture was acidified with 1N HCl, 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 3-chloro-4-isothiocyanatophenylacetate (652 mg, 100%) as a yellow oil.

MS (ESI) m/z 241 (M^+).

(Step 3) Synthesis of methyl (3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenyl)acetate



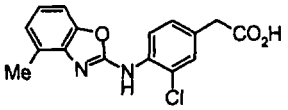
Toluene (15 ml) was added to a mixture of methyl 3-chloro-4-isothiocyanatophenylacetate (652 mg, 2.50 mmol) and 2-amino-3-methylphenol (307 mg, 2.50 mmol). The resulting mixture was heated under reflux for 2 hours. Mercuric oxide (yellow) (541 mg, 2.50 mmol) was added to the reaction mixture. The resulting mixture was heated under reflux for 5 hours. After cooling to room temperature, the reaction mixture was filtered through Celite, and washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue wad purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, methyl (3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenyl)acetate (359 mg, 43%) was

obtained as a black oil.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (s, 3H), 3.58 (s, 2H), 3.70 (s, 3H), 7.02-7.06 (m, 2H), 7.11-7.19 (m, 1H), 7.25-7.28 (m, 1H), 7.33-7.34 (m, 1H), 7.50 (broad s, 1H), 8.54-8.56 (m, 1H).

MS (ESI) m/z 331 (M^++1).

(Step 4) Synthesis of (3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenyl)acetic acid

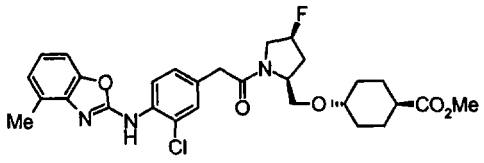


Methyl (3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenyl)acetate (359 mg, 1.08 mmol) was dissolved in THF (6 ml). To the resulting solution was added 0.5N NaOH (6.5 ml, 3.25 mmol). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in ice-1N HCl to acidify the 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 to give (3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenyl)acetic acid (281 mg, 82%) as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 2.55 (s, 3H), 3.57 (s, 2H), 6.72-6.74 (m, 1H), 7.04-7.06 (m, 2H), 7.18-7.20 (m, 2H), 8.46-8.48 (m, 1H).

MS (ESI) m/z 317 (M^++1).

(Step 5) Synthesis of methyl trans-4-(1-(3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



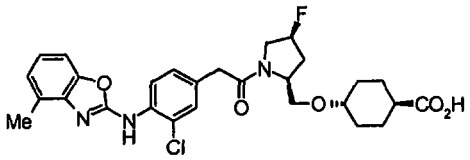
To a mixture of methyl (4-(2-(4-methylbenzoxazolyl))amino-3-chlorophenyl)acetate (281 mg, 0.89 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (230 mg, 0.89 mmol), EDC·HCl (255 mg, 1.33 mmol), HOBt (180 mg, 1.33 mmol), and triethylamine (185 µl, 1.33 mmol) was added DMF (8 ml). The resulting mixture was stirred at room temperature for 15 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 toluene/acetone (6:1, v/v) eluate fractions, methyl trans-4-(1-(3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (368 mg, 74%)

was obtained as a white amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.53 (m, 4H), 1.97-2.32 (m, 7H), 2.56 (s, 3H), 3.23-3.36 and 3.49-3.52 (each m, total 2H), 3.57-4.11 (m, 8H), 4.19-4.23 and 4.37 (each m, total 1H), 5.17-5.19 and 5.31-5.32 (each m, total 1H), 7.05-7.06 (m, 2H), 7.16-7.24 (m, 2H), 7.34-7.36 (m, 1H), 7.50 (broad s, 1H), 8.52-8.57 (m, 1H).

MS (ESI) m/z 558 (M^++1).

(Step 6) Synthesis of trans-4-(1-(3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (4 ml) was dissolved methyl trans-4-(1-(3-chloro-4-(2-(4-methylbenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (368 mg, 0.66 mmol). To the resulting solution was added 0.5N NaOH (4.0 ml, 2.00 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (139 mg, 39%)

as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.36 (m, 4H), 1.87-2.20 (m, 7H), 2.39 (s, 3H), 3.15-3.87 (m, 7H), 4.13 and 4.32-4.34 (each m, total 1H), 5.24-5.31 and 5.37-5.44 (each m, total 1H), 6.97-7.02 (m, 2H), 7.21-7.26 (m, 2H), 7.37-7.38 (m, 1H), 7.89-7.93 (m, 1H).

MS (ESI) m/z 544 (M^++1);

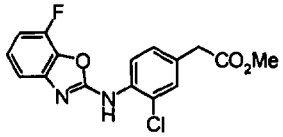
Anal. Calcd for $C_{28}H_{31}ClFN_3O_5 \cdot 1/4H_2O$: C, 61.31; H, 5.79; N, 7.66.

Found: C, 61.14; H, 6.06; N, 6.97.

Example 53

trans-4-(1-(3-Chloro-4-(2-(7-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

(Step 1) Synthesis of methyl (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetate



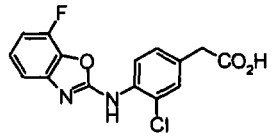
Toluene (15 ml) was added to a mixture of methyl 3-chloro-4-isothiocyanatophenylacetate (672 mg, 2.78 mmol) and 2-amino-6-fluorophenol (353 mg, 2.78 mmol). The resulting mixture was heated under reflux for 1.5 hours. Mercuric oxide (yellow) (1.03 g, 4.75 mmol) was added to the reaction mixture. The resulting mixture was heated

under reflux for 10 hours. After cooling to room temperature, the reaction mixture was filtered through Celite. The filtrate was washed with methanol, 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 (7:1, v/v) eluate fractions, methyl (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetate (109 mg, 12%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.60 (s, 2H), 3.71 (s, 3H), 6.91-6.96 (m, 1H), 7.15-7.21 (m, 1H), 7.27-7.32 (m, 2H), 7.37-7.38 (m, 1H), 7.59 (broad s, 1H), 8.49 (d, J=8.3Hz, 1H).

MS (ESI) m/z 335 (M^++1).

(Step 2) Synthesis of (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetic acid

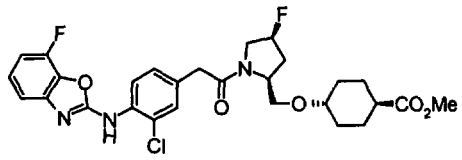


Methyl (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetate (109 mg, 0.33 mmol) was dissolved in THF (4 ml). To the resulting solution was added 0.25 N NaOH (4.0 ml, 1.00 mmol). The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was poured in -1N HCl to acidify the mixture. The crystals thus precipitated were collected by

filtration under reduced pressure, washed with water and dried under reduced pressure to give (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetic acid (95 mg, 91%) as a brown solid.

MS (ESI), m/z 321 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



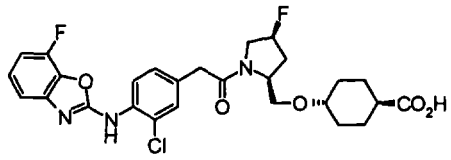
DMF (4 ml) was added to a mixture of (3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenyl)acetic acid (95 mg, 0.30 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (77 mg, 0.30 mmol), EDC·HCl (85 mg, 0.44 mmol), HOBt (60 mg, 0.44 mmol), and triethylamine (62 µl, 0.44 mmol). The resulting mixture was stirred at room temperature for 7 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 toluene/acetone (6:1, v/v) eluate fractions, methyl trans-4-(1-(3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (166 mg, 200%) was obtained as a pale yellow thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.32 (m, 2H), 1.39-1.53 (m, 2H), 1.97-2.08 (m, 4H), 2.19-2.52 (m, 3H), 3.23-3.29 and 3.32-3.54 (each m, total 2H), 3.58-4.01 (m, 8H), 4.19-4.25 and 4.35-4.41 (each m, total 1H), 5.17-5.20 and 5.30-5.34 (each m, total 1H), 6.91-6.96 (m, 1H), 7.15-7.31 (m, 3H), 7.36-7.38 (m, 1H), 7.62 (broad s, 1H), 8.44-8.49 (m, 1H).

MS (ESI) m/z 562 (M^++1).

(Step 4) Synthesis of trans-4-(1-(3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (3.6 ml) was dissolved methyl trans-4-(1-(3-chloro-4-(2-(7-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (166 mg, 0.30 mmol). To the resulting solution was added 0.25 N NaOH (3.6 ml, 0.90 mmol). The resulting mixture was stirred at room temperature for 12 hours. The reaction

mixture was poured in -1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (101 mg, 62%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.39 (m, 4H), 1.84-2.28 (m, 7H), 3.14-3.88 (m, 7H), 4.12 and 4.30-4.34 (each m, total 1H), 5.23-5.30 and 5.37-5.44 (each m, total 1H), 7.00-7.05 (m, 1H), 7.18-7.25 (m, 3H), 7.37-7.39 (m, 1H), 7.87-7.90 (m, 1H).

MS (FAB) m/z 548 (M^++1);

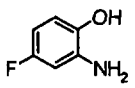
Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_5 \cdot 1/4H_2O$: C, 58.70; H, 5.20; N, 7.61.

Found: C, 58.90; H, 5.59; N, 6.77.

Example 54

trans-4-(1-(3-Chloro-4-(2-(5-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-amino-4-fluorophenol



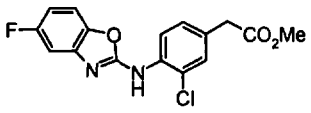
In methanol (20 ml) was dissolved 4-fluoro-2-nitrophenol (1.00 g, 6.37 mmol). To the resulting solution was added 10% palladium-carbon (0.20 g, 20 wt%). The

resulting mixture was subjected to catalytic hydrogenation under stirring for 2 days. After the reaction mixture was filtered through Celite to remove the catalyst, the filtrate was distilled under reduced pressure to remove the solvent, whereby 2-amino-4-fluorophenol (850 mg, 100%) was obtained as a reddish brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.93 (broad s, 2H), 6.30-6.35 (m, 1H), 6.44-6.48 (m, 1H), 6.62-6.65 (m, 1H).

MS (ESI) m/z 169 (M^++1+MeCN).

(Step 2) Synthesis of methyl (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetate



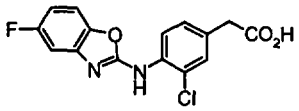
To a mixture of methyl 3-chloro-4-isothiocyanatophenylacetate (950 mg, 3.93 mmol) and 2-amino-4-fluorophenol (500 mg, 3.93 mmol) was added toluene (15 ml) and the mixture was heated under reflux for 2 hours. Mercuric oxide (yellow) (1.03 g, 4.75 mmol) was then added to the reaction mixture. The resulting mixture was heated under reflux for 2.5 hours. After cooling to room temperature, the reaction mixture was filtered through Celite. The filtrate was washed with methanol and then, distilled under reduced pressure to remove the solvent. The residue wad purified by chromatography on a silica gel

column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, methyl (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetate (107 mg, 8%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.60 (s, 2H), 3.71 (s, 3H), 6.85-6.90 (m, 1H), 7.20-7.23 (m, 1H), 7.25-7.30 (m, 2H), 7.37-7.38 (m, 1H), 7.52 (broad s, 1H), 8.45-8.47 (m, 1H).

MS (ESI) m/z 335 (M^++1).

(Step 3) Synthesis of (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetic acid



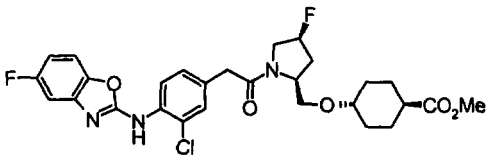
Methyl (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetate (148 mg, 0.44 mmol) was dissolved in THF (3 ml). To the resulting solution was added 0.5N NaOH (3.0 ml, 1.50 mmol), and the mixture was stirred at room temperature for 7 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetic acid (129 mg, 91%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 6.89-6.94 (m, 1H), 7.21-

7.30 (m, 2H), 7.45-7.49 (m, 2H), 7.85-7.87 (m, 1H), 10.16 (broad s, 1H), 12.44 (broad s, 1H).

MS (ESI) m/z 321 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-(3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



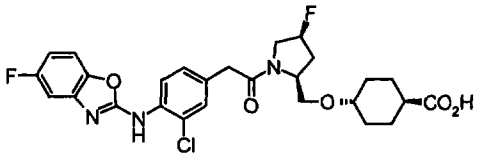
In DMF (5 ml), a mixture of (3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenyl)acetic acid (129 mg, 0.40 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (104 mg, 0.40 mmol), EDC·HCl (116 mg, 0.61 mmol), HOBt (82 mg, 0.61 mmol) and triethylamine (84 μl, 0.60 mmol) was stirred at room temperature for 20 hours. The reaction mixture was poured in water, and the crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were dissolved in ethyl acetate. The solution 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 toluene/acetone (6:1, v/v) eluate

fractions, methyl trans-4-(1-(3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (222 mg, 98%) was obtained as a pale yellow thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.14-1.32 (m, 2H), 1.39-1.53 (m, 2H), 1.96-2.51 (m, 7H), 3.21-3.37 and 3.49-3.54 (each m, total 2H), 3.58-4.01 (m, 8H), 4.19-4.25 and 4.35-4.40 (each m, total 1H), 5.17-5.20 and 5.30-5.33 (each m, total 1H), 6.83-6.89 (m, 1H), 7.13-7.28 (m, 3H), 7.36-7.37 (m, 1H), 7.52 (broad s, 1H), 8.40-8.46 (m, 1H).

MS (ESI) m/z 562 (M^++1).

(Step 5) Synthesis of trans-4-(1-(3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(3-chloro-4-(2-(5-fluorobenzoxazolyl))aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (222 mg, 0.40 mmol) was dissolved in THF (4.5 ml). To the resulting solution was added 0.25 N NaOH (4.5 ml, 1.13 mmol). The resulting mixture was stirred at room temperature for 13 hours. The reaction mixture was poured in ~1N HCl to

acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (149 mg, 69%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.38 (m, 4H), 1.88-1.95 (m, 4H), 2.15-2.21 (m, 3H), 3.16-3.88 (m, 7H), 4.13 and 4.33-4.35 (each m, total 1H), 5.25-5.33 and 5.39-5.46 (each m, total 1H), 6.89-6.93 (m, 1H), 7.21-7.25 (m, 2H), 7.39-7.40 (m, 1H), 7.46-7.49 (m, 1H), 7.83-7.86 (m, 1H).

MS (FAB) m/z 548 (M^++1);

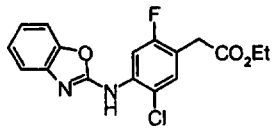
Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_5 \cdot 1/2H_2O$: C, 58.22; H, 5.25; N, 7.54.

Found: C, 58.57; H, 5.49; N, 6.97.

Example 55

trans-4-(1-(4-(2-Benzoxazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetate



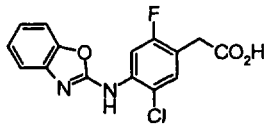
In xylene (4 ml), 2-chlorobenzoxazole (278 µl, 2.43 mmol) and ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (512 mg, 2.21 mmol) were heated under reflux for 2 hours.

After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was dissolved in ethyl acetate. 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. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, ethyl (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetate (570 mg, 74%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.1Hz, 3H), 3.62 (s, 2H), 4.19 (q, J=7.1Hz, 2H), 7.16-7.38 (m, 3H), 7.53-7.56 (m, 2H), 8.47-8.50 (m, 1H).

MS (ESI) m/z 349 (M^++1).

(Step 2) Synthesis of (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetic acid



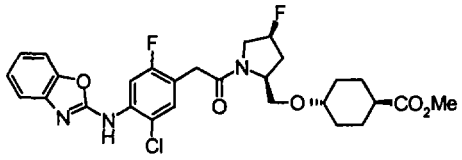
Ethyl (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetate (570 mg, 1.63 mmol) was dissolved in THF (5 ml). To the resulting solution was added 1N NaOH (5.0 ml, 5.00 mmol), followed by stirring at room temperature for 20 hours. The reaction mixture was poured

in ice-1N HCl to acidify therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetic acid (497 mg, 95%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.64 (s, 2H), 7.14-7.17 (m, 1H), 7.21-7.26 (m, 1H), 7.45-7.55 (m, 3H), 8.07-8.10 (m, 1H).

MS (ESI) m/z 321 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



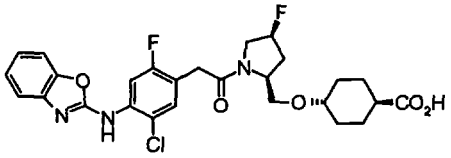
To a mixture of (4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenyl)acetic acid (140 mg, 0.44 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexane-carboxylate (the compound synthesized in (Step 3) of Example 21) (104 mg, 0.40 mmol), EDC·HCl (115 mg, 0.60 mmol), HOBt (81 mg, 0.60 mmol), and triethylamine (84 µl, 0.60 mmol) was added DMF (5 ml). The resulting mixture was stirred at room temperature for 18 hours. Water was added to the reaction mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed

with water and dried under reduced pressure to give methyl trans-4-(1-(4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-cyclohexanecarboxylate (223 mg, 99%) as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.23-1.46 (m, 4H), 1.97-2.32 (m, 7H), 3.24-3.58 (m, 2H), 3.65-3.98 (m, 8H), 4.30-4.37 (m, 1H), 5.20-5.24 and 5.33-5.37 (each m, total 1H), 7.17-7.21 (m, 1H), 7.25-7.29 (m, 1H), 7.37-7.41 (m, 2H), 7.54-7.56 (m, 1H), 8.44-8.50 (m, 1H).

MS (ESI) m/z 562 (M^++1).

(Step 4) Synthesis of trans-4-(1-(4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(4-(2-benzoxazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (223 mg, 0.40 mmol) was dissolved in THF (3.0 ml). To the reuslting solution was added 0.5N NaOH (2.5 ml, 1.25 mmol). The resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were

collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (173 mg, 80%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.17-1.37 (m, 4H), 1.73-2.20 (m, 7H), 3.16-3.97 (m, 7H), 4.12 and 4.33 (each m, total 1H), 5.25-5.33 and 5.38-5.47 (each m, total 1H), 7.12-7.24 (m, 2H), 7.40-7.51 (m, 3H), 8.03 (m, 1H).

MS (ESI) m/z 548 (M^++1);

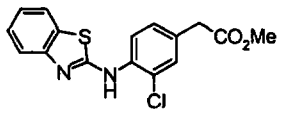
Anal. Calcd for $C_{30}H_{30}FN_3O_5 \cdot 1/2H_2O$: C, 58.22; H, 5.25; N, 7.54.

Found: C, 58.55; H, 5.41; N, 7.08.

Example 56

trans-4-(1-(4-(2-Benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (4-(2-benzothiazolyl)amino-3-chlorophenyl)acetate



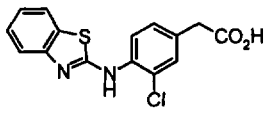
A mixture of 2-chlorobenzoxazole (489 mg, 2.88 mmol) and methyl 4-amino-3-chlorophenylacetate (567 mg, 2.84 mmol) and pyridinium·p-toluenesulfonate (pyridinium·p-toluenesulfonate (PPTS)) (214 mg, 0.85 mmol) was heated under reflux for 3 hours in xylene (10 ml). After the

reaction mixture was cooled to room temperature, 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 (7:1, v/v) eluate fractions, methyl (4-(2-benzothiazolyl)amino-3-chlorophenyl)acetate (296 mg, 32%) was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 3.58 (s, 2H), 3.71 (s, 3H), 7.16-7.24 (m, 2H), 7.33-7.38 (m, 2H), 7.63-7.69 (m, 2H), 8.33-8.35 (m, 1H).

MS (ESI) m/z 333 (M^++1).

(Step 2) Synthesis of (4-(2-benzothiazolyl)amino-3-chlorophenyl)acetic acid



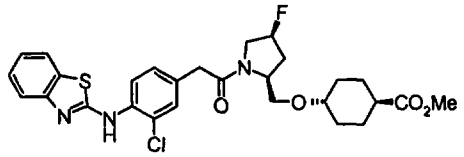
In THF (5 ml) was dissolved methyl (4-(2-benzothiazolyl)amino-3-chlorophenyl)acetate (296 mg, 0.89 mmol). To the resulting solution was added 0.5N NaOH (5.0 ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (4-(2-benzothiazolyl)amino-3-

chlorophenyl)acetic acid (263 mg, 93%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 3.59 (s, 2H), 7.11-7.15 (m, 1H), 7.25-7.31 (m, 2H), 7.42 (d, J=2.0Hz, 1H), 7.52 (d, J=8.1Hz, 1H), 7.77 (d, J=8.1Hz, 1H), 8.11-8.13 (m, 1H).

MS (ESI) m/z 319 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(4-(2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



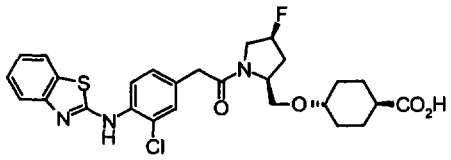
A mixture of (4-(2-benzothiazolyl)amino-3-chlorophenyl)acetic acid (263 mg, 0.83 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (214 mg, 0.83 mmol), EDC·HCl (237 mg, 1.24 mmol), HOBt (167 mg, 1.24 mmol) and triethylamine (173 μl, 1.24 mmol) was stirred at room temperature for 3 days in DMF (7 ml). The reaction mixture was poured in water. 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 on a silica gel column, whereby from chloroform/methanol (60:1, v/v)

eluate fractions, methyl trans-4-(1-(4-(2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (460 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.32 (m, 2H), 1.39-1.53 (m, 2H), 1.97-2.51 (m, 7H), 3.21-4.01 (m, 10H), 4.20-4.25 and 4.35-4.40 (each m, total 1H), 5.16-5.20 and 5.30-5.33 (each m, total 1H), 7.17-7.23 (m, 2H), 7.34-7.38 (m, 2H), 7.64-7.69 (m, 2H), 8.29-8.36 (m, 1H).

MS (ESI) m/z 560 (M^++1).

(Step 4) Synthesis of trans-4-(1-(4-(2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(4-(2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (460 mg, 0.82 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.5N NaOH (5.0 ml, 2.50 mmol), followed by stirring at room temperature for 3 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration

under reduced pressure, washed with water and dried under reduced pressure to give the title compound (314 mg, 70%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.39 (m, 4H), 1.84-1.94 (m, 4H), 2.06-2.20 (m, 3H), 3.15-3.87 (m, 7H), 4.12 and 4.30-4.36 (each m, total 1H), 5.24-5.32 and 5.38-5.45 (each m, total 1H), 7.11-7.15 (m, 1H), 7.19-7.23 (m, 1H), 7.27-7.31 (m, 1H), 7.36-7.38 (m, 1H), 7.50-7.52 (m, 1H), 7.77-7.79 (m, 1H), 8.06-8.10 (m, 1H).

MS (ESI) m/z 546 (M^++1);

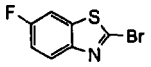
Anal. Calcd for $C_{27}H_{29}ClFN_3O_4S \cdot 3/2H_2O$: C, 56.59; H, 5.63; N, 7.33.

Found: C, 56.73; H, 5.58; N, 6.88.

Example 57

trans-4-(1-(3-Chloro-4-(6-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-bromo-6-fluorobenzothiazole



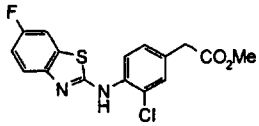
Copper (I) bromide (619 mg, 4.32 mmol) was suspended in acetonitrile (10 ml). To the resulting suspension was added tert-butyl nitrite (640 µl, 5.38 mmol), followed by stirring at 60°C for 5 minutes. To the reaction mixture

was added 2-amino-6-fluorobenzothiazole (605 mg, 3.60 mmol). The resulting mixture was stirred at 60°C for 10 minutes. After cooling to the room temperature, the reaction mixture was diluted with ethyl acetate. The ethyl acetate solution was washed with 1N HCl, 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, 2-bromo-6-fluorobenzothiazole (330 mg, 40%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 7.19-7.24 (m, 1H), 7.49-7.52 (m, 1H), 7.92-7.96 (m, 1H).

MS (ESI) m/z 273.8 (M^++1+MeCN).

(Step 2) Synthesis of methyl (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetate



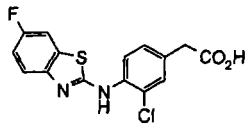
In xylene (8 ml), 2-bromo-6-fluorobenzothiazole (330 mg, 1.42 mmol), methyl 4-amino-3-chlorophenylacetate (284 mg, 1.42 mmol), and pyridinium p-toluenesulfonate (PPTS) (107 mg, 0.43 mmol) were heated under reflux for 10 hours. After cooling, the reaction mixture was distilled under reduced pressure to 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 (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetate (158 mg, 32%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.58 (s, 2H), 3.70 (s, 3H), 7.05-7.10 (m, 1H), 7.22-7.25 (m, 1H), 7.34-7.37 (m, 2H), 7.59-7.63 (m, 1H), 8.32-8.34 (m, 1H).

MS (ESI) m/z 351 (M^++1).

(Step 3) Synthesis of (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetic acid

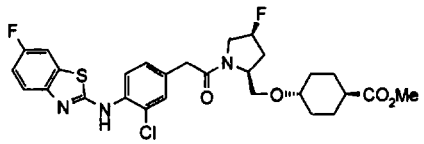


Methyl (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetate (158 mg, 0.45 mmol) was dissolved in THF (3 ml). To the resulting solution was added 0.5N NaOH (3.0 ml, 1.50 mmol), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetic acid (127 mg, 84%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.59 (s, 2H), 7.11-7.15 (m, 1H), 7.25-7.27 (m, 1H), 7.41-7.42 (m, 1H), 7.50-7.53 (m, 1H), 7.70-7.73 (m, 1H), 8.12-8.14 (m, 1H), 9.97 (broad s, 1H), 12.42 (broad s, 1H).

MS (ESI) m/z 337 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-(3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



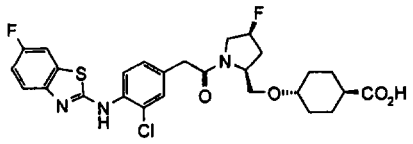
In DMF (8 ml), (3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenyl)acetic acid (127 mg, 0.38 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (98 mg, 0.38 mmol), EDC·HCl (108 mg, 0.56 mmol), HOBt (76 mg, 0.56 mmol), and triethylamine (80 μl, 0.57 mmol) in DMF (8 ml) were stirred at room temperature for 18 hours. The reaction mixture was poured in water. 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 on a silica gel column, whereby from chloroform/methanol (60:1, v/v) eluate

fractions, methyl trans-4-(1-(3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (266 mg, 100%) was obtained as a pale yellow thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.32 (m, 2H), 1.40-1.53 (m, 2H), 1.97-2.08 (m, 4H), 2.20-2.52 (m, 3H), 3.22-4.02 (m, 10H), 4.20-4.26 and 4.36-4.38 (each m, total 1H), 5.18-5.21 and 5.32-5.34 (each m, total 1H), 7.05-7.11 (m, 1H), 7.20-7.23 (m, 1H), 7.34-7.37 (m, 2H), 7.57-7.63 (m, 2H), 8.28-8.35 (m, 1H).

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

(Step 5) Synthesis of trans-4-(1-(3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (3 ml) was dissolved methyl trans-4-(1-(3-chloro-4-(6-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (266 mg, 0.46 mmol). To the resulting solution was added 0.5N NaOH (3.0 ml, 1.50 mmol), followed by stirring at room temperature for 20 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 (189 mg, 73%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.17-1.38 (m, 4H), 1.74-2.21 (m, 7H), 3.18-3.87 (m, 7H), 4.14 and 4.33-4.35 (each m, total 1H), 5.25-5.32 and 5.38-5.45 (each m, total 1H), 7.12-7.23 (m, 2H), 7.37-7.38 (m, 1H), 7.51-7.54 (m, 1H), 7.71-7.74 (m, 1H), 8.09-8.13 (m, 1H), 9.94 (broad s, 1H).

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

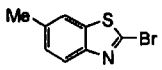
Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_4S \cdot 1H_2O$: C, 55.71; H, 5.19; N, 7.22; S, 5.51.

Found: C, 55.88; H, 5.25; N, 6.74; S, 5.26.

Example 58

trans-4-(1-(3-Chloro-4-(6-methyl-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-bromo-6-methylbenzothiazole

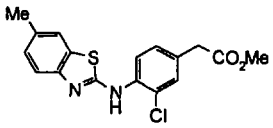


Copper (I) bromide (1.57 g, 10.9 mmol) was suspended in acetonitrile (25 ml). To the resulting suspension was added tert-butyl nitrite (1.63 ml, 13.7 mmol). The resulting mixture was stirred at 60°C for 10 minutes. To the reaction mixture was added 2-amino-6-methylbenzothiazole (1.50 g, 9.13 mmol), followed by stirring at 60°C for 1 hour. After cooling, the reaction

mixture was diluted with ethyl acetate. The ethyl acetate solution was washed with 1N HCl 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 (7:1, v/v) eluate fractions, 2-bromo-6-methylbenzothiazole (703 mg, 34%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 2.47 (s, 3H), 7.27-7.29 (m, 1H), 7.58-7.59 (m, 1H), 7.84-7.87 (m, 1H).

(Step 2) Synthesis of methyl (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetate



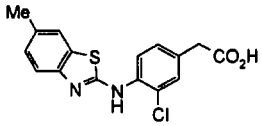
In xylene (10 ml), 2-bromo-6-methylbenzothiazole (703 mg, 3.08 mmol), methyl 4-amino-3-chlorophenylacetate (615 mg, 3.08 mmol), and pyridinium p-toluenesulfonate (PPTS) (232 mg, 0.92 mmol) were heated under reflux for 10 hours. After cooling, the reaction mixture was distilled under reduced pressure 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 (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetate (274 mg, 26%) was

obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.43 (s, 3H), 3.59 (s, 2H), 3.71 (s, 3H), 7.17-7.19 (m, 1H), 7.23-7.25 (m, 1H), 7.35 (m, 1H), 7.46 (s, 1H), 7.58 (d, J=8.3Hz, 1H), 8.35 (d, J=8.3Hz, 1H).

MS (ESI) m/z 347 (M^++1).

(Step 3) Synthesis of (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetic acid

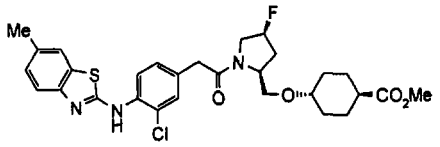


Methyl (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetate (274 mg, 0.79 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.5N NaOH (5.0 ml, 2.50 mmol), followed by stirring at room temperature for 15 hours. The reaction mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetic acid (202 mg, 77%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 2.35 (s, 3H), 3.60 (s, 2H), 7.10-7.13 (m, 1H), 7.25-7.27 (m, 1H), 7.41-7.42 (m, 2H), 7.59 (s, 1H), 8.13-8.15 (m, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

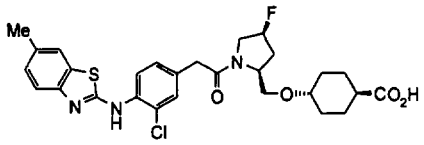


In DMF (5 ml), (3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenyl)acetic acid (202 mg, 0.61 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (157 mg, 0.61 mmol), EDC·HCl (175 mg, 0.91 mmol), HOBt (123 mg, 0.91 mmol), and triethylamine (130 μl, 0.93 mmol) were stirred at room temperature for 24 hours. The reaction mixture was poured in water. 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 on a silica gel column, whereby from chloroform/methanol (60:1, v/v) eluate fractions, methyl trans-4-(1-(3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (331 mg, 95%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.32 (m, 2H), 1.39-1.53 (m, 2H), 1.96-2.11 (m, 4H), 2.19-2.51 (m, total 6H, including s, 3H, at δ: 2.43), 3.22-3.53 (m, 2H), 3.57-4.01 (m, 8H), 4.19-

4.25 and 4.35-4.40 (each m, total 1H), 5.17-5.20 and 5.30-5.33 (each m, total 1H), 7.16-7.23 (m, 2H), 7.33-7.35 (m, 1H), 7.46 (s, 1H), 7.52 (broad s, 1H), 7.56-7.59 (m, 1H), 8.30-8.38 (m, 1H).

(Step 5) Synthesis of trans-4-(1-(3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(3-chloro-4-(6-methyl-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (331 mg, 0.58 mmol) was dissolved in THF (3.5 ml). To the resulting solution was added 0.5N NaOH (3.5 ml, 1.75 mmol), followed by stirring at room temperature for 2 days. 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 (199 mg, 62%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.36 (m, 4H), 1.76-1.94 (m, 4H), 2.14-2.40 (m, total 6H, including s, 3H, at δ 2.34), 3.15-3.86 (m, 7H), 4.12 and 4.32-4.33 (each m, total 1H), 5.24-

5.31 and 5.38-5.45 (each m, total 1H), 7.09-7.11 (m, 1H), 7.19-7.22 (m, 1H), 7.35-7.49 (m, 3H), 7.57 (s, 1H), 8.10-8.12 (m, 1H).

MS (ESI) m/z 560 (M^++1).

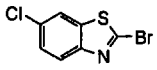
Anal. Calcd for $C_{28}H_{31}ClFN_3O_4S \cdot 3/2H_2O$: C, 57.28; H, 5.84; N, 7.16; S, 5.46.

Found: C, 57.20; H, 5.66; N, 6.91; S, 5.39.

Example 59

trans-4-(1-(4-(6-Chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-bromo-6-chlorobenzothiazole

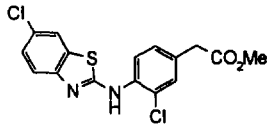


Copper (I) bromide (1.40 g, 9.76 mmol) was suspended in acetonitrile (25 ml). To the resulting suspension was added tert-butyl nitrite (1.45 ml, 12.2 mmol) and the mixture was stirred at 60°C for 15 minutes. To the reaction mixture was added 2-amino-6-chlorobenzothiazole (1.50 g, 8.12 mmol), followed by stirring at 60°C for 30 minutes. After cooling, the reaction mixture was diluted with ethyl acetate. The ethyl acetate solution was washed with 1N HCl 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 (7:1, v/v) eluate fractions, 2-bromo-6-chlorobenzothiazole (1.39 g, 69%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.42-7.46 (m, 1H), 7.76-7.90 (m, 2H).

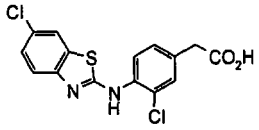
(Step 2) Synthesis of methyl (4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate



In xylene (10 ml), 2-bromo-6-chlorobenzothiazole (760 mg, 3.06 mmol), methyl 4-amino-3-chlorophenylacetate (610 mg, 3.06 mmol), and pyridinium·p-toluenesulfonate (PPTS) (230 mg, 0.92 mmol) were heated under reflux for 1 hour. After cooling, 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-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate (271 mg, 24%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.60 (s, 2H), 3.71 (s, 3H), 7.23-7.37 (m, 3H), 7.57-7.62 (m, 3H), 8.31-8.33 (m, 1H).

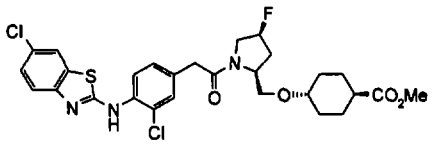
(Step 3) Synthesis of (4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid



Methyl (4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate (271 mg, 0.74 mmol) was dissolved in THF (4.5 ml). To the resulting solution was added 0.5N NaOH (4.5 ml, 2.25 mmol), followed by stirring 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, washed with water and dried under reduced pressure to give (4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid (248 mg, 95%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.61 (s, 2H), 7.26-7.33 (m, 2H), 7.43-7.44 (m, 1H), 7.50-7.52 (m, 1H), 7.92-7.93 (m, 1H), 8.08-8.10 (m, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



In DMF (6 ml), (4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid (248 mg, 0.70 mmol), methyl trans-4-((4S)-fluoro-(2S)-

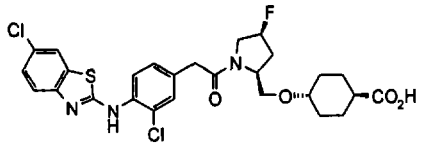
pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (182 mg, 0.70 mmol), EDC·HCl (202 mg, 1.05 mmol), HOBt (142 mg, 1.05 mmol), and triethylamine (150 μl, 1.08 mmol) were stirred at room temperature for 24 hours. The reaction mixture was poured in water. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The crude crystals were dissolved in ethyl acetate. The resulting solution 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 (60:1, v/v) eluate fractions, methyl trans-4-(1-(4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (382 mg, 92%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.23-1.50 (m, 4H), 1.97-2.52 (m, 7H), 3.25-4.03 (m, 10H), 4.23-4.24 and 4.39 (each m, total 1H), 5.19-5.22 and 5.33-5.35 (each m, total 1H), 7.21-7.36 (m, 3H), 7.56-7.69 (m, 3H), 8.26-8.34 (m, 1H).

MS (ESI) m/z 594 (M^++1).

(Step 5) Synthesis of trans-4-(1-(4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(4-(6-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (382 mg, 0.64 mmol) was dissolved in THF (4 ml). To the resulting solution was added 0.5N NaOH (4.0 ml, 2.00 mmol), followed by stirring at room temperature for 2 days. 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. The crude crystals were purified by chromatography on a silica gel column, whereby from chloroform/methanol (30:1 to 15:1, v/v) eluate fractions, the title compound (320 mg, 86%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.36 (m, 4H), 1.87-2.20 (m, 7H), 3.15-3.87 (m, 7H), 4.13 and 4.32-4.34 (each m, total 1H), 5.24-5.32 and 5.38-5.45 (each m, total 1H), 7.21-7.23 (m, 1H), 7.29-7.32 (m, 1H), 7.37-7.38 (m, 1H), 7.48-7.51 (m, 1H), 7.92 (s, 1H), 8.05-8.09 (m, 1H).

MS (ESI) m/z 580 (M^++1).

Anal. Calcd for $C_{27}H_{28}Cl_2FN_3O_4S \cdot 2H_2O$: C, 52.60; H, 5.23; N,

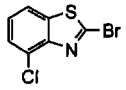
6.82; S, 5.20.

Found: C, 52.37; H, 4.65; N, 6.62; S, 5.16.

Example 60

trans-4-(1-(4-(4-Chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

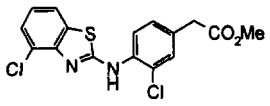
(Step 1) Synthesis of 2-bromo-4-chlorobenzothiazole



Copper (I) bromide (1.40 g, 9.76 mmol) was suspended in acetonitrile (25 ml). To the resulting suspension was added tert-butyl nitride (1.45 ml, 12.2 mmol) and the mixture was stirred at 60°C for 10 minutes. To the reaction mixture was added 2-amino-4-chlorobenzothiazole (1.50 g, 8.12 mmol), followed by stirring at 60°C for 2 hours. After cooling, the reaction mixture was diluted with ethyl acetate. The ethyl acetate solution was washed with 1N HCl 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 (7:1, v/v) eluate fractions, 2-bromo-4-chlorobenzothiazole (1.32 g, 65%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.33-7.38 (m, 1H), 7.49-7.53 (m, 1H), 7.67-7.71 (m, 1H).

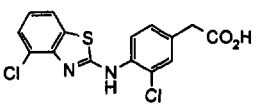
(Step 2) Synthesis of methyl (4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate



In xylene (7 ml), 2-bromo-4-chlorobenzothiazole (647 mg, 2.60 mmol), methyl 4-amino-3-chlorophenylacetate (520 mg, 2.60 mmol), and pyridinium·p-toluenesulfonate (PPTS) (200 mg, 0.80 mmol) were heated under reflux for 7 hours. After cooling, 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-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate (556 mg, 58%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 3.61 (s, 2H), 3.72 (s, 3H), 7.10-7.14 (m, 1H), 7.27-7.29 (m, 1H), 7.39-7.41 (m, 2H), 7.54-7.56 (m, 1H), 7.75 (broad s, 1H), 8.25-8.27 (m, 1H).

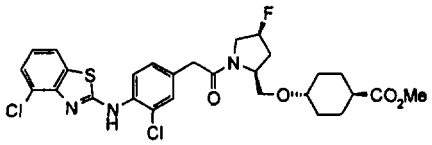
(Step 3) Synthesis of (4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid



In THF (5 ml) was dissolved methyl (4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetate (556 mg, 1.51 mmol). To the resulting solution was added 1N NaOH (4.5 ml, 4.50 mmol), followed by stirring at room temperature for 20 hours. The 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 (4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid (468 mg, 88%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.63 (s, 2H), 7.12-7.16 (m, 1H), 7.29-7.31 (m, 1H), 7.38-7.41 (m, 1H), 7.46-7.47 (m, 1H), 7.76-7.78 (m, 1H), 8.18-8.21 (m, 1H), 10.26 (broad s, 1H), 12.45 (broad s, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



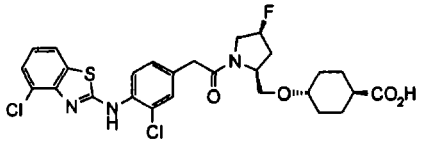
In DMF (7 ml), (4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenyl)acetic acid (258 mg, 0.73 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (189 mg, 0.73 mmol),

EDC·HCl (210 mg, 1.10 mmol), HOBt (148 mg, 1.10 mmol), and triethylamine (155 μl, 1.11 mmol) were stirred at room temperature for 14 hours. The mixture was poured in water. 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 on a silica gel column, whereby from n-hexane/ethyl acetate (1:1 to 1:2, v/v) eluate fractions, methyl trans-4-(1-(4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (430 mg, 99%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.50 (m, 4H), 2.01-2.29 (m, 7H), 3.27-3.89 (m, 10H), 4.23-4.24 and 4.40 (each m, total 1H), 5.20 and 5.35 (each m, total 1H), 7.10-7.24 (m, 2H), 7.37-7.40 (m, 2H), 7.54-7.56 (m, 1H), 7.77 (m, 1H), 8.21-8.29 (m, 1H).

MS (ESI) m/z 594 (M^++1).

(Step 5) Synthesis of trans-4-(1-(4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-(4-(4-chloro-2-benzothiazolyl)amino-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (430 mg, 0.72 mmol) was dissolved in THF (4 ml). To the resulting solution was added 0.5N NaOH (4.2 ml, 2.10 mmol), followed by stirring at room temperature for 13 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 (375 mg, 89%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.37 (m, 4H), 1.86-1.95 (m, 4H), 2.08-2.33 (m, 3H), 3.16-3.88 (m, 7H), 4.13 and 4.34-4.36 (each m, total 1H), 5.25-5.34 and 5.39-5.46 (each m, total 1H), 7.11-7.15 (m, 1H), 7.23-7.26 (m, 1H), 7.38-7.41 (m, 2H), 7.75-7.77 (m, 1H), 8.14-8.18 (m, 1H), 10.23 (broad s, 1H), 12.05 (broad s, 1H).

MS (FAB) m/z 580 (M^++1).

Anal. Calcd for $C_{27}H_{28}Cl_2FN_3O_4S \cdot 1/2H_2O$: C, 55.01; H, 4.96; N, 7.13; S, 5.44.

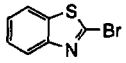
Found: C, 54.73; H, 5.00; N, 6.70; S, 5.28.

Example 61

trans-4-(1-(4-(2-Benzothiazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

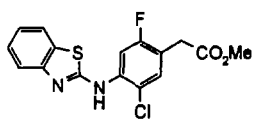
(Step 1) Synthesis of 2-bromobenzothiazole



Copper (I) bromide (1.93 g, 13.5 mmol) was suspended in acetonitrile (30 ml). To the resulting suspension was added tert-butyl nitrite (2.00 ml, 16.8 mmol) and the mixture was stirred at 60°C for 15 minutes. To the reaction mixture was added 2-aminobenzothiazole (1.68 g, 11.2 mmol) and the mixture was stirred at 60°C for 1 hour. After cooling, the reaction mixture was poured in 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 (7:1, v/v) eluate fractions, 2-bromobenzothiazole (1.36 g, 57%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 7.39-7.51 (m, 2H), 7.77-7.82 (m, 1H), 7.94-8.00 (m, 1H).

(Step 2) Synthesis of methyl (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)acetate

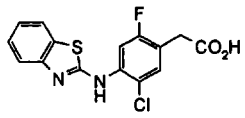


In xylene (10 ml), 2-bromobenzothiazole (740 mg, 3.46 mmol), methyl 4-amino-3-chloro-2-fluorophenylacetate (800 mg, 3.45 mmol), and pyridinium·p-toluenesulfonate (PPTS) (1.13 g, 4.50 mmol) were heated under reflux for 10 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, methyl (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)-acetate (559 mg, 44%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.26-1.30 (m, 3H), 3.62 (s, 2H), 4.10 (broad s, 1H), 4.15-4.21 (m, 2H), 7.21-7.42 (m, 3H), 7.67-7.76 (m, 2H), 8.47-8.50 (m, 1H).

MS (ESI) m/z 365 (M^++1).

(Step 3) Synthesis of (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)acetic acid

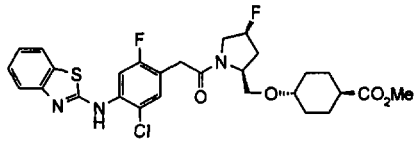


Methyl (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)acetate (613 mg, 1.68 mmol) was dissolved in THF (5 ml). To the resulting solution was added 1N NaOH (5.0 ml, 5.00 mmol). The resulting mixture was stirred at room temperature for 17 hours. Water was added to the reaction mixture. The mixture was washed with ether. The

water layer was poured in ice-1N HCl to acidify the water layer. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)acetic acid (464 mg, 82%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.63 (s, 2H), 7.17-7.21 (m, 1H), 7.32-7.39 (m, 1H), 7.52-7.54 (m, 1H), 7.61-7.63 (m, 1H), 7.82-7.84 (m, 1H), 8.38 (m, 1H), 10.17 (broad s, 1H), 12.52 (broad s, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



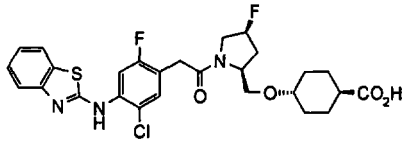
In DMF (8 ml), (4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenyl)acetic acid (290 mg, 0.86 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (223 mg, 0.86 mmol), EDC·HCl (247 mg, 1.29 mmol), HOBt (174 mg, 1.29 mmol), and triethylamine (180 µl, 1.29 mmol) were stirred at room temperature for 15 hours. The reaction mixture was poured

in water. The crystals thus precipitated were collected by filtration under reduced pressure, and washed with water. The crude crystals were dissolved in ethyl acetate. The solution 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-(4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (362 mg, 73%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.53 (m, 4H), 1.97-2.54 (m, 7H), 3.23-4.02 (m, 10H), 4.28-4.41 (m, 1H), 5.20-5.24 and 5.34-5.38 (each m, total 1H), 7.21-7.30 (m, 1H), 7.35-7.44 (m, 2H), 7.63-7.83 (m, 3H), 8.42-8.50 (m, 1H).

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

(Step 5) Synthesis of trans-4-(1-(4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (4 ml) was dissolved methyl trans-4-(1-(4-(2-benzothiazolyl)amino-5-chloro-2-fluorophenylacetyl)-(4S)-

fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (362 mg, 0.63 mmol). To the resulting solution was added 0.5N NaOH (4.0 ml, 2.00 mmol). The resulting mixture was stirred at room temperature for 1 hour. 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 (60:1 to 30:1, v/v) eluate fractions, the title compound (299 mg, 85%) was obtained as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.38 (m, 4H), 1.89-2.23 (m, 7H), 3.17-3.93 (m, 7H), 4.13 and 4.34-4.36 (each m, total 1H), 5.26-5.35 and 5.40-5.48 (each m, total 1H), 7.17-7.21 (m, 1H), 7.32-7.36 (m, 1H), 7.40-7.45 (m, 1H), 7.61-7.63 (m, 1H), 7.82-7.84 (m, 1H), 8.32-8.34 (m, 1H).

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

Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_4S \cdot 2H_2O$: C, 54.04; H, 5.37; N, 7.00; S, 5.34.

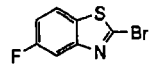
Found: C, 53.80; H, 4.63; N, 6.86; S, 5.17.

Example 62

trans-4-(1-(3-Chloro-4-(5-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

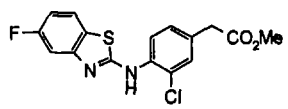
(Step 1) Synthesis of 2-bromo-5-fluorobenzothiazole



Copper (I) bromide (1.26 g, 7.31 mmol) was suspended in acetonitrile (25 ml). To the resulting suspension was added tert-butyl nitrite (1.47 ml, 10.9 mmol) and the mixture was stirred at 60°C for 10 minutes. To the reaction mixture was added 2-amino-5-fluorobenzothiazole (1.23 g, 7.31 mmol), followed by stirring at 60°C for 60 minutes. After cooling, the reaction mixture was poured in 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were dissolved in ethyl acetate. The solution was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, 2-bromo-5-fluorobenzothiazole (1.07 g, 63%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.18-7.23 (m, 1H), 7.64-7.77 (m, 2H).

(Step 2) Synthesis of methyl (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetate

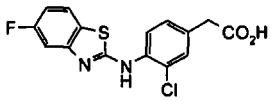


In xylene (5 ml), 2-bromo-5-fluorobenzothiazole (516

mg, 2.22 mmol), methyl 4-amino-3-chlorophenylacetate (444 mg, 2.22 mmol), and pyridinium·p-toluenesulfonate (PPTS) (168 mg, 0.67 mmol) were heated under reflux for 10 hours. After cooling, 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 (7:1, v/v) eluate fractions, methyl (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetate (292 mg, 37%) was obtained as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.61 (s, 2H), 3.72 (s, 3H), 6.93-6.98 (m, 1H), 7.25-7.27 (m, 1H), 7.37-7.41 (m, 2H), 7.55-7.58 (m, 1H), 7.65 (broad s, 1H), 8.31-8.33 (m, 1H).

(Step 3) Synthesis of (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetic acid

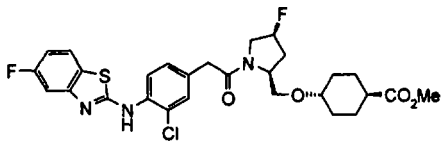


In THF (5 ml) was dissolved methyl (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetate (292 mg, 0.83 mmol). To the resulting solution was added 0.5N NaOH (5.0 ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with

water and dried under reduced pressure to give (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetic acid (226 mg, 81%) as a pale solid.

^{1}H-NMR (DMSO-d_6) δ: 3.61 (s, 2H), 6.98-7.03 (m, 1H), 7.27 (dd, J=2.0, 8.3Hz, 1H), 7.34-7.37 (m, 1H), 7.44 (d, J=2.0Hz, 1H), 7.78-7.82 (m, 1H), 8.05 (d, J=8.3Hz, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

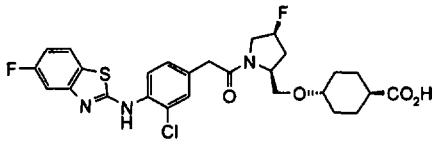


In DMF (5 ml), (3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenyl)acetic acid (216 mg, 0.64 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (166 mg, 0.64 mmol), EDC·HCl (184 mg, 0.96 mmol), HOBt (130 mg, 0.96 mmol), and triethylamine (134 µl, 0.96 mmol) were stirred at room temperature for 2 days. The reaction mixture was poured in water. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were dissolved in ethyl acetate. The solution 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 1:2, v/v) eluate fractions, methyl trans-4-(1-(3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (355 mg, 96%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.32 (m, 2H), 1.39-1.53 (m, 2H), 1.97-2.52 (m, 7H), 3.22-3.37 and 3.48-3.54 (each m, total 2H), 3.58-4.02 (m, 8H), 4.21-4.26 and 4.35-4.41 (each m, total 1H), 5.18-5.23 and 5.31-5.35 (each m, total 1H), 6.92-6.98 (m, 1H), 7.21-7.25 (m, 1H), 7.36-7.40 (m, 2H), 7.54-7.58 (m, 1H), 7.65 (broad s, 1H), 8.26-8.34 (m, 1H).

(Step 5) Synthesis of trans-4-(1-(3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (4 ml) was dissolved methyl trans-4-(1-(3-chloro-4-(5-fluoro-2-benzothiazolyl)aminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (355 mg, 0.61 mmol). To the resulting solution was added 0.5N NaOH (4.0 ml, 2.00 mmol), followed by stirring at room temperature for 20 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 (287 mg, 83%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.38 (m, 4H), 1.78-1.95 (m, 4H), 2.15-2.21 (m, 3H), 3.16-3.88 (m, 7H), 4.13 and 4.34-4.35 (each m, total 1H), 5.26-5.33 and 5.39-5.46 (each m, total 1H), 6.98-7.02 (m, 1H), 7.23-7.24 (m, 1H), 7.34-7.39 (m, 2H), 7.78-7.82 (m, 1H), 8.01-8.05 (m, 1H), 10.11 (broad s, 1H), 12.06 (broad s, 1H).

MS (LC) m/z 564.4 (M^++1).

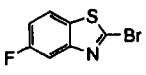
Anal. Calcd for $C_{27}H_{28}ClF_2N_3O_4S \cdot 1H_2O$: C, 55.71; H, 5.19; N, 7.22; S, 5.51.

Found: C, 56.00; H, 4.99; N, 6.89; S, 5.38.

Example 63

trans-4-(1-(5-Chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 2-bromo-5-fluorobenzothiazole

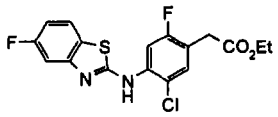


Copper (I) bromide (1.26 g, 7.31 mmol) was suspended in acetonitrile (25 ml). To the resulting suspension was added tert-butyl nitrite (1.47 ml, 10.9 mmol) and the mixture was stirred at 60°C for 10 minutes. To the

reaction mixture was added 2-amino-5-fluorobenzothiazole (1.23 g, 7.31 mmol), followed by stirring at 60°C for 60 minutes. After cooling, the reaction mixture was poured in 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were dissolved in ethyl acetate. The resulting solution was washed successively with 1N HCl 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 (7:1, v/v) eluate fractions, 2-bromo-5-fluorobenzothiazole (1.07 g, 63%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 7.18-7.23 (m, 1H), 7.64-7.77 (m, 2H).

(Step 2) Synthesis of ethyl (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetate

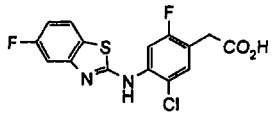


In xylene (5 ml), 2-bromo-5-fluorobenzothiazole (548 mg, 2.36 mmol), ethyl 4-amino-5-chloro-2-fluorophenylacetate (547 mg, 2.36 mmol), and pyridinium p-toluenesulfonate (PPTS) (178 mg, 0.71 mmol) were heated under reflux for 3 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the

solvent. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (7:1, v/v) eluate fractions, ethyl (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetate (298 mg, 33%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.1Hz, 3H), 3.61 (s, 2H), 4.17 (q, J=7.1Hz, 2H), 6.95-6.98 (m, 1H), 7.28-7.30 (m, 1H), 7.39-7.42 (m, 1H), 7.54-7.57 (m, 1H), 7.69 (broad s, 1H), 8.40-8.43 (m, 1H).

(Step 3) Synthesis of (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetic acid

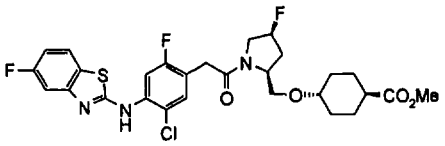


Ethyl (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetate (298 mg, 0.78 mmol) was dissolved in THF (5 ml). To the resulting solution was added 0.5N NaOH (5.0 ml, 2.50 mmol). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured in ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetic acid (237 mg, 86%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.64 (s, 2H), 7.03-7.08 (m, 1H), 7.45-

7.55 (m, 2H), 7.83-7.86 (m, 1H), 8.28-8.31 (m, 1H), 10.26 (broad s, 1H), 12.56 (broad s, 1H).

(Step 4) Synthesis of methyl trans-4-(1-(5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

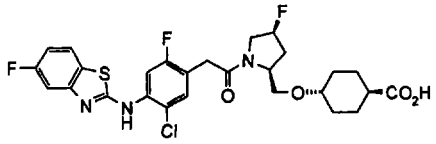


In DMF (5 ml), (5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenyl)acetic acid (233 mg, 0.66 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (170 mg, 0.66 mmol), EDC·HCl (189 mg, 0.99 mmol), HOBt (133 mg, 0.98 mmol), and triethylamine (137 µl, 0.98 mmol) were stirred at room temperature for 3 hours. The reaction mixture was poured in water. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were dissolved in ethyl acetate. The resulting solution 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 1:2, v/v) eluate fractions, methyl trans-4-(1-(5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenylacetyl)-

(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (368 mg, 94%) was obtained as a pale yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.33 (m, 2H), 1.39-1.53 (m, 2H), 1.96-2.18 (m, 4H), 2.22-2.53 (m, 3H), 3.23-4.03 (m, 10H), 4.27-4.31 and 4.37 (each m, total 1H), 5.19 and 5.23-5.37 (each m, total 1H), 6.95-6.99 (m, 1H), 7.36-7.44 (m, 2H), 7.56-7.59 (m, 1H), 7.65 (broad s, 1H), 8.34-8.43 (m, 1H).

(Step 5) Synthesis of trans-4-(1-(5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (4 ml) was dissolved methyl trans-4-(1-(5-chloro-4-(5-fluoro-2-benzothiazolyl)amino-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (368 mg, 0.62 mmol). To the resulting solution was added 0.5N NaOH (4.0 ml, 2.00 mmol), followed by stirring 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 (266 mg, 74%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.18-1.38 (m, 4H), 1.86-1.99 (m, 4H), 2.10-2.21 (m, 3H), 3.17-4.02 (m, 7H), 4.13 and 4.35-4.36 (each m, total 1H), 5.26-5.35 and 5.40-5.48 (each m, total 1H), 7.03-7.08 (m, 1H), 7.41-7.48 (m, 2H), 7.83-7.87 (m, 1H), 8.25-8.27 (m, 1H)

MS (LC) m/z 582.4 (M^++1), 580.4 (M^+-1).

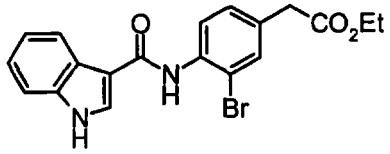
Anal. Calcd for $C_{27}H_{27}ClF_3N_3O_4S \cdot 1/2H_2O$: C, 54.87; H, 4.77; N, 7.11; S, 5.43.

Found: C, 54.68; H, 4.62; N, 6.85; S, 5.45.

Example 64

trans-4-(1-((3-Bromo-4-((3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

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

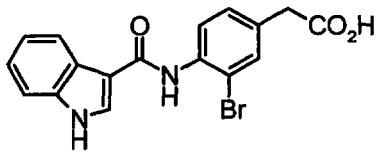


In DMF (20 ml) were dissolved indole-3-carboxylic acid (1.00 g, 6.21 mmol) and 4-amino-3-bromophenylacetic acid (1.60 g, 6.21 mmol). To the resulting solution was added EDC HCl (1.43 g, 7.45 mmol) under stirring at room temperature. After the reaction mixture was stirred at room temperature for 4 hours, water was added thereto,

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, ethyl (3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetate (664 mg, 27 %) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, J=7.1Hz, 3H), 3.59 (s, 2H), 4.19 (q, J=7.1Hz, 2H), 7.24-7.33 (m, 3H), 7.41-7.51 (m, 2H), 7.82 (d, J=2.7Hz, 1H), 8.20 (m, 1H), 8.31 (broad s, 1H), 8.48 (d, J=8.6Hz, 1H), 9.35 (broad s, 1H).

(Step 2) Synthesis of (3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetic acid



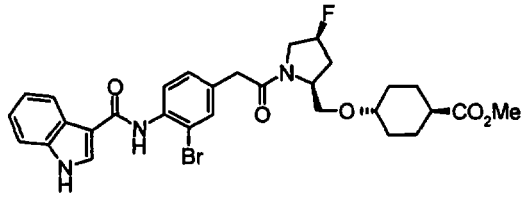
Ethyl (3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetate (664 mg, 1.65 mmol) was dissolved in THF (17 ml). To the resulting solution was added 0.25N NaOH (10.0 ml, 2.48 mmol). After stirring at room temperature for 24 hours, the reaction mixture was poured in 1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced

pressure, washed with water, and dried under reduced pressure to give (3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetic acid (341 mg, 55 %) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 7.13-7.21 (m, 2H), 7.29 (dd, J=8.3, 1.7Hz, 1H), 7.47 (d, J=8.3Hz, 1H), 7.60 (d, J=1.7Hz, 1H), 7.63 (d, J=8.3Hz, 1H), 8.14 (d, J=7.6Hz, 1H), 8.27 (d, J=3.2Hz, 1H), 9.27 (s, 1H).

MS (ESI) m/z 373 (M^++1), 375 (M^++3).

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



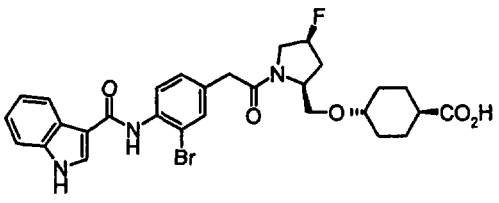
To a solution of 3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetic acid (341 mg, 0.91 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (237 mg, 0.91 mmol), HOBt (25.0 mg, 0.18 mmol), and DMAP (22.0 mg, 0.13 mmol) in DMF (5.0 ml) was added EDC HCl (228 mg, 1.19 mmol) under stirring at room temperature. After the reaction mixture was stirred at room temperature for 20 hours, water was

added thereto. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give methyl trans-4-(1-((3-bromo-4-((3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (500 mg, 89 %) as a colorless solid.

^{1}H NMR (DMSO-d_6) δ: 1.15-1.28 (m, 2H), 1.32-1.45 (m, 2H), 1.87-2.33 (m, 7H), 3.21 (m, 1H), 3.46 (m, 1H), 3.57 (s, 3H), 3.59-3.93 (m, 5H), 4.16 and 4.34 (each m, total 1H), 5.31 and 5.38 (each m, total 1H), 7.12-7.20 (m, 2H), 7.24 (m, 1H), 7.47 (d, J=7.67Hz, 1H), 7.54 and 7.56 (each d, J=1.5Hz, total 1H), 7.62 and 7.64 (each d, J=8.3Hz, total 1H), 8.14 (d, J=7.6Hz, 1H), 8.26 (s, 1H), 9.24 (s, 1H), 11.73 (broad s, 1H).

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

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



In THF (28 ml) was dissolved methyl trans-4-(1-((3-bromo-(3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (500 mg, 0.81 mmol). To the resulting solution was added 0.25N NaOH (5.00 ml, 1.25 mmol), followed by stirring at room temperature for 3 hours. Methanol - water (1:1, v/v; 10 ml) was added to the reaction mixture. After the resulting mixture was stirred for 1 hour, the solvent was distilled off under reduced pressure. To the residue was added water and then, the mixture was acidified with 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 (390 mg, 80 %) as a pale yellow solid.

IR (ATR) ν 3411, 3208, 2938, 2861, 1691, 1627, 1509, 1432 cm^{-1};

^1H NMR (DMSO-d_6) δ: 1.19-1.42 (m, 4H), 1.87-2.28 (m, 7H), 3.19 (m, 1H), 3.42-3.93 (m, 6H), 4.14 and 4.34 (each m, total 1H), 5.32 and 5.38 (each m, total 1H), 7.12-7.21 (m, 2H), 7.24 (m, 1H), 7.47 (d, J=7.5Hz, 1H), 7.54 and 7.56 (each d, J=1.7Hz, total 1H), 7.62 and 7.64 (each d, J=8.0Hz, total 1H), 8.14 (d, J=7.5Hz, 1H), 8.26 (d, J=2.9Hz, 1H), 9.24 (s, 1H), 11.73 (broad s, 1H), 12.01 (broad s, 1H).

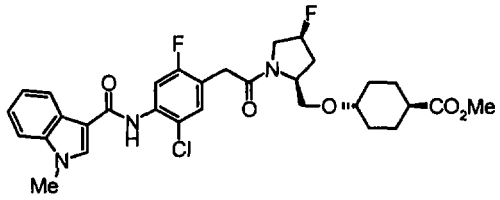
MS (ESI) m/z 600 (M^++1), 602 (M^++3);

Anal. Calcd for $C_{29}H_{31}BrFN_3O_5 \cdot H_2O$: C, 56.32; H, 5.38; N, 6.79. Found: C, 56.10; H, 5.32; N, 6.68.

Example 65

trans-4-(1-((5-Chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(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)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



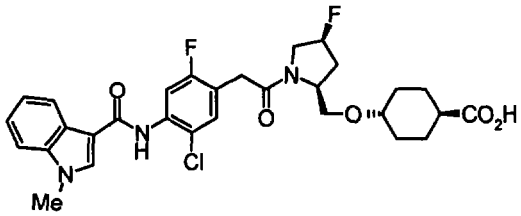
To a solution of (5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (210 mg, 0.58 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (151 mg, 0.58 mmol), HOBt (16.0 mg, 0.12 mmol), and DMAP (14.0 mg, 0.12 mmol) in DMF (6.0 ml) was added EDC HCl (167 mg, 0.87 mmol) under stirring at room temperature. The reaction mixture was stirred further for 13 hours at room temperature. 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 ethyl acetate eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (354 mg, 100 %) was obtained as a pale yellow amorphous substance.

^{1}H NMR ($CDCl_3$) δ: 1.20-1.28 (m, 2H), 1.31-1.52 (m, 2H), 1.96-2.52 (m, 7H), 3.25 (m, 1H), 3.34 and 3.52 (each m, total 1H), 3.57 (m, 1H), 3.64 and 3.66 (each s, total 3H), 3.71-3.99 (m, 7H, including singlet, 3H, at δ 3.87), 4.28 and 4.36 (each m, total 1H), 5.25 and 5.29 (each m, total 1H), 7.32-7.35 (m, 2H), 7.38-7. 42 (m, 2H), 7.79 (m, 1H), 8.12 (m, 1H), 8.28 (m, 1H), 8.48 and 8.51 (each d, J=8.3Hz, total 1H).

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

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



In THF (6.0 ml) was dissolved methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (354 mg, 0.59 mmol). To the resulting solution was added 0.25N NaOH (3.53 ml, 0.88 mmol), followed by stirring for 6 hours at room temperature. The reaction mixture was poured in 1N HCl (10 ml) to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give the title compound (298 mg, 86 %) as a colorless solid.

IR (ATR) ν 2940, 2863, 1718, 1652, 1585, 1521, 1465 cm^{-1};

^1H NMR (DMSO-d_6) δ: 1.16-1.41 (m, 4H), 1.86-2.32 (m, 7H), 3.17-3.84 (m, 6H), 3.89 (s, 3H), 4.13 and 4.35 (each m, total 1H), 5.32 and 5.40 (each m, total 1H), 7.21 (m, 1H), 7.27 (m, 1H), 7.42 and 7.45 (each d, J=7.3Hz, total 1H), 7.54 (d, J=8.4Hz, 1H), 7.70 and 7.72 (each d, J=5.6Hz, total 1H), 8.15 (d, J=7.6Hz, 1H), 8.30 (m, 1H), 9.28 (s, 1H), 12.01 (broad s, 1H).

MS (ESI) m/z 588 (M^++1);

Anal. Calcd for $C_{30}H_{32}ClF_2N_3O_5$ 0.25H_2O: C, 60.81; H, 5.53; N, 7.09.

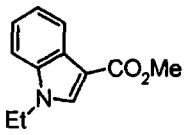
Found: C, 61.07; H, 5.65; N, 6.71.

Example 66

trans-4-(1-(3-Chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid :

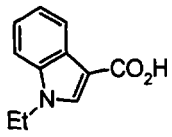
(Step 1) Synthesis of methyl 1-ethylindole-3-carboxylate



In DMF (8.0 ml) was suspended sodium hydride (60% in oil, 273.9 mg, 6.846 mmol). To the resulting suspension was added methyl indole-3-carboxylate (399.8 mg, 2.282 mmol) under stirring at 0°C. The reaction mixture was stirred for 40 minutes at the same temperature. To the mixture was added ethyl iodide (0.27 ml, 3.423 mmol) at 0°C, followed by stirring at the same temperature for further 2 hours. Water was added to the reaction mixture to terminate the reaction. The reaction mixture was extracted with ethyl acetate. The extract was washed successively with 1N HCl and saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 1-ethylindole-3-carboxylate was obtained. The resulting compound was provided for the subsequent reaction without further purification.

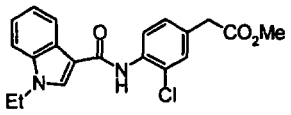
^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, t, J=7.2Hz), 3.93 (3H, s), 4.20 (2H, q, J=7.2Hz), 7.22-7.34 (2H, m), 7.38 (1H, m), 7.86 (1H, s), 8.20 (1H, m).

(Step 2) Synthesis of 1-ethylindole-3-carboxylic acid



In THF (9.0 ml) was dissolved the methyl 1-ethylindole-3-carboxylate obtained in the above-described (Step 1). To the resulting solution was added 0.25N NaOH (9.0 ml) at room temperature. After the reaction mixture was stirred at 50°C for 36 hours, 1N NaOH (1.0 ml) was added thereto, followed by stirring at 70°C for 9 hours. The reaction mixture was cooled to room temperature, and then neutralized with 1N HCl (4.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 1-ethylindole-3-carboxylic acid (388.0 mg, 90%, yield of 2 steps) as a pale pink amorphous substance. ^{1}H-NMR (DMSO-d_6) δ: 1.38 (3H, t, J=7.2Hz), 4.26 (2H, q, J=7.2Hz), 7.12-7.28 (2H, m), 7.55 (1H, d, J=8.0Hz), 8.01 (1H, d, J=8.0Hz), 8.07 (1H, s), 11.93 (1H, br s).

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

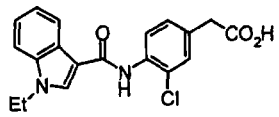


To 1-ethylindole-3-carboxylic acid (160.2 mg, 0.847 mmol) were added methylene chloride (3.5 ml) and oxalyl

chloride (108.9 µl, 1.270 mmol) under stirring at 15°C. The reaction mixture was stirred for 2.5 hours at room temperature. The solvent was then distilled off under reduced pressure. To the residue was added methylene chloride (3.5 ml). Under stirring at room temperature, a solution of methyl 3-chloro-4-aminophenylacetate (177.5 mg, 0.889 mmol) in methylene chloride (3.5 ml) and triethylamine (0.37 ml, 2.667 mmol) were added and the mixture was heated under reflux for 18 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue was dissolved in chloroform. The resulting solution was washed with 1N HCl ad saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to give methyl 3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetate (277.7 mg, 88%) as a brown amorphous substance. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, t, J=7.6Hz), 3.59 (2H, s), 3.71 (3H, s), 4.23 (2H, m), 7.15-7.49 (5H, m), 7.78 (1H, s), 8.14 (1H, m), 8.26 (1H, m), 8.59 (1H, d, J=8.4Hz).

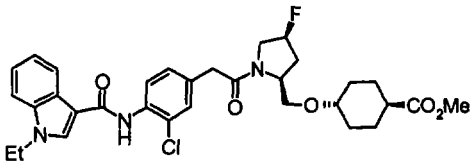
(Step 4) Synthesis of 3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetic acid



In THF (6.0 ml) was dissolved methyl 3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetate. To the resulting solution was added 0.25N NaOH (6.0 ml) at room temperature. After stirring at 50°C for 18 hours, the reaction mixture was cooled to room temperature and distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl (2.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and then, dried under reduced pressure to give 3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetic acid (250.7 mg, 94%) as a brown amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.43 (3H, m, OCH_2Me), 3.62 (2H, s), 4.28 (2H, m, OCH_2Me), 7.12-7.30 (2H, m, ArH), 7.44 (1H, m), 7.58 (1H, m), 7.66 (1H, m), 7.91-8.10 (1H, m), 8.15 (1H, m), 8.35 (1H, m), 9.31 (1H, s).

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

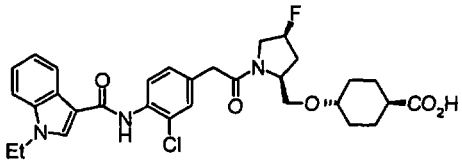


To a solution of methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (171.2 mg, 0.660 mmol), 3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetic acid (235.6 mg, 0.660 mmol) and HOBt (17.8 mg, 0.132 mmol) in DMF (8.0 ml) was added EDC HCl (189.9 mg, 0.990 mmol) under stirring at room temperature. After stirring at room temperature for 18 hours, the reaction mixture was poured in ice-1N HCl, followed by extraction with ethyl acetate. The extract 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 hexane-ethyl acetate (1:2, v/v) eluate fractions, methyl trans-4-(1-(3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (334.1 mg, 85%) was obtained as a light brown amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1.34 (2H, m), 1.36-1.58 (total 5H, m, including 3H, t, J=7.2Hz, at δ: 1.53), 1.92-2.15 (5H, m), 2.16-2.50 (2H, m), 3.19-4.02 (total 10H, series of m, including total 3H, s at δ: 3.63, 3.65), 4.15-4.40 (total 3H, m, including 2H, q, J=7.2Hz, at δ: 4.21), 5.24 (1H, m),

7.18 (1H, m), 7.32 (2H, m), 7.36 (1H, m), 7.42 (1H, m), 7.86 (1H, s), 8.13 (1H, m), 8.27 (1H, m), 8.56 (1H, dd, J=7.2, 8.4Hz).

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



In THF (6.0 ml) was dissolved methyl 4-(1-(3-chloro-4-((1-ethyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (334.1 mg, 0.559 mmol). 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 thus obtained was acidified with 1N HCl (2.0 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 (293.6 mg, 90%) as a white amorphous substance.

IR (ATR) ν 2937, 1649, 1511 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (4H, m), 1.45 (3H, t, J=7.2Hz, OCH_2Me), 1.80-2.04 (4H, m), 2.04-2.36 (3H, m), 3.10-3.97

(total 7H, series of m), 4.07-4.39 (total 3H, m, including 2H, q, J=7.2Hz, at δ: 4.29), 5.32 and 5.39 (total 1H, d, J=54.4Hz), 7.10-7.30 (3H, m), 7.38 (1H, d, J=6.8Hz), 7.59 (1H, d, J=8.0Hz), 7.65 (1H, m), 8.16 (1H, d, J=8.0Hz), 8.35 (1H, s), 9.31 (1H, s), 12.05 (1H, br s, CO_2H).

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

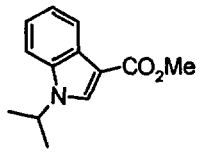
Anal. Calcd for $C_{31}H_{35}ClFN_3O_5$ $0.25H_2O$: C, 63.26; H, 6.08; N, 7.14; Cl, 6.02; F, 3.23.

Found: C, 63.20; H, 6.08; N, 6.96; Cl, 5.86; F, 3.18.

Example 67

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

(Step 1) Synthesis of methyl 1-isopropylindole-3-carboxylate

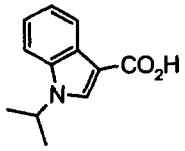


In DMF (8.0 ml) was suspended sodium hydride (60% in oil, 275.2 mg, 6.881 mmol). To the resulting suspension was added methyl indole-3-carboxylate (401.8 mg, 2.294 mmol) at 0°C under stirring. After stirring for further 45 minutes at the same temperature, isopropyl iodide (0.34 ml, 3.440 mmol) was added to the reaction mixture. Stirring

was then conducted for 1.5 hours at 0°C and for 7 hours at room temperature. Water was added to the reaction mixture to terminate the reaction, followed by extraction with ethyl acetate. The extract was washed successively with 1N HCl and saturated saline, 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, v/v) eluate fractions, methyl 1-isopropylindole-3-carboxylate (387.6 mg, 78%) was obtained as a light yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.56 (6H, d, J=6.8Hz), 3.91 (3H, s,), 4.67 (1H, hep, J=6.8Hz), 7.28 (2H, m), 7.40 (1H, m), 7.94 (1H, s), 8.19 (1H, m).

(Step 2) Synthesis of 1-isopropylindole-3-carboxylic acid

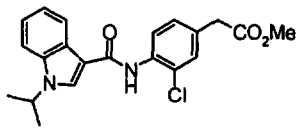


In THF (8.0 ml) was dissolved methyl 1-isopropylindole-3-carboxylate (387.6 mg, 1.784 mmol). To the resulting solution was added 0.25N NaOH (8.0 ml). The resulting mixture was stirred at 50°C for 18 hours. After cooling to room temperature, the reaction mixture was acidified with 1N HCl (4.5 ml). The crystals thus

precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 1-isopropylindole-3-carboxylic acid (327.8 mg, 90%) as a pale pink amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.38 (6H, d, J=6.4Hz), 4.78 (1H, m), 7.20 (2H, m), 7.59 (1H, d, J=8.0Hz), 8.02 (1H, d, J=7.6Hz), 8.12 (1H, s), 11.96 (1H, br s).

(Step 3) Synthesis of methyl 3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetate

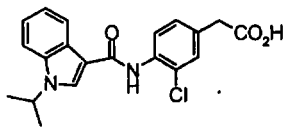


To a solution of 1-isopropylindole-3-carboxylic acid (159.6 mg, 0.785 mmol) in methylene chloride (3.5 ml) was added oxalyl chloride (101.0 µl, 1.178 mmol) under stirring at -15°C. The reaction mixture was stirred for 2.5 hours at room temperature and then distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (3.5 ml), followed by the addition of a solution of methyl 3-chloro-4-aminophenylacetate (164.6 mg, 0.824 mmol) in methylene chloride (3.5 ml) and triethylamine (0.35 ml, 2.474 mmol) under stirring at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then

distilled under reduced pressure to remove the solvent. The residue was dissolved in chloroform. The resulting solution was washed successively with 1N HCl and saturated saline, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetate (275.3 mg, 91%) was obtained as a brown solid. The resulting compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 1.60 (6H, d, J=6.8Hz), 3.60 (2H, s), 3.71 (3H, s), 4.73 (1H, m), 7.15-7.54 (5H, m), 8.00 (1H, s), 8.11 (1H, m), 8.28 (1H, m), 8.60 (1H, d, J=8.4Hz).

(Step 4) Synthesis of 3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetic acid

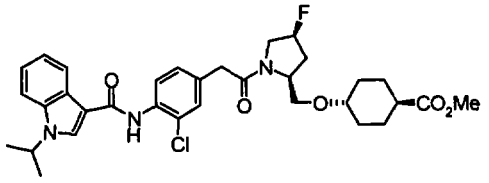


In THF (6.0 ml) was dissolved the methyl 3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetate obtained in the above-described (Step 3). To the resulting solution was added 0.25N NaOH (6.0 ml), followed by stirring at 50°C for 18 hours. After cooling, the reaction mixture was distilled under reduced pressure to remove the solvent. The resulting residue was acidified with 1N HCl

(2.0 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-isopropyl-3-indolylcarbonyl)amino)phenylacetic acid (246.2 mg, 93%) as a brown amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 1.52 (6H, d, J=6.4Hz), 3.62 (2H, s), 4.84 (1H, hep, J=6.4Hz), 7.13-7.30 (3H, m), 7.44 (1H, m), 7.62 (2H, m), 8.18 (1H, m), 8.48 (1H, s), 9.36 (1H, s), 12.32 (1H, br s).

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

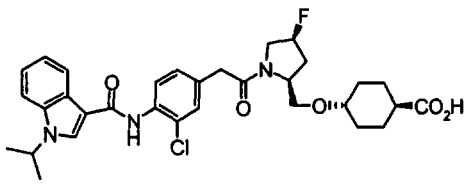


A mixture of methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (163.8 mg, 0.632 mmol), 3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetic acid (234.3 mg, 0.632 mmol) and HOBt (17.1 mg, 0.126 mmol) was dissolved in DMF (8.0 ml). To the resulting solution was added EDC HCl (181.7 mg, 0.948 mmol) under stirring at room temperature. The reaction mixture was stirred for further 18 hours at

room temperature. The mixture was diluted with ethyl acetate, 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-(3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (322.9 mg, 84%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.33 (2H, m), 1.36-1.55 (2H, m), 1.58 (6H, d, J=6.8Hz), 1.75 (1H, m), 1.92-2.15 (4H, m), 2.15-2.51 (2H, m), 3.19-4.02 (total 10H, series of m), 4.20 and 4.36 (total 1H, m), 4.72 (1H, hep, J=6.8Hz), 5.23 (1H, d, J=54.4Hz), 7.18 (1H, m), 7.28-7.40 (3H, m), 7.45 (1H, m), 7.98 (1H, s), 8.11 (1H, m), 8.29 (1H, s), 8.56 (1H, dd, J=7.2Hz).

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



In THF (6.0 ml) was dissolved methyl trans-4-(1-(3-chloro-4-((1-isopropyl-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (322.9 mg, 0.528 mmol). To the resulting solution was added 0.25N NaOH (6.0 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 resulting residue was acidified with 1N HCl (2.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the compound (283.9 mg, 90%) as a white amorphous substance.

IR (ATR) ν 2933, 1643, 1511 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.08-1.44 (4H, m), 1.53 (6H, d, J=6.8Hz), 1.80-2.05 (4H, m), 2.05-2.34 (3H, m), 3.12-4.40 (total 8H, series of m), 4.85 (1H, hep, J=6.8Hz), 5.32 and 5.39 (total 1H, d, J=54.4Hz), 7.12-7.28 (3H, m), 7.39 (1H, d, J=6.8Hz), 7.60 (2H, m), 8.17 (1H, d, J=8.0Hz), 8.48 (1H, s), 9.35 (1H, s), 12.04 (1H, s).

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

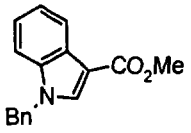
Anal. Calcd for $C_{31}H_{35}ClFN_3O_5$ $0.25H_2O$: C, 63.78; H, 6.27; N, 6.97; Cl, 5.88; F, 3.15.

Found: C, 63.62; H, 6.32; N, 6.77; Cl, 5.72; F, 3.13.

Example 68

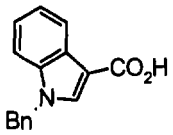
trans-4-(1-(4-((1-Benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl 1-benzylindole-3-carboxylate



Sodium hydride (60% in oil, 274.1 mg, 6.853 mmol) was suspended in DMF (8.0 ml). To the resulting suspension was added methyl indole-3-carboxylate (400.2 mg, 2.284 mmol) under stirring at 0°C, followed by stirring at the same temperature for 30 minutes. To the reaction mixture was added benzyl bromide (0.41 ml, 3.427 mmol) at 0°C. After stirring at room temperature for 1 hour, the reaction mixture was added with water to terminate the reaction. The reaction mixture was then extracted with ethyl acetate. The extract 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 (6:1, v/v) eluate fractions, methyl 1-benzylindole-3-carboxylate (100%) was obtained as a gum. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s), 5.31 (2H, s), 7.13 (2H, m), 7.18-7.38 (6H, m), 7.83 (1H, s), 8.19 (1H, d, J=8.0Hz).

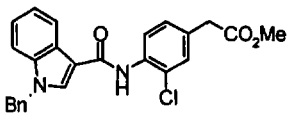
(Step 2) Synthesis of 1-benzylindole-3-carboxylic acid



In THF (15 ml) was dissolved methyl 1-benzylindole-3-carboxylate (606.1 mg, 2.284 mmol). To the resulting solution was added 0.25N NaOH (8.0 ml) and the mixture was stirred at 70°C for 18 hours. After the reaction mixture was cooled to room temperature, the solvent was distilled off under reduced pressure. The residue thus obtained was acidified with 1N HCl (5.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 1-benzylindole-3-carboxylic acid (100%) as a light pink amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 5.49 (2H, s), 7.14-7.38 (7H, m), 7.52 (1H, m), 8.00 (1H, m), 8.21 (1H, s), 12.01 (1H, br s).

(Step 3) Synthesis of methyl 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetate

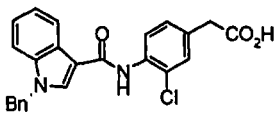


To a solution of 1-benzylindole-3-carboxylic acid (201.3 mg, 0.801 mmol) in methylene chloride (4.0 ml) was added oxalyl chloride (103.1 μl, 1.202 mmol) under stirring

at -15°C. The reaction mixture was stirred at room temperature for 2.5 hours and then, distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (4.0 ml) and to the resulting solution were added a solution of methyl 3-chloro-4-aminophenylacetate (167.9 mg, 0.841 mmol) in methylene chloride (4.0 ml) and triethylamine (0.35 ml, 2.523 mmol) under stirring at room temperature. The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was diluted with chloroform, washed with 1N HCl, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent, whereby methyl 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetate (341.3 mg, 98%) was obtained. The compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$) δ: 3.59 (2H, s), 3.71 (3H, s,), 5.38 (2H, s), 7.08-7.42 (10H, m), 7.87 (1H, s), 8.16 (1H, d, J=7.6Hz), 8.29 (1H, s), 8.58 (1H, d, J=8.0Hz).

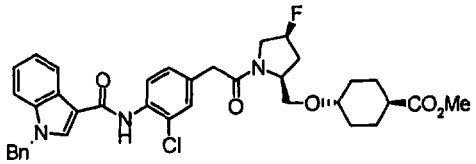
(Step 4) Synthesis of 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetic acid



In THF (7.0 ml) was dissolved methyl 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetate (341.3 mg, 0.788 mmol). To the resulting solution was added 0.25N NaOH (7.0 ml). The resulting mixture was stirred at 50°C for 18 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 (2.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetic acid (285.8 mg, 86%) as a light pink amorphous substance.

^{1}H-NMR (DMSO-d_6) δ: 3.57 (2H, s), 5.52 (2H, s), 7.13-7.41 (8H, m), 7.44 (1H, s), 7.56 (1H, d, J=8.0Hz), 7.64 (1H, d, J=8.0Hz), 8.16 (1H, d, J=6.4Hz), 8.43 (1H, s), 9.40 (1H, s).

(Step 5) Synthesis of methyl trans-4-(1-(4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

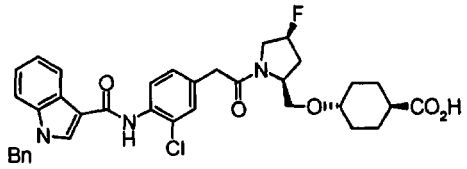


A mixture of methyl trans-4-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (174.3 mg, 0.672

mmol), 4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetic acid (281.5 mg, 0.672 mmol) and HOBt (18.2 mg, 0.134 mmol) was dissolved in DMF (8.0 ml). To the resulting solution was added EDC HCl (193.2 mg, 1.008 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate, 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) to (10:1, v/v) eluate fractions, methyl trans-4-(1-(4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (409.2 mg, 92%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.36 (2H, m), 1.40-1.56 (2H, m), 1.95-2.16 (5H, m), 2.17-2.54 (2H, m), 3.22-4.43 (total 11H, series of m), 5.16-5.38 (1H, m), 5.39 (2H, s), 7.14-7.43 (10H, m), 7.88 (1H, s), 8.17 (1H, d, J=7.2Hz), 8.30 (1H, m), 8.59 (1H, dd, J=8.0Hz).

(Step 6) Synthesis of trans-4-(1-(4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (8.0 ml) was dissolved methyl trans-4-(1-(4-((1-benzyl-3-indolylcarbonyl)amino)-3-chlorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (409.2 mg, 0.620 mmol). To the resulting solution was added 0.25N NaOH (8.0 ml) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was then distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl (2.5 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 (355.6 mg, 89%) as a white amorphous substance.

IR (ATR) ν 2935, 1643, 1511 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.08-1.44 (4H, m), 1.80-2.05 (4H, m), 2.05-2.34 (3H, m), 3.11-3.94 (total 7H, series of m), 4.14 and 4.34 (total 1H, m), 5.32 and 5.46 (total 1H, d, J=55.2Hz), 5.23 (2H, s), 7.12-7.45 (total 9H, series of m), 7.57 (1H, d, J=7.6Hz), 7.65 (1H, m), 8.17 (1H, d, J=7.6Hz), 8.43 (1H, s), 9.40 (1H, s), 12.05 (1H, s, CO_2H).

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

Anal. Calcd for $C_{36}H_{37}ClFN_3O_5$ 0.25H_2O: C, 66.45; H, 5.81; N,

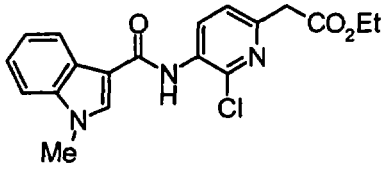
6.46; Cl, 5.45; F, 2.92.

Found: C, 66.34; H, 5.83; N, 6.27; Cl, 5.35; F, 2.88.

Example 69

trans-4-(1-(2-Chloro-3-((1-methyl-3-indolylcarbonyl)amino)-6-pyridyl)acetyl)-(4S)-fluoro-(2S)-cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridyl))acetate



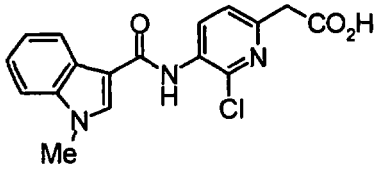
Oxalyl chloride (1.10 ml, 12.5 mmol) was added to a solution of 1-methylindole-3-carboxylic acid (2.00 g, 11.4 mmol) and DMF (0.18 ml, 2.28 mmol) in methylene chloride (25 ml) and the resulting mixture was stirred for 3 hours at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent to give 1-methylindole-3-carboxylic acid chloride (2.19 g, 99 %) as a pale yellow solid. The resulting 1-methylindole-3-carboxylic acid chloride (752 mg, 3.88 mmol) was added in portions to a solution of ethyl 3-amino-2-chloro-6-pyridylacetate (833 mg, 3.88 mmol) and triethylamine (1.08 ml, 7.77 mmol) in methylene chloride (20 ml) under stirring at 0°C. The reaction mixture was heated under reflux for 8

hours. After cooling to room temperature and addition of water, the mixture was extracted 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 chromatography on a silica gel column, whereby from n-hexane - ethyl acetate (2:1, v/v) eluate fractions, ethyl 2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridylacetate (859 mg, 60%) was obtained as a yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.21 (t, J=7.1Hz, 3H), 3.85 (s, 2H), 3.90 (s, 3H), 4.12 (q, J=7.1Hz, 2H), 7.21 (m, 1H), 7.28 (m, 1H), 7.42 (d, J=8.1Hz, 1H), 7.55 (d, J=8.1Hz, 1H), 8.04 (m, 1H), 8.15 (m, 1H), 8.31 (m, 1H), 9.41 (broad s, 1H).

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

(Step 2) Synthesis of (2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridyl)acetic acid



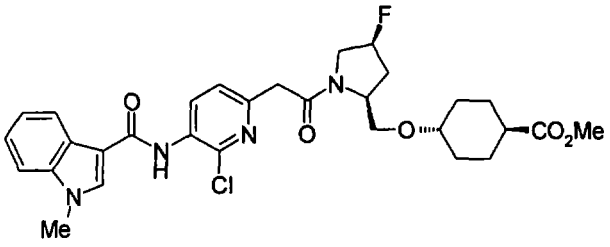
Ethyl 2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridylacetate (859 mg, 2.31 mmol) was dissolved in THF (25 ml). To the resulting solution was added 0.25N NaOH (13.9 ml, 3.47 mmol), followed by stirring at room temperature for 4 hours. Methanol - water (1:1, v/v, 10 ml) was added,

and the mixture was stirred at 50°C for 2 hours. The reaction mixture was acidified with 1N HCl (5.0 ml). The crystals thus precipitated were collected by filtration, washed with water, and dried under reduced pressure to give 2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridylacetic acid (702 mg, 88%) as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.76 (s, 2H), 3.89 (s, 3H), 7.21 (t, J=8.3Hz, 1H), 7.28 (t, J=8.3Hz, 1H), 7.41 (d, J=8.1Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 8.15 (d, J=8.1Hz, 1H), 8.31 (s, 1H), 9.40 (broad s, 1H), 12.50 (broad s, 1H).

MS (ESI) m/z 344 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(2-chloro-3-((1-methyl-3-indolylcarbonyl)amino)-6-pyridyl)acetyl)-(4S)-fluoro-(2S)-cyclohexanecarboxylate



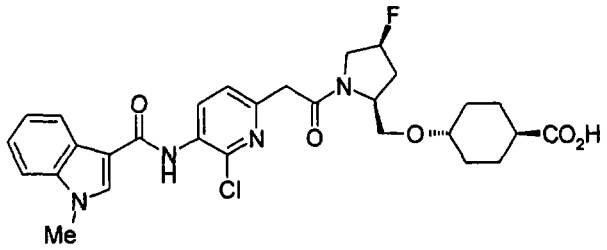
To a solution of (2-chloro-3-(1-methyl-3-indolylcarbonyl)amino-6-pyridyl)acetic acid (254 mg, 0.74 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (192 mg, 0.74 mmol), HOBt (20.0 mg, 0.15 mmol), and DMAP (18.0 mg, 0.15 mmol) in

DMF (8.0 ml) was added EDC HCl (212 mg, 1.11 mmol). After stirring at room temperature for 20 hours, the reaction mixture was added with water. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give methyl trans-4-(1-(2-chloro-3-((1-methyl-3-indolylcarbonyl)amino)-6-pyridyl)acetyl)-(4S)-fluoro-(2S)-cyclohexanecarboxylate (377 mg, 887 %) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.33 (m, 2H), 1.41-1.54 (m, 2H), 1.98-2.54 (m, 7H), 3.28 (m, 1H), 3.34 and 3.53 (each m, total 1H), 3.66 and 3.68 (each 2, total 3H), 3.70-3.89 (m, 4H), 3.91 (s, 3H), 3.92-4.12 (m, 2H), 4.39 and 4.46 (each m, total 1H), 5.28 (m, 1H), 7.30-7.39 (m, 2H), 7.44 (m, 1H), 7.83 (m, 1H), 8.13 (m, 1H), 8.24 (m, 1H), 8.92 and 8.95 (each d, J=8.3Hz, total 1H).

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

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



In THF (7.0 ml) was dissolved methyl trans-4-(1-(2-chloro-3-((1-methyl-3-indolylcarbonyl)amino)-6-pyridyl)acetyl)-(4S)-fluoro-(2S)-cyclohexanecarboxylate (377 mg, 0.64 mmol). To the resulting solution was added 0.25N NaOH (4.00 ml, 1.00 mmol), followed by stirring at room temperature for 19 hours. The reaction mixture was poured in 1N HCl (1.0 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 (252 mg, 69 %) as a pale yellow solid.

IR (ATR) ν 2940, 2861, 1710, 1654, 1617, 1581, 1519, 1488 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.17-1.38 (m, 4H), 1.86-2.21 (m, 7H), 3.18-3.87 (m. 6H), 3.90 (s, 3H), 3.93 (m, 1H), 4.14 and 4.40 (each m, total 1H), 5.33 and 5.40 (each m, total 1H), 7.21 (t, J=8.1Hz, 1H), 7.27 (t, J=8.1Hz, 1H), 7.34 (d, J=8.1Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 8.12-8.17 (m, 2H), 8.30 (s, 1H), 9.39 (broad s, 1H), 12.00 (broad s, 1H).

MS (ESI) m/z 571 (M^++1);

Anal. Calcd for $C_{29}H_{32}ClFN_4O_5$ 0.25H_2O: C, 60.52; H, 5.69; N, 9.73.

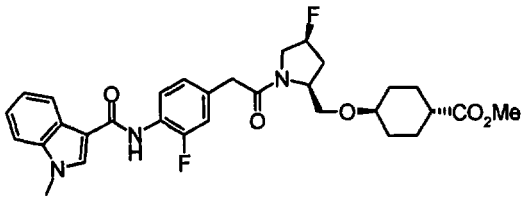
Found: C, 60.46; H, 5.76; N, 9.43.

Example 70

trans-4-(1-(3-Fluoro-4-(1-methyl-3-

indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

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

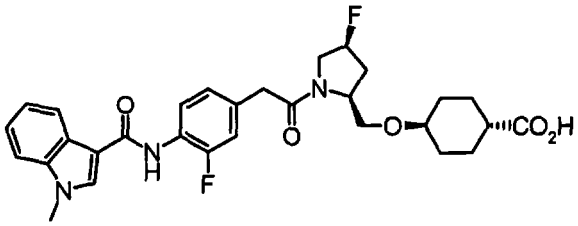


In THF (10 ml) and acetonitrile (10 ml) were dissolved methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (65 mg, 0.25 nnol), (3-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenyl)acetic acid (90 mg, 0.25 mmol), HOBt (34 mg, 0.25 mmol), and triethylamine (104 µl, 0.75 mmol). After EDC·HCl (72 mg, 0.37 mmol) was added at 0°C, the mixture was stirred at room temperature for 16 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was added with water, followed by extraction with ethyl acetate. The extract was washed successively with a saturated aqueous solution of sodium bicarbonate, a 2M aqueous citric acid solution, 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 thin-layer plate, whereby from n-hexane-ethyl acetate (1:4, v/v) eluate fractions, methyl trans-4-(1-(3-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (130 mg, 90%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.50 (m, 4H), 2.00-2.50 (m, 6H), 3.20-4.40 (m, 15H), 5.15-5.35 (m, 1H), 7.07-7.45 (m, 5H), 7.78 (s, 1H), 7.91 (br s, 1H), 8.03-8.06 (m, 1H), 8.45-8.47 (m, 1H).

(Step 2) Synthesis of 4-(1-(3-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (10 ml) and methanol (5.0 ml) was dissolved methyl trans-4-(1-(3-fluoro-4-(1-methyl-3-indolyl)carbonylaminophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (130 mg, 0.23 mmol). To the resulting solution was added 1N NaOH (0.8 ml, 0.8 mmol), followed by stirring at 70°C 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 (90 mg, 71%) as a white solid.

IR (ATR) ν 2933, 1639, 1627, 1521, 1427, 1099 cm^{-1};

^{1}H-NMR (DMSO-d^6) δ: 1.16-1.37 (m, 4H), 1.88-2.18 (m, 6H), 3.10-4.30 (m, 12H), 5.22-5.45 (m, 1H), 7.00-7.27 (m, 4H), 7.53 (d, J=8.3Hz, 1H), 7.60-7.63 (m, 1H), 8.14 (d, J=7.8Hz, 1H), 8.25 (s, 1H), 9.46 (s, 1H).

MS (FAB) m/z 553 $(M+H)^+$;

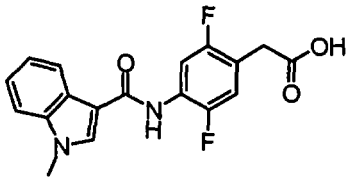
Anal. calcd for $C_{30}H_{33}CFN_3O_5$ $0.4H_2O$: C, 64.25; H, 6.07; N, 7.49.

Found: C, 64.38; H, 6.16; N, 7.38.

Example 71

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

(Step 1) Synthesis of (2,5-difluoro-4-((1-methyl-1H-indolylcarbonyl)amino)phenyl)acetic acid



In methylene chloride (20 ml) were dissolved 1-

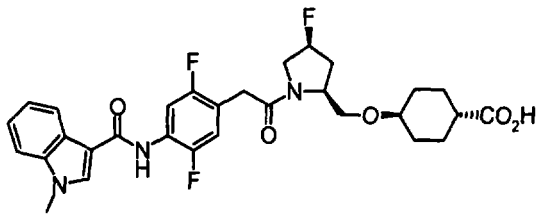
methyl-1H-indole-3-carboxylic acid (814 mg, 4.65 mmol), triethylamine (2.6 ml, 18.6 mmol) and diphenylphosphinic chloride (1.72 ml, 9.3 mmol). The resulting solution was stirred for 3 days at room temperature. The reaction mixture was poured in 1M HCl, followed by extraction with chloroform. The extract were washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. To the residue were added THF (10 ml) and 0.25M NaOH (8 ml, 2 mmol) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in water and acidified with 1M HCl. The acidic solution was extracted with a chloroform/methanol mixture. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent to give 2,5-difluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (483 mg, 30%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 3.90 (s, 3H), 7.20 (t, J=7.5Hz, 1H), 7.29 (t, J=7.5Hz, 1H), 7.55 (d, J=8.1Hz, 1H), 7.70 (dd, J=6.5, 8.8Hz, 1H), 8.15 (d, J=7.5Hz, 1H), 8.32 (s, 1H), 9.57 (s, 1H), 12.52 (br, 1H).

MS (ESI) m/z 345 $(M+1)^+$.

(Step 2) Synthesis of trans-4-(1-(2,5-difluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-

fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (10 ml) were dissolved 2,5-difluoro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (480 mg, 1.39 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (301 mg, 1.16 mmol), HOBt (357 mg, 2.64 mmol), DMAP (catalytic amount) and EDC·HCl (400 mg, 2.09 mmol). The resulting solution 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 chromatography on a silica gel column (middle pressure Yamazen, linear gradient of chloroform and methanol form 100:0 to 95:5, 12 ml/min, ϕ 37 mm x 300 mm), whereby a condensate was obtained. The resulting compound was added with THF (14 ml) and 0.25M NaOH (7 ml, 1.7 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was acidified with 1M HCl. The crystals

thus precipitated were collected by filtration under reduced pressure. The crude crystals thus obtained were recrystallized from chloroform/n-hexane/acetone to give the title compound (329 mg, 50%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20 (m, 2H), 1.33 (m, 2H), 1.90 (m, 4H), 2.18 (m, 2H), 3.18 (t, J=9.5Hz, 1H), 3.50 (m, 1H), 3.62 (m, 1H), 3.70 (m, 1H), 3.90 (s, 3H), 3.80-4.00 (m, 2H), 4.12 and 4.32 (2m, total 1H), 5.40 (m, 1H), 7.20 (m, 3H), 7.52 (d, J=8.1Hz, 1H), 7.65 (m, 1H), 8.14 (d, J=7.8Hz, 1H), 8.30 (s, 1H), 9.55 (s, 1H), 12.04 (br, 1H).

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

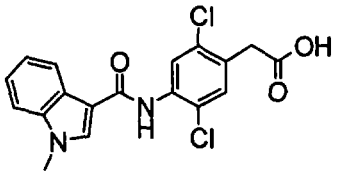
Anal. Calcd for $C_{30}H_{32}F_3N_3O_5 \cdot 1.0\ H_2O$: C, 61.11; H, 5.81; N, 7.13.

Found: C, 60.92; H, 5.55; N, 6.97.

Example 72

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

(Step 1) Synthesis of 2,5-dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid



In methylene chloride (25 ml) was dissolved 1-methyl-

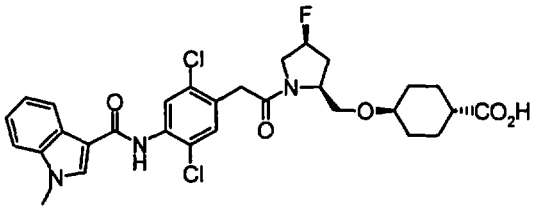
1H-indole-3-carboxylic acid (794 mg, 4.53 mmol). Oxalyl chloride (0.79 ml, 9.1 mmol) was added to the solution under stirring at 0°C. The reaction mixture was stirred at room temperature for 1 hour and then, distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (25 ml). The resulting solution was added to a solution of triethylamine (0.84 ml, 9.0 mmol) and ethyl 4-amino-2,5-dichlorophenylacetate (750 mg, 3.02 mmol) at 0°C. The reaction mixture was heated under reflux for 18 hours. After cooling to room temperature, the reaction mixture was poured in water, 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 chromatography on a silica gel column (middle pressure Yamazen, linear gradient of chloroform and methanol form 100:0 to 95:5, 12 ml/min, ϕ 37 mm x 300 mm), whereby the purified ester was obtained. To the purified ester were added THF (45 ml) and 0.25M NaOH (18 ml, 4.5 mmol), followed by stirring at room temperature for 4 hours. Water and 1M HCl were added to acidify the reaction mixture. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were recrystallized from chloroform/n-hexane to

give 2,5-dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (807 mg, 71%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.72 (s, 2H), 3.90 (s, 3H), 7.22 (t, J=8.1Hz, 1H), 7.28 (t, J=8.1Hz, 1H), 7.56 (d, J=8.3Hz, 1H), 7.64 (s, 1H), 7.92 (s, 1H), 8.15 (d, J=7.8Hz, 1H), 8.31 (s, 1H), 9.39 (s, 1H).

MS (ESI) m/z 378 $(M+1)^+$.

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



In DMF (10 ml) were dissolved (2,5-dichloro-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (438 mg, 1.16 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (301 mg, 1.16 mmol), HOBt (357 mg, 2.64 mmol), DMAP (catalytic amount) and EDC·HCl salt (400 mg, 2.09 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 chromatography on a silica gel column (middle pressure Yamazen, linear gradient of chloroform and methanol form 100:0 to 95:5, 12 ml/min, ϕ 37 mm x 300 mm). The purified ester was dissolved in THF (14 ml) and 0.25M NaOH (7 ml, 1.7 mmol). The resulting mixture was stirred for 18 hours at room temperature and poured in water. The solution was acidified with 1M HCl. Crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were recrystallized from chloroform/n-hexane/acetone to give the title compound (528 mg, 75%) as a colorless crystalline substance.

^{1}H-NMR (DMSO-d_6) δ: 1.20 (m, 2H), 1.32 (m, 2H), 1.90 (m, 4H), 2.20 (m, 2H), 3.21 (m, 1H), 3.49 (m, 1H), 3.65-4.00 (m, 4H), 3.90 (s, 3H), 4.12 and 4.40 (2m, total 1H), 5.40 (m, 1H), 7.21 (t, J=7.4Hz, 1H), 7.28 (t, J=7.4Hz, 1H), 7.50 (d, J=15.7Hz, 1H), 7.55 (d, J=8.1Hz, 1H), 7.88 (d, J=3.4Hz, 1H), 8.14 (d, J=7.8Hz, 1H), 8.30 (s, 1H), 9.38 (s, 1H), 12.04 (s, 1H).

MS (ESI) m/z 605 $(M+1)^+$.

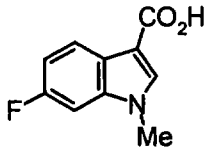
Anal. Calcd for $C_{30}H_{32}Cl_2FN_3O_5 \cdot 0.25\ H_2O$: C, 59.17; H, 5.38; N, 6.90.

Found: C, 59.18; H, 5.38; N, 6.71.

Example 73

trans-4-(1-((5-Chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 6-fluoro-1-methylindole-3-carboxylic acid



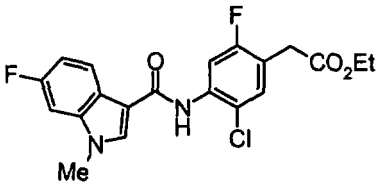
In acetone (200 ml) was dissolved 6-fluoro-1-methylindole-3-carbaldehyde (3.10 g, 17.5 mmol). To the resulting solution was added potassium permanganate (0.2M aqueous solution, 175 ml, 35.0 mmol) in portions under stirring at room temperature. After stirring at room temperature for 10 hours, the reaction mixture was filtered through Celite. After the filtrate was distilled under reduced pressure 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 6-fluoro-1-methylindole-3-carboxylic acid (2.37 g, 70%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.82 (s, 3H), 7.05 (m, 1H), 7.41 (d,

J=9.8Hz, 1H), 7.98 (dd, J=8.6, 5.6Hz, 1H), 8.04 (s, 1H), 12.03 (s, 1H).

MS (ESI) m/z 194 (M^++1).

(Step 2) Synthesis of ethyl (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetate



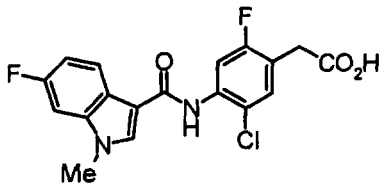
To a suspension of 6-fluoro-1-methylindole-3-carboxylic acid (500 mg, 2.59 mmol) and DMF (0.02 ml, 0.26 mmol) in methylene chloride (15 ml) was added dropwise oxalyl chloride (0.25 ml, 2.85 mmol) under stirring at room temperature. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was then distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (10.0 ml), followed by the dropwise addition to a solution of ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (600 mg, 2.59 mmol) and triethylamine (1.08 ml, 7.77 mmol) in methylene chloride (5.0 ml). After completion of the dropwise addition, the reaction mixture was heated under reflux for 10 hours. After the reaction mixture was cooled to room temperature, the precipitated crystals were removed under reduced

pressure. 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, ethyl (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (665 mg, 63%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.1Hz, 3H), 3.62 (s, 2H), 3.84 (s, 3H), 4.19 (q, J=7.1Hz, 2H), 7.07-7.12 (m, 2H), 7.34 (d, J=7.3Hz, 1H), 7.74 (s, 1H), 8.10 (dd, J=9.1, 5.2Hz, 1H), 8.19 (broad s, 1H), 8.49 (d, J=12.0Hz, 1H).

MS (ESI) m/z 407 (M^++1).

(Step 3) Synthesis of (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid



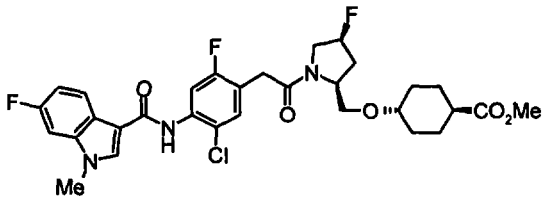
In THF (17 ml) was dissolved ethyl (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (665 mg, 1.63 mmol). To the resulting solution was added 0.25N NaOH (9.81 ml, 2.45 mmol) and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured in 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 (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (600 mg, 97%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.65 (s, 2H), 3.86 (s, 3H), 7.06 (m, 1H), 7.44 (dd, J=10.3,2.5Hz, 1H), 7.54 (d, J=7.6Hz, 1H), 7.69 (d, J=11.2Hz, 1H), 8.12 (dd, J=8.8,5.6Hz, 1H), 8.32 (s, 1H), 9.38 (s, 1H), 12.58 (broad s, 1H).

MS (ESI) m/z 379 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



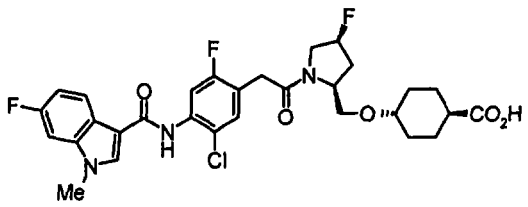
To a solution of (5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.53 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (137 mg, 0.53 mmol), HOBt (14.0 mg, 0.11 mmol), and DMAP (13.0 mg, 0.11 mmol) in DMF (5.0 ml) was added EDC HCl (152 mg, 0.79 mmol). After stirring at room temperature for 18 hours, the reaction

mixture was diluted with water, followed by extraction with ethyl acetate. The extract was washed 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 trans-4-(1-((5-chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)-amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)-cyclohexanecarboxylate (303 mg, 92%) as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.53 (m, 4H), 1.93-2.53 (m, 7H), 3.23-3.98 (m, 13H), 4.30 and 4.37 (each m, total 1H), 5.26 and 5.28 (each m, total 1H), 7.06-7.11 (m, 2H), 7.39 and 7.40 (each d, J=7.1Hz, total 1H), 7.73 (s, 1H), 8.10 (dd, J=9.0,4.9Hz, 1H), 8.18 (m, 1H), 8.45 and 8.46 (each d, J=12.0Hz, total 1H)

MS (ESI) m/z 620 (M^++1).

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



In THF (49 ml) was dissolved methyl trans-4-(1-((5-

chloro-2-fluoro-4-((6-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (303 mg, 0.49 mmol). To the resulting solution was added 0.25N NaOH (3.00 ml, 0.75 mmol) and the mixture was stirred at room temperature for 17 hours. The reaction mixture was poured in 1N HCl (1.0 ml). The crystals thus precipitated were collected by filtration, washed with water, and dried under reduce pressure to give the title compound (236 mg, 79 %) as a colorless solid.

IR (ATR) ν 3417, 2940, 2865, 1708, 1619, 1646, 1585, 1517, 1467 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.18-1.41 (m, 4H), 1.86-2.33 (m, 7H), 3.17-3.98 (m, 10H), 4.13 and 4.35 (each m, total 1H), 5.32 and 5.41 (each m, total 1H), 7.06 (m, 1H), 7.42-7.46 (m, 2H), 7.65 and 7.66 (each d, J=11.2Hz, total 1H), 8.12 (dd, J=8.6, 5.9Hz, 1H), 8.31 (s, 1H), 9.37 (s, 1H), 12.03 (broad s, 1H).

MS (ESI) m/z 606 (M^++1);

Anal. Calcd for $C_{30}H_{31}ClF_3N_3O_5 \cdot 0.75H_2O$: C, 58.16; H, 5.29; N, 6.78.

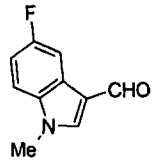
Found: C, 58.35; H, 5.23; N, 6.39.

Example 74

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

indolyl)carbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

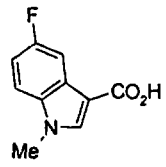
(Step 1) Synthesis of (5-fluoro-1-methylindol)-3-carbaldehyde



In DMF (100 ml) was dissolved 5-fluoroindol-3-carbaldehyde (5.17 g, 36.7 mmol). To the resulting solution was added sodium hydride (60% in oil, 1.39 g, 34.9 mmol) in portions under stirring at 0°C. After the reaction mixture was stirred at the same temperature for 1 hour, methyl iodide (4.57 ml, 73.4 mmol) was added thereto at 0°C. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl, followed by extraction 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 crystallized by adding thereto chloroform/hexane. The crystals thus precipitated were collected by filtration under reduced pressure and dried under reduced pressure to give 5-fluoro-1-methylindole-3-carbaldehyde (2.53 g, 39%) as a white crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 3.86 (s, 3H), 7.08 (brt, J=9.2Hz, 1H), 7.27 (dd, J=4.4,8.8Hz, 1H), 7.68 (s, 1H), 7.95 (brd, J=9.6Hz, 1H).

(Step 2) Synthesis of 5-fluoro-1-methylindole-3-carboxylic acid

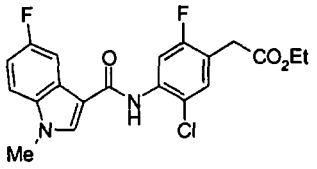


In acetone (50 ml) was dissolved 5-fluoro-1-methylindole-3-carbaldehyde (1.33 g, 7.52 mmol). To the resulting solution was added dropwise an 1N aqueous solution of potassium permanganate (7.15 ml, 7.15 mmol) under stirring at 0°C. After stirring at room temperature for 18 hours, another 1N aqueous solution of potassium permanganate (4.0 ml, 4.0 mmol) was added, and the mixture was stirred at room temperature for 18 hours. The mixture was filtered through Celite. After washing with water, the filtrate was added with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 5-fluoro-1-methylindole-3-carboxylic acid (885 mg, 61%) as a white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 3H), 7.06-7.11 (m, 1H), 7.53 (dd, J=4.8,9.2Hz, 1H), 7.67 (brd, J=10.0Hz, 1H), 8.08 (s,

1H), 12.00 (brs, 1H).

(Step 3) Synthesis of ethyl (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetate



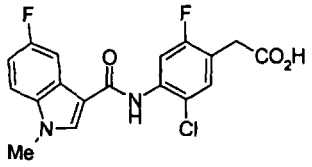
In methylene chloride (30 ml) was dissolved 5-fluoro-1-methylindole-3-carboxylic acid (885 mg, 4.58 mmol). To the resulting solution was added oxalyl chloride (600 µl, 6.87 mmol) under stirring at 0°C, and the resulting mixture was stirred at room temperature for 1 hour. From the reaction mixture, the solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride (50 ml). The resulting solution was added dropwise to a solution of ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (1.06 g, 4.58 mmol) in methylene chloride (20 ml), followed by heating under reflux for 15 minutes. The reaction mixture was cooled and triethylamine (3.19 ml, 22.9 mmol) was added thereto. The resulting mixture was heated under reflux for 18 hours. The reaction mixture was cooled and poured in 1N HCl, 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 hexane/ethyl acetate (2/1) eluate fractions, ethyl (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetate (868 mg, 47%) was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.2Hz, 3H), 3.61 (s, 2H), 3.87 (s, 3H), 4.18 (dd, J=7.2,14.0Hz, 2H), 7.08 (dt, J=2.0,8.8Hz, 1H), 7.29-7.34 (m, 2H), 7.5 (s, 1H), 7.83 (dd, J=2.4,9.6Hz, 1H), 8.11 (brs, 1H), 8.80 (d, J=12Hz, 1H).

MS (ESI) m/z 407 (M^++1).

(Step 4) Synthesis of (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetic acid



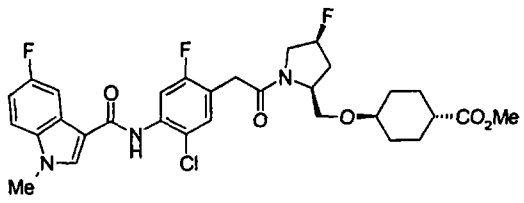
THF/methanol (1/1, 60 ml) and 0.25N NaOH (43 ml, 10.6 mmol) were added to ethyl (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetate (865 mmol, 2.13 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured in 1N HCl, followed by extraction 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 solidified with

methanol/chloroform/hexane. The crystals thus precipitated were collected by filtration under reduced pressure and dried under reduced pressure to give (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetic acid (736 mg, 91%) as a white crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.72 (s, 2H), 3.90 (s, 3H), 7.11 (dt, J=2.8, 9.2Hz, 1H), 7.53-7.58 (m, 2H), 7.83 (dd, J=2.4,9.6Hz, 1H), 8.37.

MS (ESI) m/z 379 (M^++1).

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



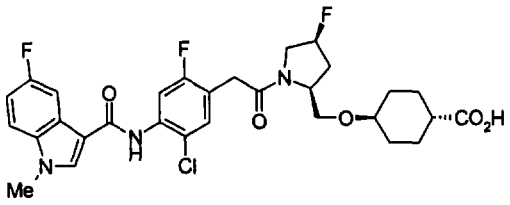
In DMF (20 ml) were dissolved (5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acic acid (483 mg, 1.28 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (331 mg, 1.28 mmol) and EDC-HCl (294 mg, 1.53 mmol). To the resulting solution was added HOBt (35.0 mg, 0.26 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 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 (1/2) eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-(((5-fluoro-1-methyl-3-indolyl)carbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (718 mg, 91%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.23-1.31 (m, 2H), 1.40-1.52 (m, 2H), 1.96-2.52 (series of m, 7H), 3.20-4.00 (series of m, 7H), 3.65 and 3.67 (s, total 3H), 3.78 (s, 3H), 4.28-4.42 (m, 1H), 5.18-5.38 (m, 1H), 7.08 (brt, J=9.2Hz, 1H), 7.31 (dd, J=4.4,9.2Hz, 1H), 7.39 (dd, J=4.4,7.6Hz, 1H), 7.75 (d, J=2.8Hz, 1H), 7.84 (dd, J=2.8,9.6Hz, 1H), 8.11 (d, J=5.2Hz, 1H), 8.43 and 8.46 (d, J=9.2Hz, total 1H).

MS (ESI) m/z 621 (M^++2).

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



To the methyl ester (687 mg, 1.11 mmol) were added THF/methanol (1/1, 40 ml) and 0.25N NaOH (22 ml, 5.54 mmol), and the resulting mixture was stirred at room temperature for 3.5 hours. The reaction mixture was poured in 1N HCl, 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. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (10/1) eluate fractions, the title compound (694 mg, 100%) was obtained as a colorless amorphous substance.

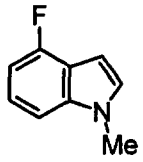
^{1}H-NMR (DMSO-d_6), mixture of rotamars, δ: 1.18-1.39 (series of m, 4H), 1.87-2.51 (series of m, 7H), 3.16-4.40 (series of m, 8H), 3.90 (s, 3H), 5.23-5.55 (m, 1H), 7.08 (dt, J=2.8, 9.2Hz, 1H), 7.41 and 7.44 (d, J=7.6Hz, total 1H), 7.55 and 7.58 (d, J=4.4Hz, total 1H), 7.66 and 7.69 (d, J=6.0Hz, total 1H), 7.83 (dd, J=2.4,10.0Hz, 1H), 8.38 (s, 1H), 9.33 (s, 1H).

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

Example 75

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

(Step 1) Synthesis of 4-fluoro-1-methylindole

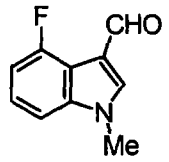


In DMF (40 ml) was dissolved 4-fluoroindole (2.00 g, 14.8 mmol). To the resulting solution was added sodium hydride (60 % in oil, 0.71 g, 17.8 mmol) in portions under stirring at 0°C. After the reaction mixture was stirred for 40 minutes at the same temperature, methyl iodide (1.11 ml, 17.8 mmol) was added at 0°C. The reaction mixture was stirred further at the same temperature for 4 hours. A saturated aqueous solution of ammonium chloride was added to terminate the reaction. The reaction mixture was extracted with ether, and 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, 4-fluoro-1-methylindole (2.20 g, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.78 (s, 3H), 6.55 (m, 1H), 6.77 (m, 1H), 7.01 (d, J=3.2Hz, 1H), 7.08-7.15 (m, 2H).

MS (ESI) m/z 150 (M^++1).

(Step 2) Synthesis of 4-fluoro-1-methylindole-3-carbaldehyde

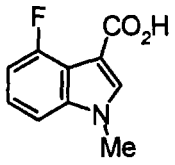


Under stirring at 0°C, phosphoryl chloride (2.07 ml, 22.1 mmol) was added dropwise to DMF (30 ml). After completion of the dropwise addition, a solution of 4-fluoro-1-methylindole (2.20 g, 14.7 mmol) in DMF (15 ml) was added dropwise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in 1N NaOH (120 ml), 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, 4-fluoro-1-methylindole-3-carbaldehyde (1.43 g, 55%) was obtained as a red solid.

^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H), 7.17 (d, J=7.1Hz, 1H), 7.23-7.28 (m, 2H), 7.81 (s, 1H), 10.21 (s, 1H).

MS (ESI) m/z 178 (M^++1).

(Step 3) Synthesis of 4-fluoro-1-methylindole-3-carboxylic acid

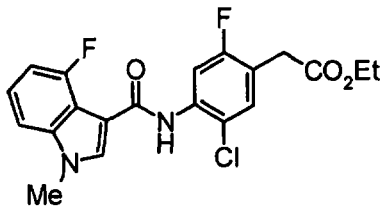


In acetone (95 ml) was dissolved 4-fluoro-1-methylindole-3-carbaldehyde (1.43 g, 8.08 mmol), followed by the addition of potassium permanganate (a 0.2M aqueous solution, 62.0 ml, 12.4 mmol) in portions at room temperature. After the reaction mixture was stirred at room temperature for 16 hours, the precipitate was filtered off through Celite. The filtrate 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 4-fluoro-1-methylindole-3-carboxylic acid (0.91 g, 58 %) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.85 (s, 3H), 6.93 (dd, J=11.5,7.8Hz, 1H), 7.23 (m, 1H), 7.35 (d, J=8.3Hz, 1H), 8.08 (s, 1H), 11.88 (broad s, 1H).

MS (ESI) m/z 194 (M^++1).

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

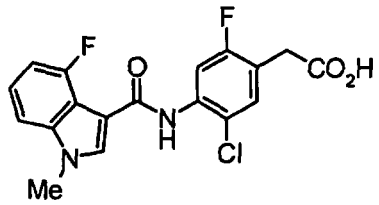


To a suspension of 4-fluoro-1-methylindole-3-carboxylic acid (700 mg, 3.62 mmol) and DMF (28.0 µl, 0.36 mmol) in methylene chloride (20 ml) was added oxalyl chloride (0.35 ml, 3.99 mmol) in portions under stirring at room temperature. After the reaction mixture was stirred at room temperature for 50 minutes, oxalyl chloride (30 µl) was added, and the mixture was stirred for further 40 minutes. To the reaction mixture, a solution of ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (839 mg, 3.62 mmol) and triethylamine (1.52 ml, 10.9 mmol) in methylene chloride (5 ml) was added and the mixture was heated under reflux at room temperature for 4 hours. After cooling to room temperature, the reaction mixture was added with water, followed by extraction with chloroform. The extract was washed with brine, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent. The residue was purified by chromatography opn a silica gel column, whereby from n-hexane - ethyl acetate (2:1, v/v) eluate fractions, ethyl (5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (762 mg, 52%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.27 (t, J=7.3Hz, 3H), 3.61 (s, 2H), 3.87 (s, 3H), 4.18 (q, J=7.3Hz, 2H), 7.02 (dd, J=12.2,8.1Hz, 1H), 7.20 (d, J=8.1Hz, 1H), 7.27 (m, 1H), 7.32 (d, J=7.3Hz, 1H), 8.02 (s, 1H), 8.48 (d, J=12.2Hz, 1H), 9.26 (m, 1H).

MS (ESI) m/z 407 (M^++1).

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

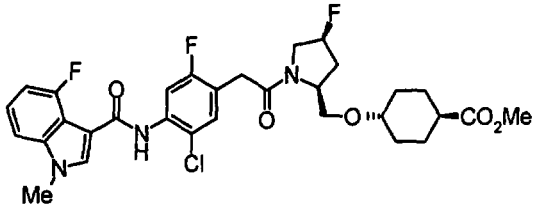


In THF (19 ml) was dissolved ethyl (5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetate (762 mg, 1.87 mmol). To the resulting solution was added 0.25N NaOH (11.2 ml, 2.81 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into 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 (5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (698 mg, 99%) as a purple solid.

^{1}H-NMR (DMSO-d_6) δ: 3.64 (s, 2H), 3.90 (s, 3H), 7.07 (dd, J=12.5,7.8Hz, 1H), 7.29 (m, 1H), 7.44 (d, J=8.4Hz, 1H), 7.55 (d, J=7.8Hz, 1H), 8.11 (d, J=11.7Hz, 1H), 8.25 (s, 1H), 9.30 (d, J=10.3Hz, 1H), 12.54 (broad s, 1H).

MS (LCMS) m/z 379 (M^++1).

(Step 6) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate

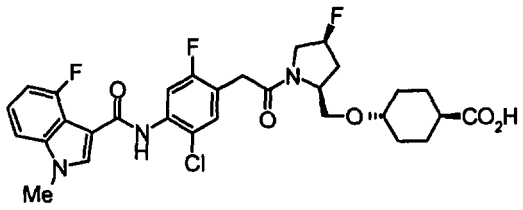


To a solution of (5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.53 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (137 mg, 0.53 mmol), HOBt (14.0 mg, 0.11 mmol), and DMAP (13.0 mg, 0.11 mmol) in DMF (5.0 ml) was added EDC HCl (152 mg, 0.79 mmol). After stirring at room temperature for 23 hours, 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 ethyl acetate eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (332 mg, 100%)

was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.22-1.33 (m, 2H), 1.41-1.54 (m, 2H), 1.98-2.18 (m, 4H), 2.23-2.54 (m, 3H), 3.25-4.03 (m, 13H), 4.30 and 4.39 (each m, total 1H), 5.27 and 5.31 (each m, total 1H), 7.03 (dd, J=12.2,7.8Hz, 1H), 7.21-7.31 (m, 2H), 7.38 and 7.39 (each d, J=7.3Hz, total 1H), 8.03 (s, 1H), 8.46 and 8.48 (each d, J=12.2Hz, total 1H), 9.26 (m, 1H). MS (LCMS) m/z 620 (M^++1).

(Step 7) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (5.5 ml) was dissolved methyl trans-4-(1-((5-chloro-2-fluoro-4-((4-fluoro-1-methyl-3-indolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (323 mg, 0.52 mmol). To the resulting solution was added 0.25N NaOH (3.13 ml, 0.78 mmol). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into 1N HCl (1.0 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 (266 mg, 84%) as a yellow solid.

IR (ATR) ν 3399, 2937, 2863, 1724, 1648, 1621, 1587, 1521, 1450 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.41 (m, 4H), 1.86-2.00 (m, 4H), 2.10-2.32 (m, 3H), 3.17-3.88 (m, 7H), 3.90 (s, 3H), 4.13 and 4.35 (each m, total 1H), 5.32 and 5.40 (each m, total 1H), 7.07 (dd J=12.5,8.1Hz, 1H), 7.29 (m, 1H), 7.42-7.45 (m, 2H), 8.10 (d, J=11.7Hz, 1H), 8.26 (s, 1H), 9.28 (d, J=8.5Hz, 1H), 12.03 (broad s, 1H).

MS (LCMS) m/z 606 (M^++1);

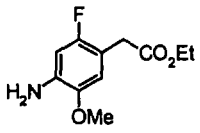
Anal. Calcd for $C_{30}H_{31}ClF_3N_3O_5$ 0.5H_2O: C, 58.59; H, 5.24; N, 6.83.

Found: C, 58.65; H, 5.27; N, 6.55.

Example 76

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

(Step 1) Synthesis of ethyl (4-amino-2-fluoro-5-methoxyphenyl)acetate



To 1,2-difluoro-4-methoxybenzene (5 g, 34.7 mmol) was added concentrated H_2SO_4 (9.25 ml, 174 mmol). Concentrated HNO_3 (2.64 ml, 34.7 mmol) was added dropwise under stirring

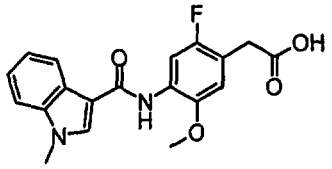
at 0°C. After stirring for 3 hours at room temperature, the reaction mixture was poured into ice water, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was dissolved in DMF (100 ml). Under stirring at 0°C, sodium hydride (4.16 g, 104 mmol) was added in portions. After the reaction mixture was stirred at the same temperature for 15 minutes, a solution of ethyl tert-butyl ethyl malonate (6.57 ml, 34.7 mmol) in DMF (50 ml) was added dropwise in portions thereto. After completion of the dropwise addition, stirring was conducted at room temperature for 18 hours. The reaction mixture was poured into ice water - an aqueous ammonium chloride solution, 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 added with methylene chloride - trifluoroacetic acid (100 ml, 1:1, v/v), followed by heating under reflux for 18 hours. After cooling to room temperature, the reaction mixture was distilled under reduced pressure to remove the solvent. An iron powder (6.2 g, 0.11 mol) was added to the residue and the mixture was sonicated for 5 minutes. To the reaction mixture were added methanol/water (175 ml, 1:4), sodium acetate (4.7 g,

35 mmol) and acetic acid (13.5 ml, 230 mmol), followed by heating under reflux for 3 hours (without using a stirrer). After cooling to room temperature, the reaction mixture was filtered through Celite under reduced pressure and the filtrate was washed with methanol. The filtrate was distilled under reduced pressure to remove the solvent. The residue was dissolved in ethyl acetate. 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 silica gel column chromatography (middle pressure chromatography system YAMAZEN YFLC-5404, hexane/ethyl acetate 9:1, ϕ 50 mm x 500 mm, 15 ml/min) to give ethyl 4-amino-2-fluoro-5-methoxyphenylacetate (1.75 g, 22%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.28 (t, J=7.1Hz), 1.60 (br s), 3.52 (s, 2H), 3.80 (s, 3H), 3.92 (br s, 1H), 4.15 (q, J=7.1Hz), 6.42 (d, J=10.5Hz), 6.62 (d, J=6.8Hz).

MS (ESI) m/z 228 $(M+1)^+$.

(Step 2) Synthesis of 2-fluoro-5-methoxy-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetic acid



1-Methyl-1H-indole-3-carboxylic acid (700 mg, 4.0

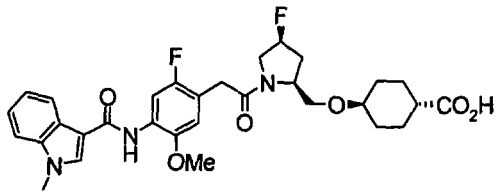
mmol) was dissolved in methylene chloride (8 ml). Oxalyl chloride (0.53 ml, 6.1 mmol) was added dropwise to the solution under stirring at 0°C. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 1 hour and distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (6 ml). The resulting solution was added to a solution of triethylamine (0.84 ml, 6.0 mmol) and ethyl 4-amino-2-fluoro-5-methoxyphenylacetate (909 mg, 4.0 mmol) in methylene chloride (3 ml) under stirring at 0°C. The reaction mixture was heated at reflux for 18 hours. After cooling to room temperature, the reaction mixture was poured into ice water, 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 7:3, 12 ml/min, ϕ 50 mm x 300 mm, charged by dry silica gel method). The purified ester was added with THF (45 ml) and 0.25M NaOH (18 ml, 4.5 mmol), followed by stirring at room temperature for 4 hours. The reaction mixture was poured into water and 1M HCl was added to the resulting mixture to make it acidic. The crystals thus precipitated were collected by filtration under reduced

pressure, washed with water and dried under reduced pressure to give 2-fluoro-5-methoxy-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenylacetic acid (1.01 g, 71%) as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.60 (s, 2H), 3.90 (s, 6H), 7.05 (d, J=6.8Hz, 1H), 7.22 (t, J=7.5Hz, 1H), 7.30 (t, J=7.5Hz, 1H), 7.58 (d, J=7.6Hz, 1H), 7.95 (d, J=11.5Hz, 1H), 8.12 (d, J=7.3Hz, 1H), 8.31 (s, 1H), 8.80 (s, 1H).

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

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



In DMF (5 ml) were dissolved 2-fluoro-5-methoxy-4-((1-methyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (214 mg, 0.6 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (155 mg, 0.6 mmol), HOBt (154 mg, 1.14 mmol), DMAP (catalytic amount) and EDC·HCl (173 mg, 0.9 mmol). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was poured in 1M HCl to acidify the 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 silica gel column chromatography (middle pressure Yamazen, chloroform, 10 ml/min, ϕ 15 mm x 300 mm). To the purified ester 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. Water was poured into the reaction mixture 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 (160 mg, 46%) as a colorless solid.

^{1}H-NMR (DMSO) δ: 1.10-1.40 (m, 4H), 1.85-2.25 (m, 6H), 3.20 (t, J=8.5Hz, 1H), 3.42-3.80 (m, 7H), 3.88 (s, 3H), 3.90 (s, 3H), 4.15 and 4.33 (2m, total 1H), 3.35 (m, 1H), 6.95 (dd, J=6.9,14.7Hz, 1H), 7.23 (t, J=7.5Hz, 1H), 7.28 (t, J=7.5Hz, 1H), 7.55 (d, J=7.8Hz, 1H), 7.92 (dd, J=5.3,7.3Hz, 1H), 8.12 (d, J=7.5Hz, 1H), 8.30 (s, 1H), 8.88 (s, 1H).

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

Anal. Calcd for $C_{31}H_{35}F_2N_3O_6 \cdot 0.25\ H_2O$: C, 63.31; H, 6.08; N, 7.14.

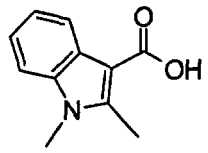
Found: C, 63.07; H, 6.10; N, 7.05.

Example 77

trans-4-(1-(5-Chloro-2-fluoro-4-((1,2-dimethyl-1H-3-

indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 1,2-dimethyl-1H-indole-3-carboxylic acid



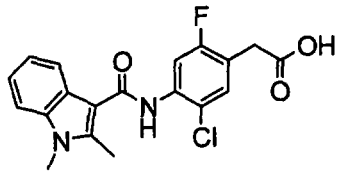
Diisopropylamine (2.83 ml, 20.0 mmol) was dissolved in THF (35 ml). Under stirring at -78°C, n-butyl lithium (12.7 ml, 20.0 mmol, a 1.57M hexane solution) was added to the resulting solution. After stirring at 0°C for 15 minutes, the reaction mixture was cooled again to -78°C. Under stirring, a solution of 1-methyl-1H-indole-3-carboxylic acid (1.75 g, 10.0 mmol) in THF (5 ml) was added. After the reaction mixture was stirred at the same temperature for 30 minutes, methyl iodide (3.42 ml, 55.0 mmol) was added. The reaction mixture was caused to rise back to room temperature over 30 minutes. The reaction mixture was poured into water and the mixture was stirred for 18 hours at room temperature. The reaction mixture was washed with ether. The water layer was acidified with 1M HCl, followed by extraction 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 silica gel

chromatography (middle pressure, linear gradient of chloroform/methanol from 10:0 to 20:1, 20 ml/min, ϕ 50 x 300 mm) to give 1,2-dimethyl-1H-indole-3-carboxylic acid (180 mg, 10%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 2.72 (s, 3H), 3.72 (s, 3H), 7.12 (t, J=7.8Hz, 1H), 2.75 (t, J=8.3Hz, 1H), 7.48 (d, J=7.8Hz, 1H), 7.97 (d, J=7.1Hz, 1H).

MS (ESI) m/z 190 $(M+1)^+$.

(Step 2) Synthesis of (5-chloro-2-fluoro-4-((1,2-dimethyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid



In methylene chloride (8 ml) was dissolved 1,2-dimethyl-1H-indole-3-carboxylic acid (270 mg, 1.43 mmol) was dissolved. Oxalyl chloride (0.19 ml, 2.1 mmol) was added to the solution under stirring at 0°C. The reaction mixture was stirred at room temperature for 1 hour and distilled under reduced pressure to remove the solvent. The residue was dissolved in methylene chloride (6 ml) and the resulting solution was added to a solution of triethylamine (0.56 ml, 4.3 mmol) and ethyl (4-amino-3-chloro-6-fluorophenyl)acetate (331 mg, 1.4 mmol) in methylene chloride (3 ml) under stirring at 0°C. The reaction mixture was heated at reflux for 18 hours. HOBt

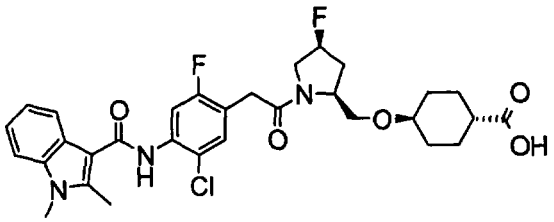
(catalytic amount) was added to the reaction mixture and the mixture was heated under reflux for 48 hours. After cooling, the reaction mixture was added with chloroform and a saturated aqueous solution of citric acid. The mixture was extracted with chloroform. The extract was washed with saturated brine, dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (middle pressure Yamazen, linear gradient of n-hexane/ethyl acetate form 9:1 to 7:3, 20 ml/min, ϕ 50 mm x 150 mm, dry silica gel adsorption method). The purified product was dissolved in THF (15 ml) and to the resulting solution was added 0.25M NaOH (8.6 ml, 2.2 mmol). The mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into 1M HCl to acidify therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (5-chloro-2-fluoro-4-((1,2-dimethyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (264 mg, 49%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 2.70 (s, 3H), 3.65 (s, 2H), 3.77 (s, 3H), 7.21 (m, 2H), 7.58 (d, J=7.3Hz, 1H), 7.93 (m, 1H), 7.99 (d, J=11.8Hz, 1H), 9.06 (s, 1H).

MS (ESI) m/z 375 $(M+1)^+$.

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

((1,2-dimethyl-1H-3-indolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



(5-Chloro-2-fluoro-4-((1,2-dimethyl-1H-3-indolylcarbonyl)amino)phenyl)acetic acid (191 mg, 0.51 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (132 mg, 0.51 mmol), HOBt (131 mg, 0.97 mmol), DMAP (catalytic amount) and EDC·HCl salt (147 mg, 0.77 mmol) were dissolved in DMF (2.5 ml). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was poured into 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, linear gradient of chloroform/methanol from 10:0 to 20:1, 20 ml/min, ϕ 50 mm x 150 mm). The residue was dissolved in THF (5 ml) and to the resulting solution was added 0.25M NaOH (3.1 ml, 0.77 mmol). The resulting

mixture was stirred for 18 hours at room temperature. The reaction mixture was added to 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 (227 mg, 74%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20-1.40 (m, 6H), 1.90 (m, 4H), 2.20 (m, 2H), 2.72 (s, 3H), 3.20 (t, J=10.0Hz, 1H), 3.50 (m, 1H), 3.60-4.00 (m, 3H), 3.75 (s, 3H), 4.12 and 4.35 (2m, total 1H), 5.38 (dd, J=35,55Hz, 1H), 7.20 (m, 2H), 7.48 (dd, J=7.3,11.8Hz, 1H), 7.55 (d, J=8.6Hz, 1H), 7.92 (d, J=8.3Hz, 1H), 7.95 (d, J=5.6Hz, 1H), 9.05 (s, 1H).

MS (ESI) m/z 603 $(M+1)^+$;

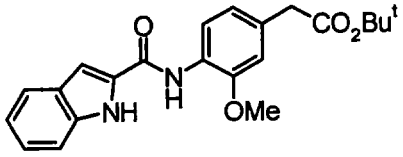
Anal. Calcd for $C_{31}H_{34}ClF_2N_3O_5 \cdot 0.5H_2O$: C, 60.93; H, 5.77; N, 6.88.

Found: C, 61.12; H, 5.75; N, 6.84.

Example 78

trans-4-(1-((4-((2-Indolylcarbonyl)amino)-3-methoxyphenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of tert-butyl (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetate

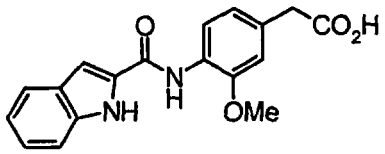


In DMF (10 ml), EDC HCl (1.43 g, 7.45 mmol) was added to indole-2-carboxylic acid (1.00 g, 6.21 mmol), tert-butyl 4-amino-3-methoxyphenylacetate (1.47 g, 6.21 mmol), HOBt (0.42 g, 3.10 mmol), and DMAP (0.38 g, 3.10 mmol). The resulting mixture was stirred at 60°C for 16 hours. Water was added to the 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 (1:1, v/v) eluate fractions, tert-butyl (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetate (1.31 g, 55%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 3.51 (s, 2H), 3.97 (s, 3H), 6.89 (broad s, 1H), 6.91 (d, J=8.1Hz, 1H), 7.00 (broad s, 1H), 7.16 (t, J=8.1Hz, 1H), 7.31 (t, J=8.1Hz, 1H), 7.46 (d, J=8.3Hz, 1H), 7.69 (d, J=8.1Hz, 1H), 8.42 (d, J=8.3Hz, 1H), 8.54 (broad s, 1H), 9.31 (broad s, 1H).

MS (ESI) m/z 381 (M^++1).

(Step 2) Synthesis of (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetic acid

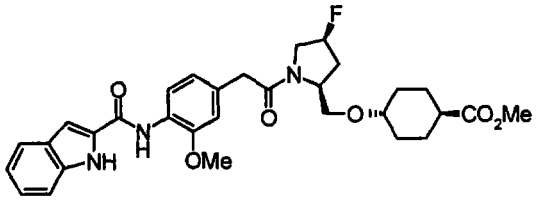


In methylene chloride (20 ml) was dissolved tert-butyl (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetate (1.31 g, 3.44 mmol). To the resulting solution was added TFA (10 ml) at 0°C. After the reaction mixture was stirred at room temperature for 1 hour, the reaction mixture was distilled under reduced pressure to remove the solvent, whereby (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetic acid (1.11 g, 99%) was obtained as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.57 (s, 2H), 3.86 (s, 3H), 6.87 (d, J=8.1Hz, 1H), 7.01 (s, 1H), 7.06 (t, J=7.8Hz, 1H), 7.21 (t, J=7.8Hz, 1H), 7.32 (s, 1H), 7.45 (d, J=8.1Hz, 1H), 7.64 (d, J=8.1Hz, 1H), 7.74 (d, J=8.1Hz, 1H), 9.32 (s, 1H), 11.72 (broad s, 1H).

MS (ESI) m/z 325 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



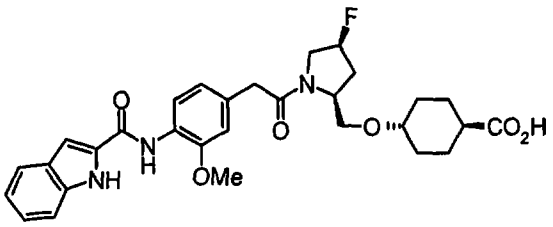
In DMF (6.0 ml) were dissolved (4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetic acid (370 mg, 1.14 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound

synthesized in (Step 3) of Example 21) (296 mg, 1.14 mmol), HOBt (31.0 mg, 0.23 mmol), and DMAP (28.0 mg, 0.23 mmol). To the resulting solution was added EDC HCl (284 mg, 1.48 mmol), followed by stirring at room temperature for 21 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 trans-4-(1-((4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (514 mg, 80%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.33 (m, 2H), 1.39-1.56 (m, 2H), 1.97-2.50 (m, 7H), 3.25 (m, 1H), 3.33 and 3.50 (each m, 1H), 3.62-3.91(m, 8H), 3.96 (s, 3H), 4.25 and 4.38 (each m, total 1H), 5.24 (m, 1H), 6.86 (d, J=8.1Hz, 1H), 6.94 (m, 1H), 7.02 (broad s, 1H), 7.17 (t, J=7.8Hz, 1H), 7.31 (t, J=7.8Hz, 1H), 7.47 (d, J=8.1Hz, 1H), 7.69 (d, J=8.1Hz, 1H), 8.42 (m, 1H), 8.55 (broad s, 1H), 9.52 (broad s, 1H).

MS (ESI) m/z 566 (M^++1).

(Step 4) Synthesis of trans-4-(1-((4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (10 ml) was dissolved methyl trans-4-(1-((4-((2-indolylcarbonyl)amino)-3-methoxyphenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (514 mg, 0.91 mmol). To the resulting solution was added 0.25N NaOH (5.50 ml, 1.36 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was poured into 1N HCl (5.0 ml) to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give the title compound (479 mg, 95%) as a colorless solid.

IR (ATR) ν 3662, 3415, 3278, 2987, 2942, 2900, 1724, 1702, 1658, 1600, 1536, 1486, 1450, 1413 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.12-1.38 (m, 4H), 1.86-2.26 (m, 7H), 3.18 (m, 1H), 3.43-3.91 (m, 9H), 4.15 and 4.32 (each m, total 1H), 5.31 and 5.37 (each m, total 1H), 6.83 (m, 1H), 6.94 and 6.97 (each d, J=1.5Hz, total 1H), 7.06 (t, J=7.8Hz, 1H), 7.21 (t, J=7.8Hz, 1H), 7.32 (d, J=1.5Hz, 1H), 7.45 (d, J=8.1Hz, 1H), 7.64 (d, J=8.1Hz, 1H), 7.71 and 7.72 (each d, J=8.1Hz, total 1H), 9.34 (s, 1H), 11.74 (broad s, 1H), 12.02 (broad s, 1H).

MS (ESI) m/z 552 (M^++1);

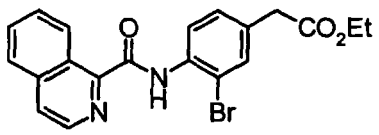
Anal. Calcd for $C_{30}H_{34}FN_3O_6$ $0.25H_2O$: C, 64.79; H, 6.25; N, 7.56.

Found: C, 64.77; H, 6.23; N, 7.40.

Example 79

trans-4-(1-((3-Bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate



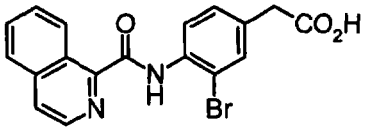
In DMF (15 ml) were dissolved 1-isoquinolinecarboxylic acid (1.00 g, 5.77 mmol), ethyl 4-amino-3-bromophenylacetate (1.49 g, 5.77 mmol), HOBt (0.39 g, 2.89 mmol), and DMAP (0.14 g, 1.15 mmol). To the resulting solution was added EDC HCl (1.33 g, 6.93 mmol). After stirring at 60°C for 5 hours, the reaction mixture was cooled to room temperature. Water 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 (4:1, v/v) eluate fractions, ethyl (3-bromo-4-((1-

isoquinolinylcarbonyl)amino)phenyl)acetate (1.64 g, 69%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.1Hz, 3H), 3.60 (s, 2H), 4.17 (q, J=7.1Hz, 2H), 7.32 (dd, J=8.5,2.0Hz, 1H), 7.57 (d, J=2.0Hz, 1H), 7.71-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.59 (d, J=5.6Hz, 1H), 8.63 (d, J=8.5Hz, 1H), 9.71 (m, 1H), 11.01 (broad s, 1H).

MS (ESI) m/z 413 (M^++1), 415 (M^++3).

(Step 2) Synthesis of (3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid



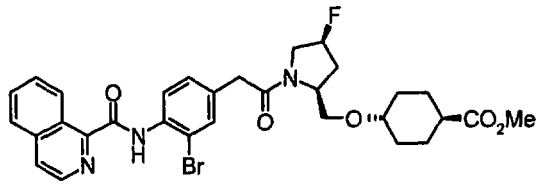
Ethyl (3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate (1.64 g, 3.97 mmol) was dissolved in THF (40 ml). To the resulting solution was added 0.25N NaOH (24.0 ml, 5.95 mmol), and the mixture was stirred at room temperature for 8 hours. The reaction mixture was poured into 1N HCl (50 ml) to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (1.50 g, 98%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.63 (s, 2H), 7.36 (d, J=8.5Hz, 1H), 7.66 (s, 1H), 7.81 (m, 1H), 7.88 (m, 1H), 8.12 (d, J=8.3Hz,

1H), 8.17 (d, J=5.4Hz, 1H), 8.21 (d, J=8.5Hz, 1H), 8.66 (d, J=5.4Hz, 1H), 9.36 (d, J=8.5Hz, 1H), 10.84 (s, 1H).

MS (ESI) m/z 385 (M^++1), 387 (M^++3).

(Step 3) Synthesis of methyl trans-4-(1-((3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



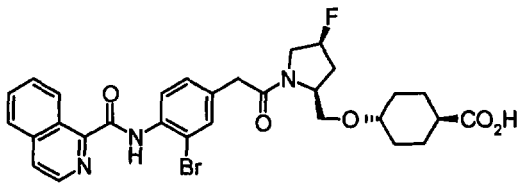
In DMF (5.0 ml) were dissolved (3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (350 mg, 0.91 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (236 mg, 0.91 mmol), HOBt (25.0 mg, 0.18 mmol), and DMAP (22.0 mg, 0.18 mmol). To the resulting solution was added EDC HCl (226 mg, 1.18 mmol) and the mixture was stirred at room temperature for 22 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 trans-4-(1-((3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (575 mg, 100%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.34 (m, 2H), 1.41-1.53 (m, 2H), 1.97-2.52 (m, 7H), 3.27 (m, 1H), 3.35 and 3.51 (each m, total 1H), 3.60-4.03 (m, 8H), 4.22 and 4.39 (each m, total 1H), 5.25 (m, 1H), 7.29 (m, 1H), 7.57 (m, 1H), 7.71-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.59-8.64 (m, 2H), 9.71 (m, 1H), 11.00 (m, 1H).

MS (ESI) m/z 626 (M^++1), 628 (M^++3).

(Step 4) Synthesis of trans-4-(1-((3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(1-((3-bromo-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (575 mg, 0.92 mmol) was dissolved in THF (10 ml), followed by the addition of 0.25N NaOH (5.50 ml, 1.36 mmol). The resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was poured into 1N HCl (5.0 ml) to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give the title compound

(529 mg, 94%) as a pale yellow solid.

IR (ATR) ν 2938, 2857, 1720, 1687, 1596, 1513, 1450 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.42 (m, 4H), 1.86-2.27 (m, 7H), 3.17-3.92 (m, 7H), 4.15 and 4.34 (each m, total 1H), 5.31 and 5.38 (each m, total 1H), 7.32 (m, 1H), 7.58 and 7.60 (each d, J=1.2Hz, total 1H), 7.80 (td, J=8.5, 1.2Hz, 1H), 7.87 (td, J=8.5,1.2Hz, 1H), 8.10 (d, J=8.3Hz, 1H), 8.15 (d, J=5.6Hz, 1H), 8.23 and 8.24 (each d, J=8.3Hz, 1H), 8.65 (d, J=5.6Hz, 1H), 9.39 (d, J=8.5Hz, 1H), 10.84 (s, 1H), 12.00 (s, 1H).

MS (ESI) m/z 612 (M^++1), 614 (M^++3);

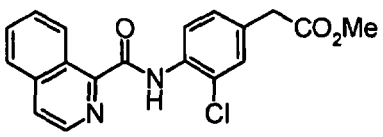
Anal. Calcd for $C_{30}H_{31}BrFN_3O_5$: C, 58.83; H, 5.10; N, 6.86.

Found: C, 58.85; H, 5.27; N, 6.45.

Example 80

trans-4-(1-((3-Chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

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



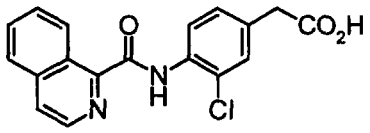
In DMF (15 ml) were dissolved 1-isoquinolinecarboxylic acid (1.00 g, 5.77 mmol), methyl 4-amino-3-chlorophenylacetate (1.23 g, 6.16 mmol), HOBt (0.16 g, 1.15

mmol), and DMAP (0.14 g, 1.15 mmol). To the resulting solution was added EDC HCl (1.33 g, 6.93 mmol), followed by stirring at room temperature for 14 hours. The reaction mixture was poured into water (40 ml). The crystals precipitated were collected by filtration under reduced pressure, washed with water and ether, dried under reduced pressure to give methyl (3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate (1.14 g, 56%) as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.62 (s, 2H), 3.72 (s, 3H), 7.29 (m, 1H), 7.40 (d, J=1.9Hz, 1H), 7.71-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.58 (d, J=5.4Hz, 1H), 8.65 (d, J=8.3Hz, 1H), 9.71 (m, 1H), 11.02 (m, 1H).

MS (ESI) m/z 355 (M^++1).

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



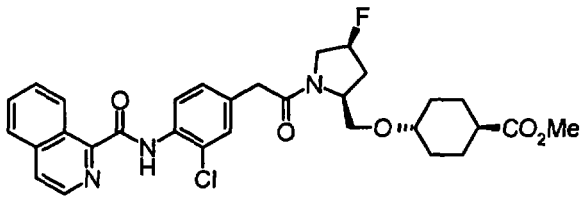
Methyl (3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate (1.14 g, 3.21 mmol) was dissolved in THF (33 ml). To the resulting solution was added 0.25N NaOH (19.3 ml, 4.82 mmol), and the mixture was stirred at room temperature for 14 hours. The reaction mixture was poured into 1N HCl (5.0 ml). 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-isoquinolinylcarbonyl)amino)phenyl)acetic acid (1.07 g, 98%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.63 (s, 2H), 7.33 (dd, J=8.3, 1.7Hz, 1H), 7.51 (d, J=1.7Hz, 1H), 7.81 (td, J=8.3,1.7Hz, 1H), 7.88 (td, J=8.3,1.7Hz, 1H), 8.12 (d, J=8.1Hz, 1H), 8.16 (d, J=5.6Hz, 1H), 8.24 (d, J=8.3Hz, 1H), 8.67 (d, J=5.6Hz, 1H), 9.34 (d, J=8.3Hz, 1H), 10.85 (s, 1H), 12.48 (broad s, 1H).

MS (ESI) m/z 341 (M^++1).

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



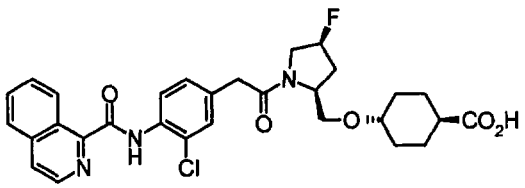
In DMF (7.5 ml) were dissolved (3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (250 mg, 0.73 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (190 mg, 0.73 mmol), HOBt (20.0 mg, 0.15 mmol), and DMAP (18.0 mg, 0.15 mmol). To the resulting solution was added EDC HCl (211 mg, 1.10 mmol), followed by stirring at room temperature for 19 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 trans-4-(1-((3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (399 mg, 94%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ 1.21-1.30 (m, 2H), 1.44-1.50 (m, 2H), 1.98-2.48 (m, 7H), 3.27 (m, 1H), 3.35 and 3.52 (each m, total 1H), 3.60-3.93 (m, 8H, including each singlet, total 3H, at δ: 3.65 and 3.67), 4.23 and 4.39 (each m, total 1H), 5.26 (m, 1H), 7.24 (m, 1H), 7.40 (m, 1H), 7.71-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.59 (d, J=5.4Hz, 1H), 8.64 (m, 1H), 9.71 (m, 1H), 11.02 (m, 1H).

MS (ESI) m/z 582 (M^++1).

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



Methyl trans-4-(1-((3-chloro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-

(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (399 mg, 0.69 mmol) was dissolved in THF (7.0 ml). To the resulting solution was added 0.25N NaOH (4.11 ml, 1.03 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was poured into 1N HCl (1.1 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 (347 mg, 89%) as a yellow solid.

IR (ATR) ν 2935, 2861, 1716, 1596, 1527, 1442 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.41 (m, 4H), 1.85-2.25 (m, 7H), 3.17-3.89 (m, 7H), 4.14 and 4.34 (each m, total 1H), 5.32 and 5.39 (each m, total 1H), 7.28 (m, 1H), 7.44 and 7.45 (m, total 1H), 7.81 (t, J=7.1Hz, 1H), 7.88 (t, J=7.1Hz, 1H), 8.12 (d, J=8.1Hz, 1H), 8.16 (d, J=5.6Hz, 1H), 8.22 (m, 1H), 8.67 (d, J=5.6Hz, 1H), 9.31 (d, J=8.5Hz, 1H), 10.84 (s, 1H), 12.02 (broad s, 1H).

MS (ESI) m/z 568 (M^++1);

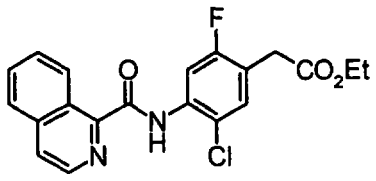
Anal. Calcd for $C_{30}H_{31}ClFN_3O_5$: C, 63.43; H, 5.50; N, 7.40.
Found: C, 63.40; H, 5.62; N, 7.40.

Example 81

trans-4-(1-((5-Chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

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

isoquinolinylcarbonyl)amino)phenyl)acetate



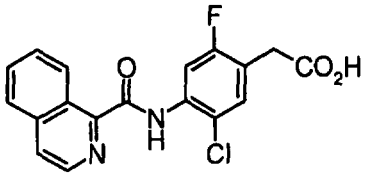
In methylene chloride (15 ml), diphenylphosphinic chloride (0.99 ml, 5.19 mmol) was added to 1-isoquinolinecarboxylic acid (375 mg, 2.17 mmol), ethyl 4-amino-3-chlorophenylacetate (501 mg, 2.17 mmol), and triethylamine (1.32 ml, 9.53 mmol), followed by stirring at room temperature for 24 hours. Water was added to the reaction mixture to separate therefrom an organic layer. The methylene chloride layer 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 n-hexane-ethyl acetate (3:1, v/v) eluate fractions, ethyl (5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate (690 mg, 82%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.1Hz, 3H), 3.64 (s, 2H), 4.19 (q, J=7.1Hz, 2H), 7.36 (d, J=7.2Hz, 1H), 7.72-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.57- 8.60 (m, 2H), 9.68 (m, 1H), 11.11 (broad s, 1H).

MS (ESI) m/z 387 (M^++1).

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

isoquinolinylcarbonyl)amino)phenyl)acetic acid

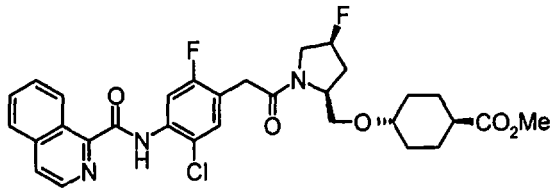


Ethyl (5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetate (690 mg, 1.78 mmol) was dissolved in THF (18 ml). To the resulting solution was added 0.25N NaOH (10.7 ml, 2.68 mmol), and the resulting mixture was stirred at room temperature for 7 hours. The reaction mixture was poured into 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 (5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (583 mg, 91%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.66 (s, 2H), 7.62 (d, J=7.5Hz, 1H), 7.82 (m, 1H), 7.88 (m, 1H), 8.12 (d, J=8.5Hz, 1H), 8.18 (d, J=5.6Hz, 1H), 8.23 (d, J=11.5Hz, 1H), 8.67 (d, J=5.6Hz, 1H), 9.38 (d, J=8.5Hz, 1H), 10.98 (broad s, 1H), 12.59 (broad s, 1H).

MS (ESI) m/z 359 (M^++1).

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



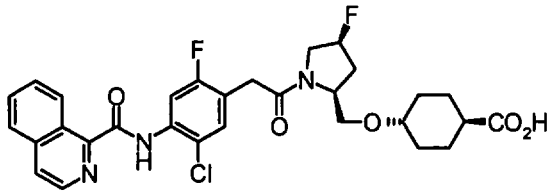
In DMF (5.5 ml) were dissolved (5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.56 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (145 mg, 0.56 mmol), HOBt (15.0 mg, 0.11 mmol), and DMAP (14.0 mg, 0.11 mmol). To the resulting solution was added EDC HCl (160 mg, 0.84 mmol), followed by stirring at room temperature for 21 hours. 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 ethyl acetate eluate fractions, methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (341 mg, 100%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.33 (m, 2H), 1.40-1.54 (m, 2H), 1.97-2.54 (m, 7H), 3.28 (m, 1H), 3.36 and 3.53 (each m, total 1H), 3.64 and 3.66 (each s, total 3H), 3.66-4.03 (m, 5H), 4.31 and 4.37 (each m, total 1H), 5.27 and 5.29 (each

m, total 1H), 7.41 and 7.43 (each d, J=7.3Hz, total 1H), 7.72-7.78 (m, 2H), 7.88-7.91 (m, 2H), 8.54 and 8.58 (each d, J=9.7Hz, total 1H), 8.56 (d, J=5.6Hz, 1H), 9.68 (m, 1H), 11.09 (d, J=8.1Hz, 1H).

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

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



To methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (341 mg, 0.57 mmol) were added THF (5.8 ml) was added 0.25N NaOH (3.40 ml, 0.85 mmol), followed by stirring at room temperature for 14 hours. The reaction mixture was poured into 1N HCl (1.0 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 (291 mg, 87%) as a yellow solid.

IR (ATR) ν 3282, 2940, 2863, 1722, 1693, 1650, 1619, 1581, 1517 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.15-1.41 (m, 4H), 1.86-2.33 (m, 7H), 3.17-4.00 (m, 7H), 4.13 and 4.36 (each m, total 1H), 5.32

and 5.41 (each m, total 1H), 7.49 and 7.53 (each d, J=7.3Hz, total 1H), 7.82 (t, J=7.3Hz, 1H), 7.88 (t, J=7.3Hz, 1H), 8.12 (d, J=8.1Hz, 1H), 8.18-8.23 (m, 2H), 8.67 (d, J=5.6Hz, 1H), 9.38 (d, J=8.8Hz, 1H), 10.95 (m, 1H), 12.02 (broad s, 1H).

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

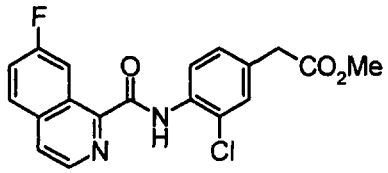
Anal. Calcd for $C_{30}H_{30}ClF_2N_3O_5$ $0.25H_2O$: C, 61.02; H, 5.21; N, 7.12.

Found: C, 61.01; H, 5.17; N, 7.00.

Example 82

trans-4-(1-((3-Chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetate



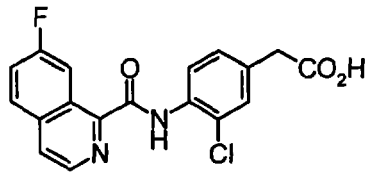
In DMF (5 ml) were dissolved 7-fluoro-1-isoquinolinecarboxylic acid (250 mg, 1.31 mmol), methyl 4-amino-3-chlorophenylacetate (262 mg, 1.31 mmol), HOBt (catalytic amount), and DMAP (192 m g, 1.57 mmol). To the resulting solution was added EDC HCl (290 mg, 6.93 mmol), followed by stirring at room temperature for 14 hours. The reaction mixture was poured into water (20 ml). The

crystals thus precipitated were collected by filtration under reduced pressure, washed with ether and then dried under reduced pressure to give methyl (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetate (250 mg, 51%) as a colorless crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 3.62 (s, 2H), 3.72 (s, 3H), 7.25 9.45 (series of m, 9H).

MS (ESI) m/z 323 (M^++1).

(Step 2) Synthesis of (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetic acid

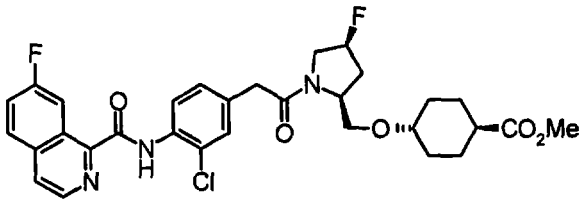


In THF (5 ml), 0.25N NaOH (4 ml, 4.82 mmol) was added to methyl (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetate (100 mg, 0.27 mmol) and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into 1N HCl (2.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (75 mg, 78%) as a colorless solid.

MS (ESI) m/z 359 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((3-chloro-4-((7-

fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



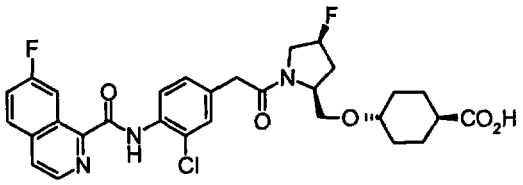
In DMF (5 ml) were suspended (3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetic acid (57 mg, 0.159 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (42 mg, 0.159 mmol), HOBt (catalytic amount), and DMAP (24 mg, 0.191 mmol). To the resulting suspension was added EDC HCl (37 mg, 0.191 mmol), followed by stirring at room temperature for 20 hours. The reaction mixture was poured into 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 trans-4-(1-((3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (105 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$) δ 1.21-1.31 (m, 2H), 1.44-1.51 (m, 2H), 1.98-2.49 (m, 7H), 3.27 (m, 1H), 3.35 and 3.52 (each m,

total 1H), 3.60-3.93 (m, 8H), 4.23 and 4.39 (each m, total 1H), 5.26 (m, 1H), 7.26 (m, 1H), 7.41 (m, 1H), 7.56 (m, 1H), 7.90 and 7.92 (each m, 2H), 8.59 and 8.63 (each m, 2H), 9.46 (m, 1H), 11.01 (br d, 1H).

MS (ESI) m/z 560 (M^++1).

(Step 4) Synthesis of trans-4-(1-((3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In THF (5 ml), 0.25N NaOH (1.9 ml) was added to methyl trans-4-(1-((3-chloro-4-((7-fluoro-1-isoquinolinylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (95 mg, 0.15 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was poured into 1N HCl (2 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 (65 mg, 71%) as a colorless crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 1.13-1.40 (m, 4H), 1.80-2.30 (m, 7H), 3.15-3.90 (m, 7H), 4.10 and 4.35 (each m, total 1H), 5.30 and 5.40 (each m, total 1H), 7.25 (m, 1H), 7.41 (m, 1H), 7.54 (m, 1H), 7.89 (m, 1H), 7.92 (m, 1H), 8.59 (m, 1H),

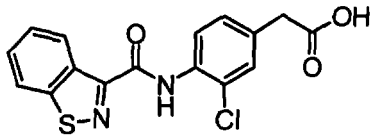
8.62 (m, 1H), 9.45 (m, 1H), 11.01 (br d, 1H).

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

Example 83

trans-4-(1-(3-Chloro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 3-chloro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetic acid



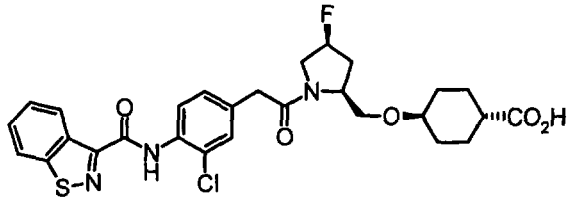
Methyl 4-amino-3-chlorphenylacetate (50 mg, 0.25 mmol), 3-benzo(d)isothiazole-3-carboxylic acid (45 mg, 0.25 mmol), HOBt (64 mg, 0.475 mmol), EDC (72 mg, 0.38 mmol) and DMAP (catalytic amount) were dissolved in DMF (2 ml). The resulting solution was stirred for 8 hours. The reaction mixture was poured into 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 THF/methanol (4 ml, 3:1) and 1M NaOH (1 ml) and the resulting mixture was stirred for 18 hours at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue 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 3-chloro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetic acid (80 mg, 92%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 7.30 (d, J=8.1Hz, 1H), 7.50 (s, 1H), 7.64 (d, J=8.1Hz, 1H), 7.70 (d, J=8.1Hz, 1H), 7.95 (d, J=8.3Hz, 1H), 8.36 (d, J=8.1Hz, 1H), 8.80 (d, J=8.1Hz, 1H), 10.27 (s, 1H).

MS (ESI) m/z 347 $(M+1)^+$.

(Step 2) Synthesis of trans-4-(1-(3-chloro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (1.2 ml) were dissolved 3-chloro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenylacetic acid (80 mg, 0.23 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (60 mg, 0.23 mmol), HOBt (59 mg, 0.44 mmol), DMAP (catalytic amount) and EDC·HCl (66 mg, 0.35 mmol). The resulting solution 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. To the residue were added THF (2.1 ml) and 0.25M NaOH (1.26 ml, 0.32 mmol) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in ice water and acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The crude crystals thus obtained were recrystallized from chloroform/n-hexane to give the title compound (85 mg, 64%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (m, 6H), 1.82-2.20 (m, 6H), 3.20 (m, 1H), 3.50-4.40 (m, 6H), 5.36 (m, 1H), 7.26 (t, J=7.7Hz, 1H), 7.64 (t, J=7.4Hz, 1H), 7.71 (t, J=7.4Hz, 1H), 7.94 (dd, J=4.9,8.3Hz, 1H), 8.36 (d, J=8.3Hz, 1H), 8.80 (d, J=8.3Hz, 1H), 10.27 (s, 1H).

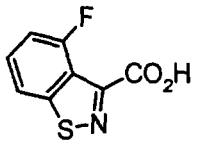
MS (ESI) m/z 575 $(M+1)^+$.

Anal. Calcd for $C_{28}H_{29}ClFN_3O_5S$: C, 58.58; H, 5.13; N, 7.02.
Found: C, 58.58; H, 5.13; N, 7.02.

Example 84

trans-4-(1-(5-Chloro-2-fluoro-4-((4-fluoro-3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 4-fluorobenzo(d)isothiazole-3-carboxylic acid



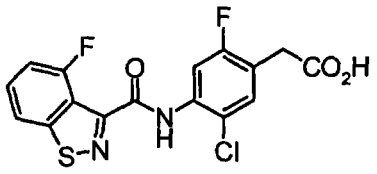
3-Fluorobenzenethiol (5.0 g, 39.0 mmol) was dissolved in methylene chloride (200 ml), and oxalyl chloride (3.57 ml, 41.0 mmol) and triethylamine (5.71 ml, 41.0 mmol) were added to the solution under stirring at 0°C. The reaction mixture was stirred for 24 hours at room temperature. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was suspended in methylene chloride (100 ml). After aluminum chloride (7.8 g, 58.5 mmol) was added to the reaction mixture under cooling at 0°C, the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in ice water, 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. To the residue were added concentrated aqueous ammonia (28%, 50 ml) and hydrogen peroxide (35% in water, 50 ml) and the mixture was stirred at room temperature for 24 hours. The crystals thus precipitated were collected by filtration and added with THF (100 ml) and 0.25M NaOH (60 ml, 15 mmol). The resulting mixture was heated under reflux for 24 hours. The reaction mixture was cooled to room temperature and poured in 1M HCl. The mixture was concentrated to dryness under reduced pressure. The

residue was purified with chromatography on a silica gel column (middle pressure chromatography system Yamazen, C-18 column, linear gradient of H_2O (0.1% HCOOH) and methanol (0.1% HCOOC) from 10% to 90%, 10 ml/min) to give 4-fluorobenzo(d)isothiazole-3-carboxylic acid (590 mg, 8%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 7.51 (dt, J=2.5,9.1Hz, 1H), 8.19 (dd, J=2.5,8.8Hz, 1H), 8.66 (dd, J=5.1,9.1Hz, 1H).

MS (ESI) m/z 198 $(M+1)^+$.

(Step 2) Synthesis of (5-chloro-2-fluoro-4-((4-fluoro-3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid

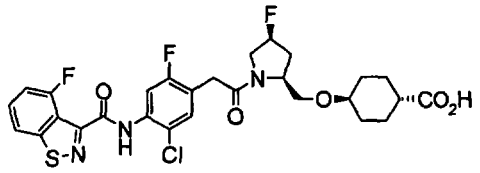


In DMF (10 ml) were dissolved 4-fluorobenzo(d)isothiazole-3-carboxylic acid (240 mg, 1.22 mmol), ethyl 4-amino-5-chloro-2-fluorophenylacetate (282 mg, 1.22 mmol), HOBt (313 mg, 2.32 mmol), EDC HCl (351 mg, 1.83 mmol) and DMAP (catalytic amount). The resulting solution was stirred for 4 days at room temperature. 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 chromatography system from Yamazen, chloroform, 8 ml/min, ϕ 15 mm x 300 mm). To the resulting ester were added THF (12 ml) and 0.25M NaOH (7.32 ml, 1.83 mmol), followed by stirring at room temperature for 4 hours. The reaction mixture was poured in 1M HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (5-chloro-2-fluoro-4-((4-fluoro-3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid (105 mg, 22%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.28 (t, J=7.2Hz, 3H), 3.64 (s, 2H), 4.19 (q, J=7.2Hz, 2H), 7.34 (dt, J=2.2,9.1Hz, 1H), 7.37 (d, J=7.1Hz, 1H), 7.64 (dd, J=2.2,8.3Hz, 1H), 8.48 (d, J=11.5Hz, 1H), 9.00 (dd, J=5.1, 9.0Hz, 1H), 9.92 (s, 1H).

(Step 3) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-((4-fluoro-3-benzo(d)isothiazolylcarbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (3 ml) were dissolved (5-chloro-2-fluoro-4-((4-fluoro-3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid (105

mg, 0.27 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (71 mg, 0.27 mmol), HOBt (70 mg, 0.52 mmol), DMAP (catalytic amount) and EDC·HCl salt (79 mg, 0.41 mmol). The resulting solution 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, whereby a crude ester was obtained. The crude ester was added with THF (3.0 ml) and 0.25M NaOH (1.6 ml, 0.4 mmol) and the mixture was stirred at room temperature for 18 hours The reaction mixture was poured in 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure. The crude crystals were purified by C-18 column chromatography (middle pressure chromatography, linear gradient water/methanol, 10%-90%) to give the title compound (69 mg, 41%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.20 (m, 4H), 1.95 (m, 4H), 2.05 (m, 2H), 3.50-4.00 (m, 6H), 4.05 and 4.20 (2m, total 1H), 5.40 (m, 1H), 7.53 (m, 3H), 7.93 (m, 1H), 8.25 (dd, J=2.2,8.6Hz, 1H), 8.81 (dd, J=5.6,9.2Hz, 1H), 10.30 (m, 1H).

MS (ESI) m/z 611 $(M+1)^+$.

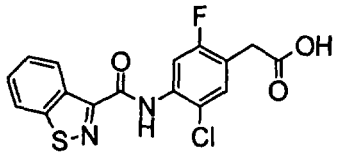
Anal. Calcd for $C_{28}H_{27}ClF_3N_3O_5$ 1.0 H_2O: C, 53.55; H, 4.65; N, 6.69.

Found: C, 53.3; H, 4.35; N, 6.68.

Example 85

trans-4-(1-(5-Chloro-2-fluoro-(4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of (5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid



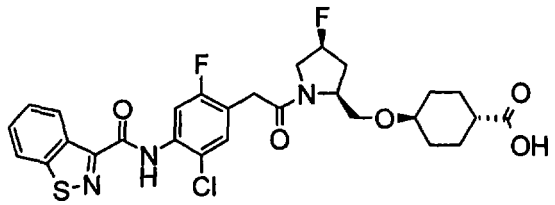
Methyl 4-amino-5-chloro-2-fluorophenylacetate (753 mg, 3.25 mmol), benzo(d)isothiazole-3-carboxylic acid (583 mg, 3.25 mmol), HOBt (834 mg, 6.18 mmol), EDC HCl (934 mg, 4.88 mmol) and DMAP (catalytic amount) were dissolved in DMF (16 ml). The resulting solution was stirred for 10 hours at 80°C. After cooling, 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, n-hexane/ethyl acetate 9:1, 15 ml/min, ϕ 50 x 300 mm) to give ethyl (5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetate. The

resulting ester was dissolved in THF/methanol (4 ml, 3:1), and to the resulting solution was added 1M NaOH (1 ml). The mixture was stirred for 18 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was poured in 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid (354 mg, 30%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.68 (s, 2H), 7.65 (d, J=7.3Hz, 1H), 7.66 (t, J=7.5Hz, 1H), 7.73 (t, J=7.5Hz, 1H), 7.99 (d, J=11.2Hz, 1H), 8.38 (d, J=8.3Hz, 1H), 8.81 (d, J=7.8Hz, 1H), 10.30 (s, 1H).

MS (ESI) m/z 365 $(M+1)^+$.

(Step 2) Synthesis of trans-4-(1-(5-chloro-2-fluoro-(4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (1.2 ml) were dissolved (5-chloro-2-fluoro-4-((3-benzo(d)isothiazolylcarbonyl)amino)phenyl)acetic acid (80 mg, 0.23 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound

synthesized in (Step 3) of Example 21) (60 mg, 0.23 mmol), HOBt (59 mg, 0.44 mmol), DMAP (catalytic amount) and EDC·HCl (66 mg, 0.35 mmol). The resulting solution 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 dissolved in THF (2.1 ml) and to the resulting solution was added 0.25M NaOH (1.26 ml, 0.32 mmol). The mixture was stirred for 18 hours at room temperature. The reaction mixture was poured in ice water and acidified with 1M HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure. The crude crystals thus obtained were recrystallized from chloroform/n-hexane to give the title compound (85 mg, 64%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ 1.10-1.40 (m, 6H), 1.82-2.20 (m, 6H), 3.20 (m, 1H), 3.50-4.40 (m, 6H), 5.36 (m, 1H), 7.26 (t, J=7.7Hz, 1H), 7.64 (t, J=7.4Hz, 1H), 7.71 (t, J=7.4Hz, 1H), 7.94 (dd, J=4.9,8.3Hz, 1H), 8.36 (d, J=8.3Hz, 1H), 8.80 (d, J=8.3Hz, 1H), 10.27 (s, 1H).

MS (ESI) m/z 575 $(M+1)^+$;

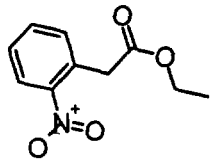
Anal. Calcd for $C_{28}H_{29}ClFN_3O_5S$: C, 58.58; H, 5.13; N, 7.02.

Found: C, 58.58; H, 5.13; N, 7.02.

Example 86

trans-4-(1-(4-((Benzo(d)isothiazole-3-carbonyl)amino)-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl (2-nitrophenyl)acetate



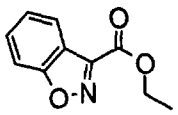
In ethanol (250 ml) was dissolved (2-nitrophenyl)acetic acid (18.5 g, 0.102 mmol), and to the resulting solution was added concentrated H_2SO_4 (0.1 ml). The mixture was heated under reflux for 24 hours. The reaction mixture was cooled to room temperature and then, diluted with ethyl acetate. The diluted solution 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, whereby ethyl (2-nitrophenyl)acetate (17.4 g, 82%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 1.25 (t, J=7.1Hz, 3H), 4.02 (s, 2H), 4.17 (q, J=7.1Hz, 2H), 7.35 (d, J=7.6Hz, 1H), 7.47 (dt, J=1.5,8.0Hz, 1H), 7.59 (dt, J=1.5,7.6Hz, 1H), 8.10 (dd, J=1,2,8.1Hz, 1H).

MS (ESI) m/z 208 $(M-1)^+$.

(Step 2) Synthesis of ethyl benzo(d)isoxazole-3-

carboxylate



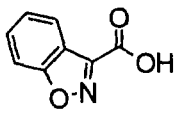
Ethyl 2-nitrophenyl)acetate (12.3 g, 58.6 mmol) and isoamyl nitrate (8.92 g, 76.1 mmol) were dissolved in ethanol (100 ml). Sodium methoxide (19.9 ml, 58.6 mmol, a 20% solution in ethanol) was added, followed by stirring at 50°C for 1.5 hours. The reaction mixture was cooled to room temperature and neutralized with 1M HCl (30 ml), followed by extraction with ether. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent. The residue was crystallized by the addition of chloroform/n-hexane and the crystals were dried under reduced pressure for 18 hours. The crystals thus obtained were dissolved in 1,2-dimethoxyethane (100 ml) and to the resulting solution, a solution of sodium hydride (2.81 g, 70.3 mmol) in 1,2-dimethoxyethane (100 ml) was added in portions. The reaction mixture was stirred at 150°C for 8 hours. Under cooling, the reaction mixture was poured to a saturated aqueous solution of sodium bicarbonate, followed by extraction with ether. 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 chromatography system Yamazen, n-hexane/ethyl acetate 9:1, 20 ml/min, ϕ 80 x 300) to give ethyl benzo(d)isoxazole-3-carboxylate (5.75 g, 51%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.50 (m, 3H), 4.56 (m, 2H), 7.45 (dt, J=1.2, 6.8Hz, 1H), 7.62 (dt, J=1.2,8.5Hz, 1H), 7.66 (dt, J=1.0,8.5Hz, 1H), 8.14 (dd, J=1.0,8.0Hz, 1H).

MS (ESI) m/z 192 $(M+1)^+$.

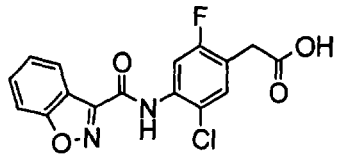
(Step 3) Synthesis of benzo(d)isoxazole-3-carboxylic acid



To ethyl benzo(d)isoxazole-3-carboxylate (2.0 g, 10.5 mmol) was added 50 ml of 70% H_2SO_4. The mixture was heated at 80°C for 4 hours. The reaction mixture was poured in ice, followed by extraction with ether. The extract was dried over anhydrous magnesium sulfate and distilled under reduced pressure to remove the solvent, whereby benzo(d)isoxazole-3-carboxylic acid (980 mg, 57%) was obtained as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 7.53 (dt, J=1.0,7.1Hz, 1H), 7.74 (dt, J=1.2,7.1Hz, 1H), 7.89 (dd, J=1.0,8.5Hz, 1H), 8.10 (dt, J=1.0,8.1Hz, 1H).

(Step 4) Synthesis of (4-((benzo(d)isoxazole-3-carbonyl)amino)-5-chloro-2-fluorophenylacetic acid



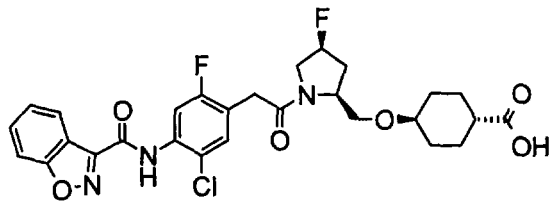
Benzo(d)isoxazole-3-carboxylic acid (475 mg, 2.91 mmol), ethyl 4-amino-5-chloro-2-fluorophenylacetate (675 mg, 2.91 mmol), HOBt (747 mg, 5.53 mmol), EDC HCl (837 mg, 4.37 mmol) and DMAP (catalytic amount) were dissolved in DMF (15 ml). The resulting solution was stirred for 24 hours at room temperature. 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 chromatography system from Yamazen, chloroform, 8 ml/min, ϕ 15 mm x 300 mm). The ester thus obtained was added with THF (30 ml) and 0.25M NaOH (17.5 ml, 4.37 mmol), followed by stirring at room temperature for 18 hours. The reaction mixture was poured in 1M HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (4-((benzo(d)isoxazole-3-carbonyl)amino)-5-chloro-2-fluorophenyl)acetic acid (100 mg, 10%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 3.66 (s, 2H), 7.58 (t, J=8.0Hz, 1H),

7.62 (d, J=7.1Hz, 1H), 7.68 (d, J=11.4Hz, 1H), 7.79 (d, J=9.0Hz, 1H), 8.15 (d, J=8.8Hz, 1H), 10.61 (d, J=4.2Hz, 1H).

MS (ESI) m/z 349 $(M+1)^+$.

(Step 5) Synthesis of trans-4-(1-(4-((benzo(d)isothiazole-3-carbonyl)amino)-5-chloro-2-fluorophenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



In DMF (3 ml) were dissolved (4-((benzo(d)isoxazole-3-carbonyl)amino)-5-chloro-2-fluorophenyl)acetic acid (100 mg, 0.29 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (74 mg, 0.29 mmol), HOBt (74 mg, 0.55 mmol), DMAP (catalytic amount) and EDC·HCl salt (83 mg, 0.43 mmol). The resulting solution 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. The ester thus obtained was added with THF (3.0 ml) and 0.25M NaOH (1.7 ml, 0.43 mmol), followed by stirring for 18 hours

at room temperature. The reaction mixture was poured in ice 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 (100 mg, 61%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.05-1.50 (m, 4H), 1.95 (m, 4H), 2.04 (m, 2H), 3.50-4.00 (m, 6H), 4.05 and 4.08 (2m, total 1H), 5.40 (m, 1H), 7.52 (m, 2H), 7.63 (m, 1H), 7.79 (t, J=7.8Hz, 1H), 7.94 (d, J=8.3Hz, 1H), 8.16 (d, J=8.1Hz, 1H), 10.65 (br, 1H), 12.05 (br, 1H).

MS (ESI) m/z 576 $(M+1)^+$.

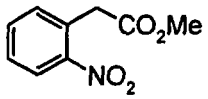
Anal. Calcd for $C_{28}H_{28}ClF_2N_3O_6$: C, C, 58.39; H, 4.90; N, 7.30.

Found: C, 58.19; H, 4.87; N, 7.18.

Example 87

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

(Step 1) Synthesis of methyl (2-nitrophenyl)acetate

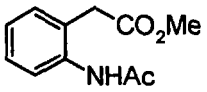


To (2-nitrophenyl)acetic acid (25.0 g, 0.14 mol) were added methanol (100 ml) and concentrated sulfuric acid (3.0 ml). The resulting mixture was heated under reflux for 10

hours. The reaction mixture was cooled to room temperature and then, distilled under reduced pressure to remove the solvent. The residue was dissolved in 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. The residue was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (2:1, v/v) eluate fractions, methyl (2-nitrophenyl)acetate (26.6 g, 97%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.72 (s, 3H), 4.03 (s, 2H), 7.36 (dd, J=7.3, 1.2Hz, 1H), 7.45 (m, 1H), 7.60 (m, 1H), 8.11 (dd, J=8.1,1.2Hz, 1H).

(Step 2) Synthesis of methyl (2-acetamidophenyl)acetate

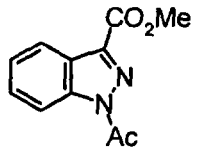


Methyl (2-nitrophenyl)acetate (26.6 g, 0.14 mol) and acetic anhydride (51.5 ml, 0.55 mol) were subjected to catalytic hydrogenation for 15 hours in toluene (150 ml) in the presence of 10% Pd/C (53.2% wet, 4.5 g). The reaction mixture was filtered to remove therefrom the catalyst, followed by washing with toluene. The filtrate was distilled under reduced pressure to remove the solvent. The residue was crystallized by the addition thereto of n-hexane and diisopropyl ether. The crystals thus

precipitated were collected by filtration, washed with n-hexane, and dried under reduced pressure to give methyl (2-acetamidophenyl)acetate (24.3 g, 84%) as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.21 (s, 3H), 3.63 (s, 2H), 3.72 (2, 3H), 7.11 (m, 1H), 7.20 (d, J=7.3Hz, 1H), 7.30 (m, 1H), 7.83 (d, J=8.1Hz, 1H), 8.68 (broad s, 1H).

(Step 3) Synthesis of methyl 1-acetylindazole-3-carboxylate

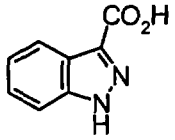


Methyl (2-acetamidophenyl)acetate (24.3 g, 0.12 mol) and acetic anhydride (24.3 ml, 0.26 mmol) were dissolved in acetic acid (60 ml). To the resulting solution, tert-butyl nitrite (90% purity, 18.6 ml, 0.14 mol) was added dropwise over 20 minutes under stirring at 90°C. After completion of the dropwise addition, the reaction mixture was stirred at 90°C for further 1 hour. The reaction mixture was cooled to room temperature and then, poured in water (500 ml), followed by stirring for 1 hour. The crystals thus precipitated were collected by filtration under reduced pressure and dissolved in chloroform. The chloroform solution 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, whereby methyl 1-acetylindazole-3-carboxylate (22.3 g, 85%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 2.88 (s, 3H), 4.09 (s, 3H), 7.46 (m, 1H), 7.61 (m, 1H), 8.22 (dd, J=8.1,1.0Hz, 1H), 8.46 (dd, J=8.6,1.0Hz, 1H).

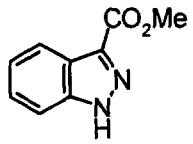
(Step 4) Synthesis of indazole-3-carboxylic acid



To methyl 1-acetylindazole-3-carboxylate (22.3 g, 0.10 mol) were added sodium hydroxide (8.18 g, 0.20 mol) and water (640 ml) and the resulting mixture was stirred at 60 to 70°C for 6.5 hours. The reaction mixture was poured in concentrated HCl (30 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give indazole-3-carboxylic acid (17.6 g, 100%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 7.29 (m, 1H), 7.44 (m, 1H), 7.65 (d, J=8.6Hz, 1H), 8.10 (d, J=8.1Hz, 1H), 12.96 (broad s, 1H), 13.77 (broad s, 1H).

(Step 5) Synthesis of methyl indazole-3-carboxylate

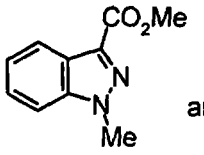
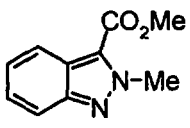


Indazole-3-carboxylic acid (5.00 g, 30.8 mmol) was dissolved in THF (200 ml) and methanol (15 ml). To the resulting solution was added (trimethylsilyl)diazomethane (a 2.0M n-hexane solution, 20 ml, 40.1 mmol) under stirring at 0°C. After stirring at room temperature for 3 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was crystallized by the addition of n-hexane, and the crystals thus obtained were collected by filtration and dried under reduced pressure to give methyl indazole-3-carboxylate (3.71 g, 68%) as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 4.07 (s, 3H), 7.34 (m, 1H), 7.47 (m, 1H), 7.70 (d, J=8.3Hz, 1H), 8.24 (d, J=8.3Hz, 1H), 11.83 (broad s, 1H).

MS (ESI) m/z 177 (M^++1).

(Step 6) Synthesis of methyl 1-methylindazole-3-carboxylate and methyl 2-methylindazole-3-carboxylate


and


Methyl indazole-3-carboxylate (3.71 g, 21.1 mmol) was dissolved in DMF (40 ml). To the resulting solution was added sodium hydride (60% in oil, 1.01 g, 25.3 mmol) in

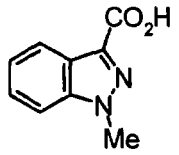
portions under stirring at 0°C. The reaction mixture was stirred at the same temperature for 30 minutes. Methyl iodide (1.57 ml, 25.3 mmol) was added to the mixture. The resulting mixture was stirred at the same temperature for 30 minutes. A saturated aqueous solution of ammonium chloride was added and 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, whereby from n-hexane-ethyl acetate (3:1, v/v) eluate fractions, methyl 2-methylindazole-3-carboxylate (1.62 g, 26%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 4.03 (s, 3H), 4.52 (s, 3H), 7.28 (m, 1H), 7.35 (m, 1H), 7.76 (d, J=8.3Hz, 1H), 8.00 (d, J=8.3Hz, 1H).
MS (ESI) m/z 191 (M^++1).

From n-hexane-ethyl acetate (1:1, v/v) eluate fractions, 1-methylindazole-3-carboxylate (4.52 g, 73%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 4.04 (s, 3H), 4.17 (s, 3H), 7.31-7.35 (m, 2H), 7.46 (d, J=4.4Hz, 1H), 8.22 (d, J=8.1Hz, 1H).
MS (ESI) m/z 191 (M^++1).

(Step 7) Synthesis of 1-methylindazole-3-carboxylic acid

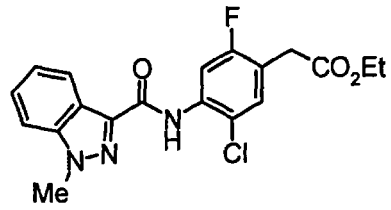


In THF (250 ml) was dissolved methyl 1-methylindazole-3-carboxylate (4.49 g, 23.6 mmol). To the resulting solution was added 0.25N NaOH (145 ml, 35.4 mmol), followed by stirring at room temperature for 24 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl (145 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give 1-methylindazole-3-carboxylic acid (2.81 g, 68%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 4.15 (s, 3H), 7.32 (m, 1H), 7.48 (m, 1H), 7.75 (d, J=8.1Hz, 1H), 8.08 (d, J=8.1Hz, 1H), 12.96 (broad s, 1H).

MS (ESI) m/z 177 (M^++1).

(Step 8) Synthesis of ethyl (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetate



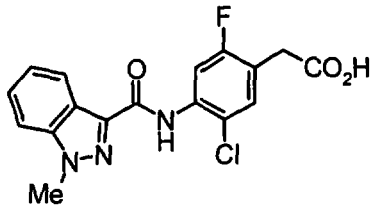
In benzene (30 ml), oxalyl chloride (0.54 ml, 6.24 mmol) was added dropwise to 1-methylindazolyl-3-carboxylic acid (1.00 g, 5.68 mmol) and DMF (44.0 µl, 0.57 mmol) under

stirring at room temperature. After completion of the dropwise addition, the reaction mixture was stirred at room temperature for 1 hour. A solution of ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (1.31 g, 5.68 mmol) and triethylamine (4.74 ml, 34.0 mmol) in benzene (5.0 ml), which solution had been prepared in advance, was added to the reaction mixture. The resulting mixture was heated under reflux for 4 hours. The reaction mixture was cooled to room temperature, 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, (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetate (1.40 g, 63%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, J=7.1Hz, 3H), 3.62 (s, 2H), 4.17 (s, 3H), 4.18 (q, J=7.1Hz, 2H), 7.33-7.39 (m, 2H), 7.44-7.50 (m, 2H), 8.38 (d, J=8.3Hz, 1H), 8.53 (d, J=11.9Hz, 1H), 9.50 (broad s, 1H).

MS (ESI) m/z 390 (M^++1).

(Step 9) Synthesis of (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid

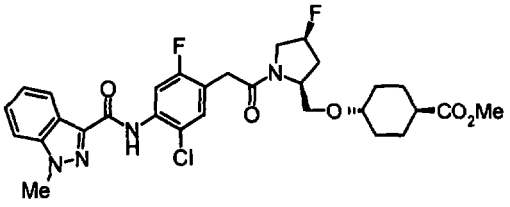


To ethyl (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetate (1.40 g, 3.59 mmol) were added THF (36 ml) and 0.25N NaOH (21.5 ml, 5.39 mmol). The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was poured in 1N HCl (6.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (1.23 g, 95%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 3.65 (s, 2H), 4.21 (s, 3H), 7.37 (m, 1H), 7.53 (m, 1H), 7.59 (d, J=7.3Hz, 1H), 7.80 (d, J=8.6Hz, 1H), 8.13 (d, J=11.4Hz, 1H), 8.21 (d, J=8.1Hz, 1H), 9.68 (s, 1H), 12.58 (broad s, 1H).

MS (ESI) m/z 362 (M^++1).

(Step 10) Synthesis of methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



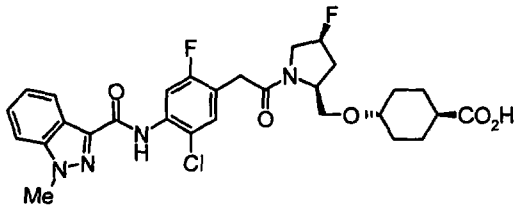
To (5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.55 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (143 mg, 0.55 mmol), HOBt (15.0 mg, 0.11 mmol), and DMAP (14.0 mg, 0.11 mmol) were added DMF (5.0 ml) and EDC HCl (159 mg, 0.83 mmol). The resulting mixture was stirred at room temperature for 6 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 trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (332 mg, 100%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.33 (m, 2H), 1.40-1.53 (m, 2H), 1.98-2.53 (m, 7H), 3.26-4.14 (m, 10H), 4.17 (s, 3H), 4.31 and 4.38 (each m, total 1H), 5.26 and 5.31 (each m, total 1H), 7.29-7.53 (m, 4H), 8.39 (d, J=8.3Hz, 1H), 8.51 (m,

1H), 9.50 (broad s, 1H).

MS (ESI) m/z 604 (M^++1).

(Step 11) Synthesis of trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((5-chloro-2-fluoro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (332 mg, 0.55 mmol) were added THF (5.5 ml) and 0.25N NaOH (3.30 ml, 0.82 mmol), and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl (1.1 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, 93%) as a colorless solid.

IR (ATR) ν 3363, 2938, 2863, 1725, 1687, 1648, 1621, 1585, 1525, 1481 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.18-1.38 (m, 4H), 1.86-2.33 (m, 7H), 3.18-3.99 (m, 7H), 4.13 and 4.35 (each m, total 1H), 4.22 (s, 3H), 5.33 and 5.42 (each m, total 1H), 7.37 (m, 1H), 7.45-7.56 (m, 2H), 7.82 (d, J=8.3Hz, 1H), 8.08 and 8.10 (each d, J=11.4Hz, total 1H), 8.21 (d, J=8.3Hz, 1H), 9.71

(broad s, 1H), 12.06 (broad s, 1H).

MS (ESI) m/z 589 (M^++1);

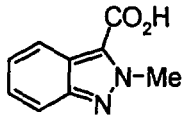
Anal. Calcd for $C_{29}H_{31}ClF_2N_4O_5 \cdot 0.25H_2O$: C, 58.68; H, 5.35; N, 9.44.

Found: C, 58.46; H, 5.31; N, 9.25.

Example 88

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

(Step 1) Synthesis of 2-methylindazole-3-carboxylic acid

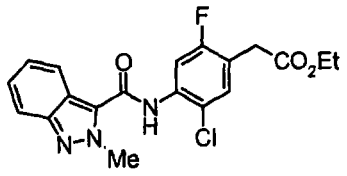


To methyl 2-methylindazole-3-carboxylate (1.59 g, 8.36 mmol) were added THF (85 ml) and 0.25N NaOH (50 ml, 12.5 mmol) and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added water, followed by the addition of 1N HCl (50 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give 2-methylindazole-3-carboxylic acid (1.34 g, 91%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 4.43 (s, 3H), 7.29 (m, 1H), 7.35 (m, 1H), 7.74 (dd, J=8.1,1.0Hz, 1H), 7.98 (d, J=8.5Hz, 1H), 13.59 (broad s, 1H).

MS (ESI) m/z 177 (M^++1).

(Step 2) Synthesis of ethyl (5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetate



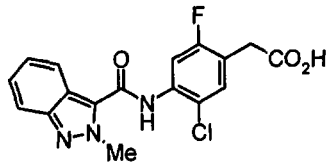
To 2-methylindazole-3-carboxylic acid (650 mg, 3.69 mmol) and DMF (29.0 µl, 0.37 mmol) was added benzene (20 ml). Under stirring at room temperature, oxalyl chloride (0.39 ml, 4.43 mmol) was added dropwise to the resulting mixture. After completion of the dropwise addition, the reaction mixture was stirred for further 1 hour at room temperature. A solution of ethyl (4-amino-5-chloro-2-fluorophenyl)acetate (855 mg, 3.69 mmol) and triethylamine (3.09 ml, 22.1 mmol) in benzene (3.0 ml), which had been prepared in advance, was added dropwise to the reaction mixture, and the mixture was heated under reflux for 16 hours. The reaction mixture was then cooled to room temperature, 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, ethyl (5-chloro-2-fluoro-4-((2-methyl-3-

indazolylcarbonyl)amino)phenyl)acetate (390 mg, 27%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, J=7.1Hz, 3H), 3.65 (s, 2H), 4.20 (q, J=7.1Hz, 2H), 4.55 (s, 3H), 7.35-7.42 (m, 3H), 7.84 (d, J=8.3Hz, 1H), 7.97 (d, J=8.1Hz, 1H), 8.49 (d, J=11.5Hz, 1H), 8.54 (broad s, 1H).

MS (ESI) m/z 390 (M^++1).

(Step 3) Synthesis of (5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid



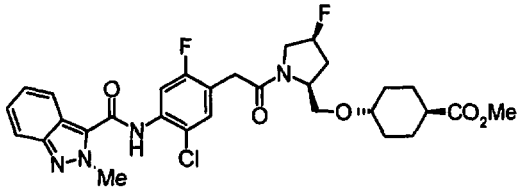
To ethyl (5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetate (390 mg, 1.00 mmol) were added THF (10 ml) and 0.25N NaOH (6.00 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was poured in 1N HCl (1.5 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (1.23 g, 95%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.68 (s, 2H), 4.39 (s, 3H), 7.30 (m, 1H), 7.38 (m, 1H), 7.62 (d, J=7.6Hz, 1H), 7.74-7.80 (m, 2H), 8.03 (d, J=8.3Hz, 1H), 10.25 (broad s, 1H), 12.62

(broad s, 1H).

MS (ESI) m/z 362 (M^++1).

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



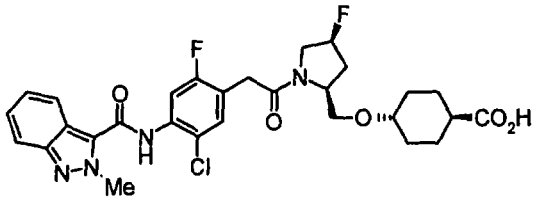
To (5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (200 mg, 0.55 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (143 mg, 0.55 mmol), HOBt (15.0 mg, 0.11 mmol), and DMAP (14.0 mg, 0.11 mmol) were added DMF (5.0 ml) and EDC HCl (159 mg, 0.83 mmol). The resulting mixture was stirred at room temperature for 6 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 trans-4-(1-((5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (313 mg, 94%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.24-1.29 (m, 2H), 1.32-1.58 (m, 2H), 1.97-2.54 (m, 7H), 3.23-4.02 (m, 10H), 4.31 and 4.38 (each m, total 1H), 4.54 (s, 3H), 5.27 and 5.32 (each m, total 1H), 7.31-7.47 (m, 3H), 7.84 (d, J=7.6Hz, 1H), 7.96 (d, J=8.3Hz, 1H), 8.47 (m, 1H), 8.54 (broad s, 1H).

MS (ESI) m/z 604 (M^++1).

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



To methyl trans-4-(1-((5-chloro-2-fluoro-4-((2-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (313 mg, 0.52 mmol) were added THF (5.0 ml) and 0.25N NaOH (3.11 ml, 0.78 mmol). The resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture was added 1N HCl (0.85 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 (253 mg, 83%) as a colorless solid.

IR (ATR) ν 3409, 2942, 2861, 1725, 1681, 1646, 1621, 1587,

1521, 1454 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.16-1.42 (m, 4H), 1.86-2.33 (m, 7H), 3.19-4.36 (m, 8H), 4.39 (s, 3H), 5.33 and 5.42 (each m, total 1H), 7.31 (m, 1H), 7.38 (m, 1H), 7.49 and 7.51 (each d, J=7.1Hz, total 1H), 7.74-7.77 (m, 2H), 8.04 (d, J=8.3Hz, 1H), 10.27 (broad s, 1H), 12.03 (broad s, 1H).

MS (ESI) m/z 589 (M^++1);

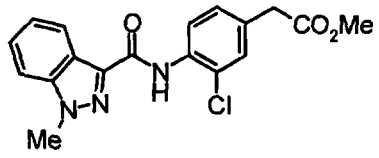
Anal. Calcd for $C_{29}H_{31}ClF_2N_4O_5$ 0.25H_2O: C, 58.68; H, 5.35; N, 9.44.

Found: C, 58.68; H, 5.38; N, 9.32.

Example 89

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

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



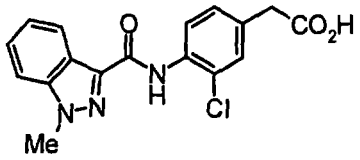
To 1-methylindazole-3-carboxylic acid (600 mg, 3.41 mmol) and DMF (27.0 μl, 0.34 mmol) was added methylene chloride (20 ml). Under stirring at room temperature, oxalyl chloride (0.36 ml, 4.09 mmol) was added dropwise to the resulting mixture. After completion of the dropwise addition, the reaction mixture was stirred at room

temperature for 50 hours and the solvent was distilled off under reduced pressure. The residue was dissolved in methylene chloride (5 ml). The resulting solution was added to a solution of methyl 4-amino-3-chlorophenylacetate (680 mg, 3.41 mmol) and triethylamine (1.42 ml, 10.2 mmol) in methylene chloride (5 ml) under stirring at room temperature. The reaction mixture was heated under reflux at room temperature for 7 hours. After the reaction mixture was cooled to room temperature, water was added thereto, 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, v/v) eluate fractions, methyl (3-chloro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetate (1.08 g, 89%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.61 (s, 2H), 3.72 (s, 3H), 4.18 (s, 3H), 7.24 (dd, J=8.6,2.0Hz, 1H), 7.34 (m, 1H), 7.38 (d, J=2.0Hz, 1H), 7.45-7.50 (m, 2H), 8.41 (d, J=8.0Hz, 1H), 8.61 (d, J=8.6Hz, 1H), 9.47 (broad s, 1H).

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

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

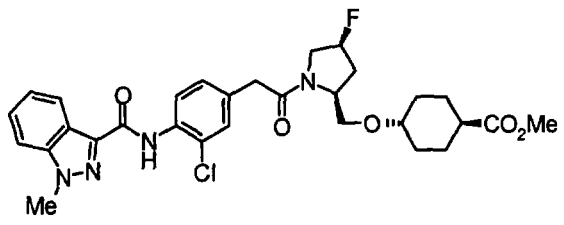


To methyl (3-chloro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetate (1.08 g, 3.02 mmol) were added THF (30 ml) and 0.25N NaOH (18.1 ml, 4.53 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was poured in 1N HCl (5.0 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (3-chloro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetic acid (0.99 g, 95%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.62 (s, 2H), 4.21 (s, 3H), 7.28 (dd, J=8.3,1.7Hz, 1H), 7.35 (m, 1H), 7.47 (d, J=1.7Hz, 1H), 7.53 (m, 1H), 7.80 (d, J=8.5Hz, 1H), 8.11 (d, J=8.3Hz, 1H), 8.21 (d, J=8.1Hz, 1H), 9.69 (s, 1H), 12.49 (broad s, 1H).

MS (LCMS) m/z 344 (M^++1).

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



To (3-chloro-4-((1-methyl-3-

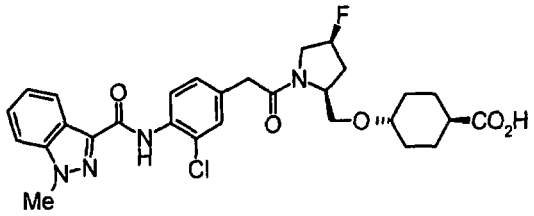
indazolylcarbonyl)amino)phenyl)acetic acid (250 mg, 0.73 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (189 mg, 0.73 mmol), HOBt (20.0 mg, 0.15 mmol), and DMAP (18.0 mg, 0.15 mmol) were added DMF (5.0 ml) and EDC HCl (209 mg, 1.09 mmol). The resulting mixture was stirred at room temperature for 17 hours. 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 (1:2, v/v) eluate fractions, methyl trans-4-(1-((3-chloro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (414 mg, 97%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.29 (m, 2H), 1.33-1.53 (m, 2H), 1.97-2.50 (m, 7H), 3.24-4.09 (m, 10H), 4.15 (s, 3H), 4.21 and 4.37 (each m, total 1H), 5.25 (m, 1H), 7.20 (m, 1H), 7.30-7.38 (m, 2H), 7.40-7.47 (m, 2H), 8.38 (d, J=8.1Hz, 1H), 8.57 and 8.59 (each d, J=7.3Hz, total 1H), 9.44 (broad s, 1H).

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

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

3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((3-chloro-4-((1-methyl-3-indazolylcarbonyl)amino)phenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (414 mg, 0.71 mmol) were added THF (7.0 ml) and 0.25N NaOH (4.25 ml, 1.06 mmol). The resulting mixture was stirred at room temperature for 20 hours. To the reaction mixture was added 1N HCl (1.5 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 (353 mg, 87%) as a colorless solid.

IR (ATR) ν 3376, 2937, 2859, 1720, 1685, 1600, 1521, 1484 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.41 (m, 4H), 1.85-1.99 (m, 4H), 2.08-2.26 (m, 3H), 3.16-3.88 (m, 7H), 4.14 and 4.34 (each m, total 1H), 4.21 (s, 3H), 5.32 and 5.39 (each m, total 1H), 7.24 (m, 1H), 7.35 (m, 1H), 7.42 (d J=7.6Hz, 1H), 7.53 (m, 1H), 7.80 (d, J=8.1Hz, 1H), 8.10 (m, 1H), 8.21 (d, J=8.1Hz, 1H), 9.69 (s, 1H), 12.06 (broad s, 1H).

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

Anal. Calcd for $C_{29}H_{32}ClFN_4O_5$ 0.25H_2O: C, 60.52; H, 5.69; N,

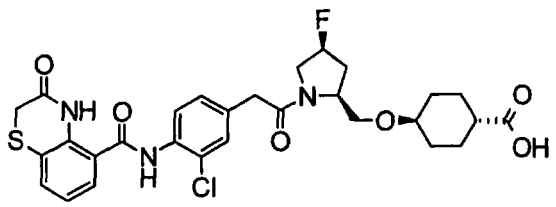
9.73.

Found: C, 60.57; H, 5.64; N, 9.50.

Example 90

trans-4-(1-(3-Chloro-4-((3-oxo-3,4-dihydro-2H-benzo(1,4)thiazine-5-yl-carbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of trans-4-(1-(3-Chloro-4-((3-oxo-3,4-dihydro-2H-benzo(1,4)thiazine-5-yl-carbonyl)amino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



A mixture of trans-4-(1-((4-amino-3-chlorophenyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid (500 μL of a 1.0M DMF solution, 0.50 mmol), 3-oxo-3,4-dihydro-2H-benzo(1,4)thiazine-5-carboxylic acid (105 mg, 0.5 mmol), HOBt (0.95 ml of a 1.0M DMF solution, 0.95 mmol), EDC HCl (1.5 ml of a 0.5M DMF/methylene chloride solution, 0.75 mmol) and DMAP (catalytic amount) was stirred in a screw vial for 18 hours at room temperature. The reaction mixture was diluted with chloroform (3 ml) and the diluted solution was poured in a fit syringe which had been pre-packed with acidic Hydromatrix. The syringe was washed

with chloroform. The solvent was distilled off and to the residue were added THF/methanol (4 ml, 3:1) and 1M NaOH. The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was distilled and the residue was purified by high-performance liquid chromatography (ARW system) to give the title compound (15 mg, 5%) as a colorless solid.

^{1}H-NMR (DMSO-d_6) δ: 1.10-1.40 (m, 4H), 1.90 (m, 4H), 2.12 (m, 4H), 3.20 (m, 1H), 3.40 (m, 1H), 3.56 (s, 2H), 3.65-3.90 (m, 4H), 4.11 and 4.32 (2m, total 1H), 5.32 (m, 1H), 7.14 (t, J=7.8Hz, 1H), 7.22 (m, 1H), 7.40 (d, J=6.0Hz, 1H), 7.51 (m, 1H), 7.59 (d, J=7.8Hz, 1H), 7.80 (d, J=8.1Hz, 1H).

MS (ESI) m/z 605 $(M+1)^+$.

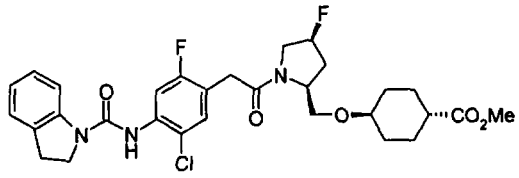
Anal. Calcd for $C_{29}H_{31}ClFN_3O_6S$ 1.0H_2O: C, 55.99; H, 5.35; N, 6.75.

Found: C, 55.85; H, 5.12; N, 6.51.

Example 91

trans-4-(1-(5-Chloro-2-fluoro-4-(1-(indolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl trans-4-(1-(5-chloro-2-fluoro-4-(1-(indolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



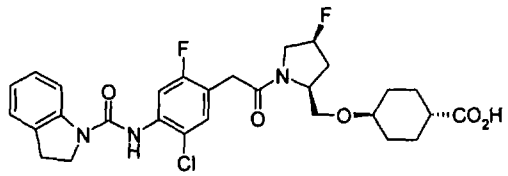
To methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (233 mg, 0.90 mmol), 5-chloro-2-fluoro-4-(1-indolinylcarbonylamino)phenylacetic acid (314 mg, 0.90 mmol) and EDC-HCl (190 mg, 0.99 mmol) were added DMF (10 ml) and HOBt (24 mg, 0.18 mmol). 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 ethyl acetate/hexane (4/1) eluate fractions, methyl trans-4-(1-(5-chloro-2-fluoro-4-(1-(indolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (421 mg, 79%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.15-1.30 (m, 2H), 1.39-1.42 (m, 2H), 1.96-2.15 (m, 5H), 2.21-2.53 (series of m, 2H), 3.20-3.37 (m, overlap, 1H), 3.26 (t, J=8.8Hz, 1H), 3.50-3.60 (m, 2H), 3.64-4.00 (series of m, overlap, 4H), 3.64 and 3.66 (s, total 3H), 4.13 (t, J=8.4Hz, 1H), 4.27-

4.40 (m, 1H), 5.18-5.36 (m, 1H), 6.98 (t, J=7.6Hz, 1H), 7.17-7.23 (m, 3H), 7.35 (dd, J=7.2,4.0Hz, 1H), 7.93 (d, J=8.0Hz, 1H), 8.22 (t, J=2.4Hz, 1H).

MS (ESI) m/z 590 (M^++1).

(Step 2) Synthesis of trans-4-(1-(5-chloro-2-fluoro-4-(1-(indolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-(5-chloro-2-fluoro-4-(1-(indolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (394 mg, 0.67 mmol) were added methanol-THF (1:1, 20 ml) and 0.25N NaOH (13.4 ml, 3.34 mmol). The resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture was added 1N HCl to acidify the mixture, followed by extraction with chloroform/methanol (10/1, v/v). The extract was washed with saturated brine, dried over anhydrous sodium sulfate, then 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 (419 mg, 100%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.20-1.33 (m, 2H),

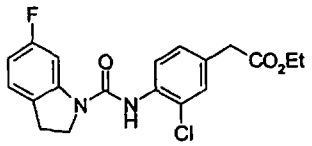
1.41-1.54 (m, 2H), 2.50-2.55 (series of m, 8H), 3.27 (t, J=8.0Hz, 2H), 3.33-4.38 (series of m, 7H), 4.14 (t, J=8.8Hz, 2H), 6.99 (t, J=7.6Hz, 1H), 7.19-7.24 (m, 3H), 7.34-7.37 (m, 1H), 7.93 (d, J=8.4Hz, 1H), 8.22 (t, J=11.6Hz, 1H).

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

Example 92

trans-4-(3-Chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of ethyl 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetate

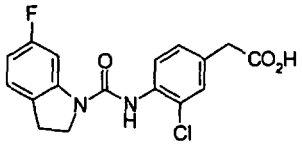


Ethyl 4-amino-3-chlorophenylacetate (520 mg, 2.43 mmol) was dissolved in THF (50 ml). Under stirring at room temperature, triphosgene (240 mg, 0.81 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture was added triethylamine (0.75 ml, 5.34 mmol), followed by the addition of a solution of 6-fluoroindoline (333 mg, 2.43 mmol) in THF (5 ml). After stirring at room temperature for 25 minutes, the reaction mixture was poured in 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 solid thus obtained was recrystallized from hexane/ethyl acetate to give ethyl 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetate (499 mg, 55%) as a colorless crystalline powder.

MS (ESI) m/z 376 (M^++1).

(Step 2) Synthesis of 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetic acid



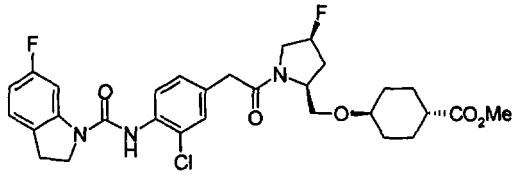
Ethyl 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetate (499 mg, 1.32 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (10.1 ml, 2.65 mmol), followed by stirring at room temperature for 2 hours. The reaction mixture was poured in aqueous 1N HCl and 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 resulting solid was recrystallized from hexane/chloroform to give 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetic acid (358 mg, 78%) as a colorless crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.16 (t, J=8.8Hz, 2H), 3.59 (s, 2H), 4.18 (t, J=8.8Hz, 2H), 6.67 (brt, J=9.2Hz, 1H), 7.17 (brt,

J=6.4Hz, 1H), 7.21 (d, J=8.0Hz, 1H), 7.40 (s, 1H), 7.50 (d, J=8.0Hz, 1H), 7.56 (dd, J=2.0,11.2Hz, 1H), 8.32 (s, 1H).

MS (ESI) m/z 349 (M^++1).

(Step 3) Synthesis of methyl trans-4-(3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



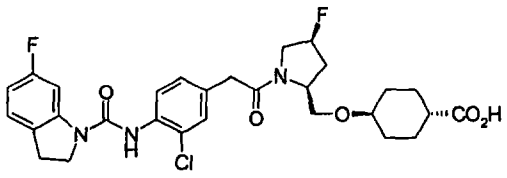
In DMF (12 ml), HOBt (28.0 mg, 0.23 mmol) was added to 3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetic acid (358 mg, 1.03 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (266 mg, 1.03 mmol) and EDC-HCl (216 mg, 1.13 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-(3-chloro-4-(1-(6-

fluoroindolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (599 mg, 99%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.20-1.31 (m, 2H), 1.42-1.53 (m, 2H), 1.97-2.10 (m, 5H), 2.22-2.61 (series of m, 2H), 3.24 (t, J=8.0Hz, 2H), 3.22-4.40 (series of m, 8H), 3.67 and 3.71 (s, total 3H), 4.20 (t, J=8.0Hz, 2H), 5.15-5.34 (m, 1H), 6.63-6.68 (m, 1H), 7.03-7.10 (m, 2H), 7.16 (d, J=8.4Hz, 1H), 7.34 (brs, 1H), 7.76 (dd, J=2.0, 10.4Hz, 1H), 8.23 (t, J=8.8Hz, 1H).

MS (ESI) m/z 590 (M^++1).

(Step 4) Synthesis of trans-4-(3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



Methyl trans-4-(3-chloro-4-(1-(6-fluoroindolinyl)carbonylamino)phenylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (575 mg, 0.98 mmol) was dissolved in THF/methanol (1/1, 20 ml). To the resulting solution was added 0.25N NaOH (11.7 ml, 2.92 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 (10/1) eluate fractions, the title compound (625 mg, 100%) was obtained as a colorless amorphous substance.

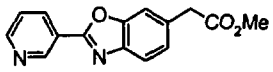
^{1}H-NMR (DMSO-d_6), mixture of rotamars, δ: 1.44-1.55 (m, 2H), 1.59-1.72 (m, 2H), 2.19-2.56 (series of m, 7H), 3.46 (t, J=8.0Hz, 2H), 3.44-4.63 (series of m, 8H), 4.49 (t, J=8.4Hz, 2H), 5.51-5.73 (m, 1H), 6.93-6.98 (m, 1H), 7.44-7.49 (m, 2H), 7.64-7.66 (m, 1H), 7.81-7.89 (m, 2H), 8.55 and 8.56 (s, total 2H) (d, J=8.4Hz, 1H), 7.34 (brs, 1H), 7.76 (dd, J=2.0, 10.4Hz, 1H), 8.23 (t, J=8.8Hz, 1H)

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

Example 93

trans-4-(1-(2-(3-Pyridyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(3-pyridyl)-6-benzoxazolyl)acetate

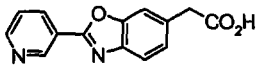


In EtOH (15 ml), pyridine-3-aldehyde (0.63 g, 5.89 mmol) and methyl 4-amino-3-hydroxyphenylacetate (1.06 g, 5.85 mmol) were stirred at room temperature for 20 hours. To the reaction mixture was added iodobenzene diacetate

(2.26 g, 7.02 mmol), followed by stirring at room temperature for 20 minutes. The reaction mixture was distilled under reduced pressure to remove the solvent and the residue was dissolved in 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. The residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (1:1, v/v) eluate fractions, methyl (2-(3-pyridyl)-6-benzoxazolyl)acetate (360 mg, 23%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.78 (s, 2H), 7.29 (s, 1H), 7.44-7.50 (m, 1H), 7.56-7.57 (m, 1H), 7.72-7.73 (m, 1H), 8.47-8.50 (m, 1H), 8.75-8.77 (m, 1H), 9.45-9.46 (m, 1H).

(Step 2) Synthesis of (2-(3-pyridyl)-6-benzoxazolyl)acetic acid

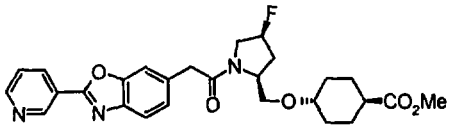


To methyl (2-(3-pyridyl)-6-benzoxazolyl)acetate (360 mg, 1.34 mmol) were added THF (8 ml) and 0.5N NaOH (8.0 ml, 4.00 mmol). The resulting mixture was stirred at room temperature for 20 hours. To the reaction mixture were added water and 1N HCl (5.0 ml, 5 mmol) to acidify the mixture, followed by extraction with ethyl acetate. The extract was washed with saturated brine, dried over

anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give (2-(3-pyridyl)-6-benzoxazolyl)acetic acid (179 mg, 52%) as a yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.78 (s, 2H), 7.34-7.36 (m, 1H), 7.62-7.79 (m, 3H), 8.52-8.55 (m, 1H), 8.80-8.82 (m, 1H), 9.35-9.36 (m, 1H).

(Step 3) Synthesis of methyl trans-4-(1-(2-(3-pyridyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



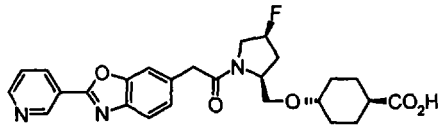
In DMF (5 ml), (2-(3-pyridyl)-6-benzoxazolyl)acetic acid (179 mg, 0.70 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (182 mg, 0.70 mmol), EDC·HCl (202 mg, 1.05 mmol), HOBt (143 mg, 1.06 mmol), and triethylamine (147 µl, 1.05 mmol) were stirred at room temperature for 2 hours. 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 chloroform-methanol (100:1 to 30:1, v/v) eluate fractions, methyl trans-4-(1-(2-(3-pyridyl)-6-benzoxazolylacetyl)-

(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (304 mg, 87%) was obtained as a reddish brown thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.53 (m, 4H), 1.97-2.52 (m, 7H), 3.23-3.55 (m, 2H), 3.65-4.08 (m, 8H), 4.25-4.30 and 4.40 (each m, total 1H), 5.19-5.22 and 5.32-5.35 (each m, total 1H), 7.29-7.31 (m, 1H), 7.45-7.49 (m, 1H), 7.56-7.57 (m, 1H), 7.71-7.74 (m, 1H), 8.48-8.50 (m, 1H), 8.75-8.76 (m, 1H), 9.45 (s, 1H).

MS (ESI) m/z 496 (M^++1).

(Step 4) Synthesis of trans-4-(1-(2-(3-pyridyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-(2-(3-pyridyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (304 mg, 0.61 mmol) were added THF (4 ml) and 0.5N NaOH (3.7 ml, 1.85 mmol). The resulting 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 (156 mg, 53%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.35 (m, 4H), 1.92-2.20 (m, 7H), 3.16-3.99 (m, 7H), 4.14 and 4.34-4.36 (each m, total 1H), 5.24-5.30 and 5.38-5.44 (each m, total 1H), 7.26-7.30 (m, 1H), 7.62-7.66 (m, 2H), 7.73-7.76 (m, 1H), 8.49-8.51 (m, 1H), 8.78-8.79 (m, 1H), 9.33 (s, 1H).

MS (ESI) m/z 482 (M^++1);

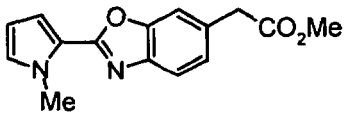
Anal. Calcd for $C_{26}H_{28}FN_3O_5$: C, 64.85; H, 5.86; N, 8.73.

Found: C, 64.65; H, 5.92; N, 8.46.

Example 94

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

(Step 1) Synthesis of methyl (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetate



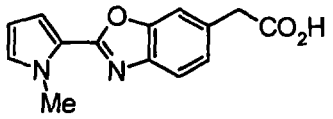
In ethanol (10 ml), 1-methylpyrrole-2-carbaldehyde (0.33 ml, 3.09 mmol) and methyl 4-amino-3-hydroxyphenylacetate (559 mg, 3.09 mmol) were stirred for 4 hours at room temperature. Iodobenzene diacetate (1.19 g, 3.70 mmol) was added to the reaction mixture. After stirring at room temperature for 30 minutes, 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

(3:1, v/v) eluate fractions, methyl (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetate (228 mg, 27%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.71 (s, 3H), 3.75 (s, 2H), 4.13 (s, 3H), 6.24 (dd, J=3.9,1.7Hz, 1H), 6.86 (m, 1H), 7.06 (dd, J=3.9, 1.7Hz, 1H), 7.20 (dd, J=8.1,1.7Hz, 1H), 7.45 (d, J=1.0Hz, 1H), 7.61 (d, J=8.3Hz, 1H).

MS (ESI) m/z 270 (M^+).

(Step 2) Synthesis of (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetic acid



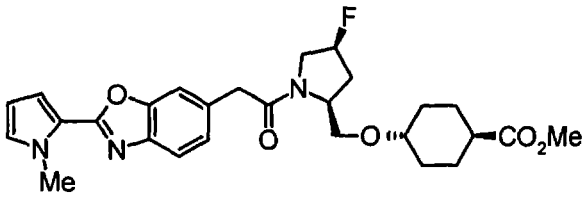
To methyl (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetate (228 mg, 0.84 mmol) were added THF (8.5 ml) and 0.25N NaOH (5.10 ml, 1.27 mmol). The resulting mixture was stirred at room temperature for 5 hours. The reaction mixture was poured in 1N HCl (10 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetic acid (144 mg, 67%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.69 (s, 2H), 4.06 (s, 3H), 6.21 (m, 1H), 6.99 (m, 1H), 7.17 (d, J=2.2Hz, 1H), 7.22 (d, J=8.1Hz, 1H), 7.56 (s, 1H), 7.61 (d, J=8.1Hz, 1H), 12.36 (broad s,

1H).

MS (ESI) m/z 256 (M^+).

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

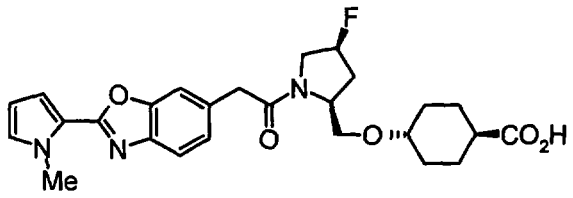


To (2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetic acid (144 mg, 0.56 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (146 mg, 0.56 mmol), HOBt (15.0 mg, 0.11 mmol) and DMAP (14.0 mg, 0.11 mmol) were added DMF (6.0 ml) and EDC HCl (162 mg, 0.83 mmol). The resulting mixture was stirred at room temperature for 24 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 trans-4-(1-((2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (271 mg, 97%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.20-1.33 (m, 2H), 1.39-1.54 (m, 2H), 1.97-2.51 (m, 7H), 3.26 (m, 1H), 3.35 and 3.51 (each m, total 1H), 3.65 and 3.67 (each s, total 3H), 3.69-4.06 (m, 5H), 4.24 and 4.39 (each m, total 1H), 5.24 (m, 1H), 6.24 (m, 1H), 6.86 (m, 1H), 7.06 (m, 1H), 7.18 (m, 1H), 7.44 (m, 1H), 7.60 (m, 1H).

MS (ESI) m/z 498 (M^++1).

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



To methyl trans-4-(1-((2-(1-methyl-2-pyrrolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (271 mg, 0.54 mmol) were added THF (5.5 ml) and 0.25N NaOH (3.27 ml, 0.82 mmol). The resulting mixture was stirred at room temperature for 3 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 (237 mg, 91%) as a colorless solid.

IR (ATR) ν 2938, 2861, 1718, 1644, 1627, 1575, 1523, 1423 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.39 (m, 4H), 1.84-2.27 (m, 7H), 3.15-4.03 (m, 7H), 4.06 (s, 3H), 4.12 and 4.32 (each m, total 1H), 5.30 and 5.36 (each m, total 1H), 6.21 (m, 1H), 6.98 (m, 1H), 7.16-7.20 (m, 2H), 7.49 and 7.51 (each m, total 1H), 7.59 and 7.60 (each d, J=8.1Hz, total 1H), 12.01 (broad s, 1H).

MS (ESI) m/z 484 (M^++1);

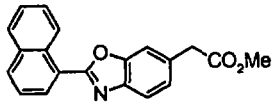
Anal. Calcd for $C_{26}H_{30}FN_3O_5$: C, 64.58; H, 6.25; N, 8.69.

Found: C, 64.35; H, 6.28; N, 8.49.

Example 95

trans-4-(1-(2-(1-Naphthyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(1-naphthyl)-6-benzoxazolyl)acetate



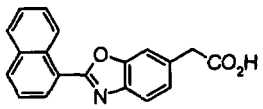
In EtOH (8 ml), 1-naphthaldehyde (263 mg, 1.68 mmol) and methyl 4-amino-3-hydroxyphenylacetate (305 mg, 1.68 mmol) were stirred at room temperature for 12 hours. Iodobenzene diacetate (651 mg, 2.02 mmol) was added to the reaction mixture, followed by stirring at room temperature for 5 minutes. After removal of the solvent by distilling the reaction mixture under reduced pressure, the residue was purified by chromatography on a silica gel column, whereby from n-hexane/ethyl acetate (6:1, v/v) eluate

fractions, methyl (2-(1-naphthyl)-6-benzoxazolyl)acetate (223 mg, 42%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.79 (s, 2H), 7.29-7.31 (m, 1H), 7.56-7.61 (m, 3H), 7.68-7.76 (m, 1H), 7.80-7.82 (m, 1H), 7.91-7.94 (m, 1H), 8.01-8.03 (m, 1H), 8.39-8.41 (m, 1H), 9.42-9.45 (m, 1H).

MS (ESI) m/z 318 (M^++1).

(Step 2) Synthesis of (2-(1-naphthyl)-6-benzoxazolyl)acetic acid

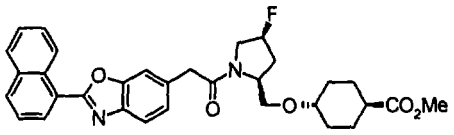


To methyl (2-(1-naphthyl)-6-benzoxazolyl)acetate (223 mg, 0.70 mmol) were added THF (4 ml) and 0.5N NaOH (4.2 ml, 2.10 mmol). The resulting mixture was stirred at room temperature for 2 days. The reaction mixture was acidified with ice-1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(1-naphthyl)-6-benzoxazolyl)acetic acid (194 mg, 91%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 3.78 (s, 2H), 7.34-7.36 (m, 1H), 7.65-7.78 (m, 4H), 7.84 (d, J=8.1Hz, 1H), 8.09 (d, J=8.1Hz, 1H), 8.21-8.23 (m, 1H), 8.43-8.45 (m, 1H), 9.40-9.42 (m, 1H).

(Step 3) Synthesis of methyl trans-4-(1-(2-(1-naphthyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate

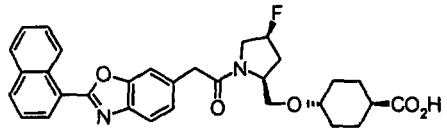


In DMF (7 ml), (2-(1-naphthyl)-6-benzoxazolyl)acetic acid (194 mg, 0.64 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (166 mg, 0.64 mmol), EDC·HCl (184 mg, 0.96 mmol), HOBt (130 mg, 0.96 mmol), and triethylamine (134 µl, 0.96 mmol) were stirred at room 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 with chloroform-methanol (100:1 to 60:1, v/v) eluate fractions, methyl trans-4-(1-(2-(1-naphthyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (310 mg, 89%) was obtained as a pale yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.53 (m, 4H), 1.96-2.51 (m, 7H), 3.25-3.54 (m, 2H), 3.63-4.10 (m, 8H), 4.25-4.30 and 4.40 (each m, total 1H), 5.17-5.19 and 5.31-5.32 (each m, total 1H), 7.27-7.29 (m, 1H), 7.56-7.61 (m, 3H), 7.68-7.72 (m, 1H), 7.79-7.82 (m, 1H), 7.93 (d, J=8.1Hz, 1H), 8.02 (d, J=8.1Hz, 1H), 8.39-8.41 (m, 1H), 9.43-9.45 (m, 1H).

MS (ESI) m/z 545 (M^++1).

(Step 4) Synthesis of trans-4-(1-(2-(1-naphthyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-(2-(1-naphthyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (310 mg, 0.57 mmol) were added THF (3.0 ml) and 0.5N NaOH (3.4 ml, 1.70 mmol). The resulting mixture was stirred at room temperature for 13 hours. The reaction mixture was acidified with 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 (110 mg, 33%) as a white solid.

^{1}H-NMR (DMSO-d_6) δ: 1.11-1.36 (m, 4H), 1.83-2.20 (m, 7H), 3.19-4.01 (m, 7H), 4.14 and 4.36-4.38 (each m, total 1H), 5.25-5.31 and 5.38-5.45 (each m, total 1H), 7.28-7.32 (m, 1H), 7.64-7.85 (m, 5H), 8.09 (d, J=8.0Hz, 1H), 8.21 (d, J=8.0Hz, 1H), 8.42-8.44 (m, 1H), 9.40-9.42 (m, 1H).

MS (ESI) m/z 531 (M^++1);

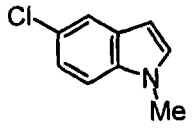
Anal. Calcd for $C_{31}H_{31}FN_2O_5 \cdot 1/2H_2O$: C, 69.00; H, 5.98; N, 5.19.

Found: C, 69.11; H, 5.76; N, 5.17.

Example 96

trans-4-(1-((2-(5-Chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 5-chloro-1-methylindole

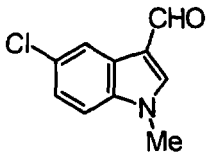


In DMF (65 ml) was dissolved 5-chloroindole (5.00 g, 33.0 mmol), followed by the addition of sodium hydride (60% in oil, 1.45 g, 36.3 mmol) in portions under stirring at 0°C. After the reaction mixture was stirred further for 30 minutes at the same temperature, methyl iodide (2.46 ml, 39.6 mmol) was added. The resulting mixture was stirred at 0°C for 30 minutes. Ice 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 (3:1, v/v) eluate fractions, 5-chloro-1-methylindole (5.89 g, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.78 (s, 3H), 6.42 (d, J=3.2Hz, 1H), 7.06 (d, J=3.2Hz, 1H), 7.17 (dd, J=8.3Hz, 1H), 7.23 (d, J=8.3Hz, 1H), 7.59 (d, J=1.9Hz, 1H).

(Step 2) Synthesis of 5-chloro-1-methylindole-3-

carbaldehyde

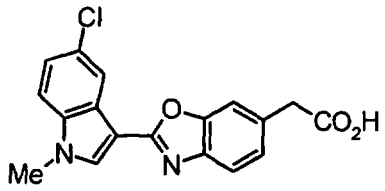


While stirring DMF (70 ml) at 0°C, phosphoryl chloride (4.97 ml, 53.3 mmol) was added dropwise in portions. After completion of the dropwise addition, the reaction mixture was stirred further for 10 minutes at the same temperature. A solution of 5-chloro-1-methylindole (5.89 g, 35.6 mmol) in DMF (10 ml) was added. The resulting mixture was stirred for cyclohexanecarboxylic time at 60°C for 6 hours. The reaction mixture was cooled to room temperature, and added to a saturated aqueous solution of sodium bicarbonate in portions, 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 under reduced pressure. The residue was purified by chromatography on a silica gel column, whereby from ethyl acetate eluate fractions, 5-chloro-1-methylindole-3-carbaldehyde (5.51 g, 80%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.87 (s, 3H), 7.27 (d, J=8.5Hz, 1H), 7.31 (dd, J=8.5,1.9Hz, 1H), 7.69 (s, 1H), 8.30 (d, J=1.9Hz, 1H), 9.96 (s, 1H).

MS (ESI) m/z 193 (M^++1).

(Step 3) Synthesis of (2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid



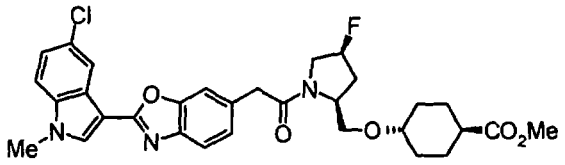
In EtOH (9.0 ml), 5-chloro-1-methylindole-3-carbaldehyde (534 mg, 2.76 mmol) and methyl 4-amino-3-hydroxyphenylacetate (500 mg, 2.76 mmol) were stirred for hours. After iodobenzene diacetate (2.03 g, 6.31 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 1 hour, 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, a mixture (594 mg) of methyl (2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetate and 5-chloro-1-methylindole-3-carboxaldehyde was obtained. To the resulting mixture were added THF (17 ml) and 0.25N NaOH (10.0 ml, 2.50 mmol) and the mixture was stirred at room temperature for 23 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl (10 ml), followed by extraction with chloroform-methanol (4:1, v/v). The extract was dried over anhydrous sodium sulfate and distilled under reduced pressure to remove the solvent to give (2-(5-chloro-1-methyl-3-indolyl)-6-

benzoxazolyl)acetic acid (88 mg, 9%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.73 (s, 2H), 3.94 (s, 3H), 7.25 (dd, J=8.1,1.7Hz, 1H), 7.36 (dd, 1H, J=8.8,1.7Hz, 1H), 7.62-7.68 (m, 3H), 8.30 (d, J=1.7Hz, 1H), 8.41 (s, 1H), 12.38 (broad s, 1H).

MS (ESI) m/z 341 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-((2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



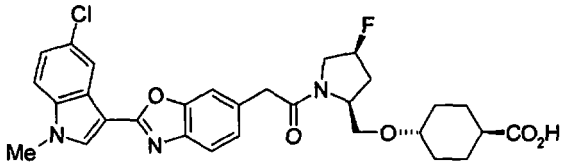
To (2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (88.0 mg, 0.26 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (67.0 mg, 0.26 mmol), HOBt (10.0 mg, 0.05 mmol), and DMAP (9.1 mg, 0.05 mmol) were added DMF (3.0 ml) and EDC HCl (74.0 mg, 0.39 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 ethyl acetate eluate fractions, methyl trans-4-(1-((2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (172 mg, 100%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.34 (m, 2H), 1.40-1.57 (m, 2H), 1.97-2.51 (m, 7H), 3.27 (m, 1H), 3.36 and 3.52 (each m, total 1H), 3.64 and 3.66 (each s, total 3H), 3.67-3.86 (m, 3H), 3.89 (s, 3H), 3.91-4.15 (m, 2H), 4.26 and 4.40 (each m, total 1H), 5.26 (m, 1H), 7.21 (m, 1H), 7.27-7.31 (m, 2H), 7.51 (m, 1H), 7.65 (m, 1H), 7.92 (m, 1H), 8.44 (m, 1H).

MS (ESI) m/z 582 (M^++1).

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



To methyl trans-4-(1-((2-(5-chloro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (172 mg, 0.30 mmol) were added THF (3.0 ml) and 0.25N NaOH (1.80 ml, 0.44 mmol). The resulting mixture was stirred at room temperature for 3 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 (110 mg, 65%) as a yellow solid.

IR (ATR) ν 2938, 2863, 1720, 1629, 1581, 1434 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.40 (m, 4H), 1.85-2.07 (m, 4H), 2.11-2.44 (m, 3H), 3.19-3.52 (m, 2H), 3.72-3.90 (m, 6H), 3.94 (s, 3H), 4.07 and 4.35 (each m, total 1H), 5.31 and 5.37 (each m, total 1H), 7.20 (m, 1H), 7.35 (dd, J=8.8, 2.0Hz, 1H), 7.55 (d, J=8.3Hz, 1H), 7.64-7.66 (m, 2H), 8.29 (d, J=2.0Hz, 1H), 8.40 (s, 1H), 12.02 (broad s, 1H).

MS (ESI) m/z 568 (M^++1);

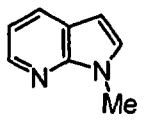
Anal. Calcd for $C_{30}H_{31}ClFN_3O_5$ 1.25H_2O: C, 61.01; H, 5.72; N, 7.12.

Found: C, 61.36; H, 5.74; N, 6.37.

Example 97

trans-4-(1-((2-(1-Methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 1-methyl-1H-pyrrolo(2,3-b)pyridine

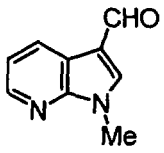


In DMF (85 ml) was dissolved 1H-pyrrolo(2,3-b)pyridine (5.00 g, 42.3 mmol), followed by the addition of sodium hydride (60% in oil, 1.86 g, 46.6 mmol) in portions under

stirring at 0°C. After stirring at 0°C for 30 minutes, the reaction mixture was added with methyl iodide (3.16 ml, 50.8 mmol). The mixture was stirred at the same temperature for 30 minutes. Ice 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-ethyl acetate (1:1, v/v) eluate fractions, 1-methyl-1H-pyrrolo(2,3-b)pyridine (4.87 g, 87%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$): 3.90 (s, 3H), 6.45 (d, J=3.4Hz, 1H), 7.05 (dd, J=7.8,4.6Hz, 1H), 7.18 (d, J=3.4Hz, 1H), 7.90 (dd, J=7.8,1.5Hz, 1H), 8.33 (dd, J=4.6,1.5Hz, 1H).

(Step 2) Synthesis of 1-methyl-1H-pyrrolo(2,3-b)pyridine-3-carbaldehyde



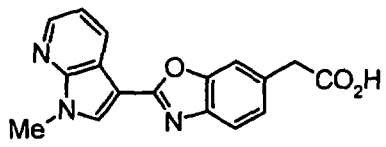
Phosphoryl chloride (5.15 ml, 55.3 mmol) was added dropwise to DMF (70 ml) under stirring at 0°C. After the reaction mixture was stirred at 0°C for 10 minutes, a solution of 1-methyl-1H-pyrrolo(2,3-b)pyridine (4.87 g, 36.8 mmol) in DMF (5 ml) was added dropwise at the same

temperature. After completion of the dropwise addition, the reaction mixture was stirred at 0°C for 4 hours and at 60°C for 3.5 hours. The reaction mixture was poured in ice water - a saturated aqueous solution of sodium bicarbonate to neutralize the mixture therewith, 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 eluate fractions, 1-methyl-1H-pyrrolo(2,3-b)pyridine-3-carbaldehyde (4.87 g, 83%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 3.98 (s, 3H), 7.28 (dd, J=7.8,4.7Hz, 1H), 7.85 (s, 1H), 8.44 (d, J=4.7Hz, 1H), 8.55 (d, J=7.8Hz, 1H), 9.97 (s, 1H).

MS (ESI) m/z 160 (M^+-H).

(Step 3) Synthesis of (2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetic acid



In ethanol (10 ml), 1-methyl-1H-pyrrolo(2,3-b)pyridine-3-carbaldehyde (500 mg, 3.12 mmol) and methyl 4-amino-3-hydroxyphenylacetate (566 mg, 3.12 mmol) were stirred for 20 hours at room temperature. Iodobenzene diacetate (1.21 g, 3.75 mmol) was added to the reaction

mixture, followed by stirring at room temperature for 1 hour. 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, a mixture (1.10 g) of methyl (2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetate and 1-methyl-1H-pyrrolo(2,3-b)pyridine-3-carbaldehyde was obtained as a black solid.

^{1}H-NMR ($CDCl_3$) δ: 3.74 (s, 3H), 3.79 (s, 2H), 4.02 (s, 3H), 7.25-7.32 (m, 2H), 7.52 (s, 1H), 7.67 (d, J=8.1Hz, 1H), 8.07 (s, 1H), 8.47 (m, 1H), 8.71 (d, J=7.8Hz, 1H).

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

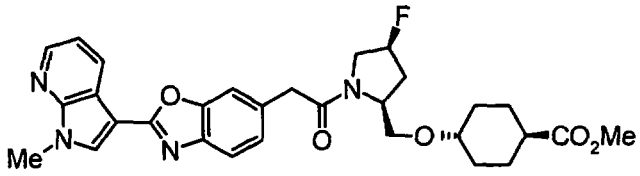
To the mixture (1.10 g) were added THF (35 ml) and 0.25N NaOH (20.6 ml, 5.15 mmol), and the resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was poured in 1N HCl (20 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetic acid (578 g, 62%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.74 (s, 2H), 3.96 (s, 3H), 7.26 (dd. J=8.1,1.5Hz, 1H), 7.36 (dd, J=7.8,4.7Hz, 1H), 7.62 (d, J=1.5Hz, 1H), 7.65 (d, J=8.1Hz, 1H), 8.45 (dd, J=4.7,1.5Hz,

1H), 8.53 (s, 1H), 8.62 (dd, J=7.8,1.5Hz, 1H), 12.37 (broad s, 1H).

MS (ESI) m/z 308 (M^++1).

(Step 4) Synthesis of methyl trans-4-(1-((2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



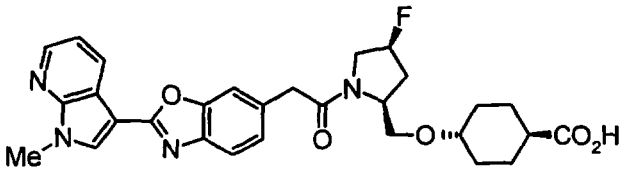
To (2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetic acid (250 mg, 0.81 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (211 mg, 0.81 mmol), HOBt (22.0 mg, 0.16 mmol), and DMAP (20.0 mg, 0.16 mmol) were added DMF (8.5 ml) and EDC HCl (234 mg, 1.22 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 ethyl acetate eluate fractions, methyl trans-4-(1-((2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetyl)-(4S)-

fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (419 mg, 94%) was obtained as a yellow solid.

^{1}H-NMR ($CDCl_3$) δ: 1.18-1.34 (m, 2H), 1.39-1.53 (m, 2H), 1.97-2.51 (m, 7H), 3.27 (m, 1H), 3.36 and 3.51 (each m, total 1H), 3.98-3.64 (m, 8H), 4.01 (s, 3H), 4. 26 and 4.40 (each m, total 1H), 5.25 (m, 1H), 7.20 (m, 1H), 7.29 (m, 1H), 7.51 (m, 1H), 7.65 (dd, J=8.1, 5.6Hz, 1H), 8.05 (d, J=1.8Hz, 1H), 8.45 (d, J=5.6Hz, 1H), 8.69 (dd, J=8.1,1.8Hz, 1H).

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

(Step 5) Synthesis of trans-4-(1-((2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((2-(1-methyl-3-(1H-pyrrolo(2,3-b)pyridinyl))-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (411 mg, 0.75 mmol) were added THF (7.5 ml) and 0.25N NaOH (4.50 ml, 1.12 mmol). The resulting mixture was stirred at room temperature for 19 hours. By the addition of 1N HCl, the pH of the reaction mixture was adjusted to 6. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under

reduced pressure to give the title compound (281 mg, 70%) as a yellow solid.

IR (ATR) ν 2940, 2861, 1716, 1631, 1569, 1525, 1486, 1442 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.37 (m, 4H), 1.85-2.09 (m, 4H), 2.11-2.21 (m, 3H), 3.17-3.31 (m, 2H), 3.45 and 3.58 (m, total 1H), 3.72-3.92 (m, 4H), 3.96 (s, 3H), 4.15 and 4.35 (each m, total 1H), 5.32 and 5.37 (each m, total 1H), 7.21 (m, 1H), 7.35 and 7.36 (each d, J=8.1Hz, total 1H), 7.55 and 7.57 (each s, total 1H), 7.61 and 7.62 (each d, J=8.1Hz, total 1H), 8.44 (dd, J=4.7,1.5Hz, 1H), 8.53 (s, 1H), 8.61 (dd, J=7.8,1.5Hz, 1H), 11.99 (broad s, 1H).

MS (ESI) m/z 535 (M^++1);

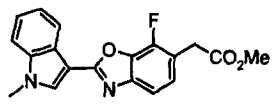
Anal. Calcd for $C_{30}H_{32}FN_3O_5$ 0.75H_2O: C, 63.55; H, 5.98; N, 10.22.

Found: C, 63.67; H, 5.91; N, 10.22.

Example 98

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

(Step 1) Synthesis of methyl (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetate



(Process A)

To 1-methylindole-3-carboxylic acid (917 mg, 5.23 mmol) was added methylene chloride (20 ml). Under stirring at 0°C, oxalyl chloride (0.68 ml, 7.85 mmol) and DMF (catalytic amount) were added. After stirring at room temperature for 1.5 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was added with xylene (20 ml). Methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (1.0 g, 5.0 mmol) and boric acid (539 mg, 8.72 mmol) were added to the resulting mixture, followed by stirring at 160°C for 3 days. After the reaction mixture was cooled to room temperature, ice water was added thereto, 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 subjected to chromatography on a silica gel column to collect chloroform/ethyl acetate (10/1) eluate fractions and then, purified by chromatography using a thin layer plate, whereby from chloroform/acetone (10/1) eluate fractions, methyl 7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolylacetate (62 mg, 4%) was obtained as a pale brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.81 (s, 2H), 3.88 (s, 3H), 7.15 and 7.17 (each d, each J=6.4Hz, total 1H, amide isomers), 7.34-7.40 (m, 3H), 7.44 (d, J=8.1Hz, 1H), 7.94

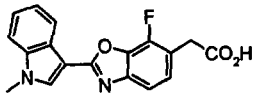
(s, 1H), 8.43 (m, 1H).

MS (ESI) m/z 339 (M^++1).

(Process B)

In methanol (50 ml), 3-formyl-1-methylindole (796 mg, 5.0 mmol), methyl (4-amino-2-fluoro-3-hydroxyphenyl)acetate (1.0 g, 5.0 mmol) and Molecular Sieves 4A (10 g) were stirred at room temperature for 5 hours and then, at 70°C for 3 hours. The reaction mixture was cooled to room temperature and iodobenzene diacetate (5.0 mmol) was added thereto. After stirring 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, whereby from n-hexane/ethyl acetate (3/1) eluate fractions, methyl 7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolylacetate (860 mg, including impurities) was obtained as a pale brown solid. The compound was provided for the subsequent reaction without further purification.

(Step 2) Synthesis of (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid

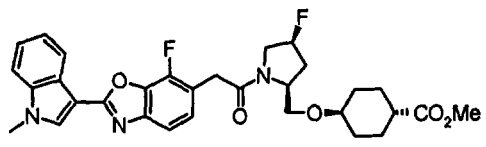


Methyl 7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolylacetate (860 mg, the product obtained by Process A of Step 1) was dissolved in THF/methanol (20/10

ml). To the resulting solution was added 1N NaOH (20 ml), followed by stirring at room temperature for 1.5 hours. The reaction mixture was then distilled under reduced pressure to remove the solvent. To the residue thus obtained were added ether and 1N NaOH to separate the mixture into layers. The water layer 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, whereby (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (350 mg, 22%) was obtained as a dark green solid. The compound was provided for the subsequent reaction without further purification.

^{1}H-NMR ($CDCl_3$-CD_3OD) δ: 3.56 (s, 3H), 3.91 (s, 2H), 7.36 (m, 3H), 7.79 (s, 1H), 8.26 (d, J=6.8Hz, 1H), 9.93 (s, 1H).
MS (ESI) m/z 325 (M^++1).

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



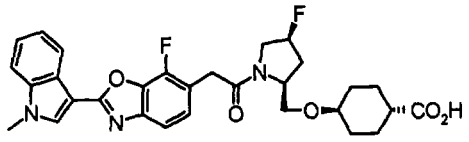
A mixture of (7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (350 mg, 1.08 mmol), methyl trans-4-((4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (280 mg, 1.08 mmol), EDC HCl (311 mg, 1.62 mmol), HOBt (219 mg, 1.62 mmol) and triethylamine (0.75 ml, 5.40 mmol) was stirred for 7 hours in DMF (10 ml). 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 on a silica gel column, whereby from n-hexane/ethyl acetate (3/1) eluate fractions, methyl trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (360 mg, 59%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.65 (m, 4H), 1.95-2.56 (m, 7H), 3.21-3.39 (m, 2H), 3.56 (dd, J=8.8,6.8Hz, 1H), 3.64 and 3.67 (each s, total 3H, amide isomers), 3.68-3.90 (m, 3H), 3.92 (s, 3H), 4.00 and 4.03 (each s, total 1H), 4.31-4.42 (m, 1H), 5.19-5.39 (m, 1H), 7.20 (q, J=8.5Hz, 1H), 7.36-7.48 (m, 4H), 7.98 (s, 1H), 8.45 (m, 1H).

MS (ESI) m/z 566 (M^++1).

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



To methyl trans-4-(1-((7-fluoro-2-(1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (130 mg, 0.23 mmol) were added THF/methanol (10/5 ml) and 1N NaOH (4 ml). The resulting mixture was stirred at room temperature for 13 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue was 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 (93 mg, 74%) as a brown solid.

IR (ATR) ν 2941, 2864, 1716, 1628, 1583, 1504, 1442, 1369 cm^{-1};

^{1}H-NMR (DMSO) δ: 1.13-1.43 (m, 5H), 1.82-2.36 (m, 7H), 3.24 (m, 1H), 3.46-3.93 (m, 4H), 3.95 (s, 3H), 4.11 and 4.15 (each s, total 1H, amide isomers), 4.42 (m, 1H), 5.25-5.50 (m, 1H), 7.22 (m, 1H), 7.35 (m, 2H), 7.48 and 7.50 (each t, J=4.4 and 3.6Hz respectively, total 1H, amide isomers), 7.63 (d, J=6.6Hz, 1H), 8.29 (d, J=7.3Hz, 1H), 8.44 and 8.45 (each s, total 1H, amide isomers).

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

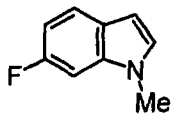
Anal. Calcd for $C_{30}H_{31}F_2N_3O_5$ $1H_2O$: C, 63.26; H, 5.84; N, 7.38.

Found: C, 63.52; H, 5.77; N, 7.25.

Example 99

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

(Step 1) Synthesis of 6-fluoro-1-methylindole

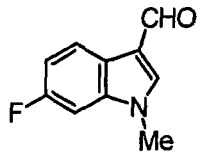


In DMF (65 ml) was dissolved 6-fluoroindole (6.10 g, 45.1 mmol). Under stirring at 0°C, sodium hydride (60% in oil, 1.45 g, 36.3 mmol) was added in portions. After stirring at 0°C for 30 minutes, methyl iodide (2.46 ml, 39.6 mmol) was added to the reaction mixture. The reaction mixture was stirred further at the same temperature for 2.5 hours. 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 (5:1, v/v) eluate fractions, 6-fluoro-1-methylindole (6.71 g, 99%) was obtained as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 6.45 (d, J=3.2Hz, 1H), 6.86 (ddd, J=9.8,8.5,2.2Hz, 1H), 6.98 (dd, J=9.8,2.2Hz, 1H), 7.01 (d, J=3.2Hz, 1H), 7.51 (dd, J=8.5,5.3Hz, 1H).

MS (ESI) m/z 150 (M^++1).

(Step 2) Synthesis of 6-fluoro-1-methylindole-3-carbaldehyde

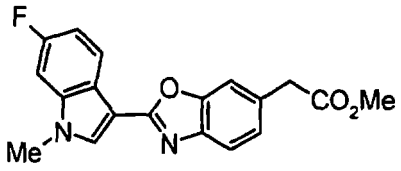


Phosphoryl chloride (5.87 ml, 63.0 mmol) was added in portions while stirring DMF (45 ml) at 0°C. After stirring at the same temperature for 20 minutes, the reaction mixture was added with a solution of 6-fluoro-1-methylindole (6.71 g, 45.0 mmol) in DMF (45 ml) at 0°C. The reaction mixture was stirred for further .5 hour. Ice water and 1N NaOH were added to the reaction mixture to neutralize the same, 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 ethyl acetate eluate fractions, 6-fluoro-1-methylindole-3-carbaldehyde (4.18 g, 52%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.85 (s, 3H), 7.03-7.11 (m, 2H), 7.68 (s, 1H), 8.25 (dd, J=8.8,5.6Hz, 1H), 9.97 (s, 1H).

MS (ESI) m/z 219 (M^++1+CH_3CN).

(Step 3) Synthesis of methyl (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid

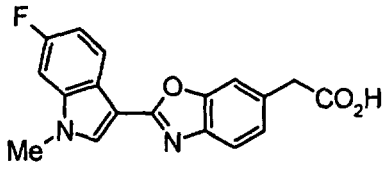


In ethanol (15 ml), 6-fluoro-1-methylindole-3-carbaldehyde (500 mg, 2.82 mmol) and methyl 4-amino-3-hydroxyphenylacetate (767 mg, 4.23 mmol) were stirred at room temperature for 2 hours. Iodobenzene diacetate (1.09 g, 3.38 mmol) was added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was then distilled under reduced pressure to remove the solvent. The residue was purified chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (1:1, v/v) eluate fractions, methyl (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetate (889 mg, 93%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.72 (s, 3H), 3.76 (s, 2H), 3.85 (s, 3H) 7.05-7.12 (m, 2H), 7.22 (dd, J=8.1,1.5Hz, 1H), 7.49 (d, J=1.5Hz, 1H), 7.65 (d, J=8.1Hz, 1H), 7.89 (s, 1H), 8.38 (dd, J=8.9,5.4Hz, 1H).

MS (ESI) m/z 339 (M^++1).

(Step 4) Synthesis of (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid

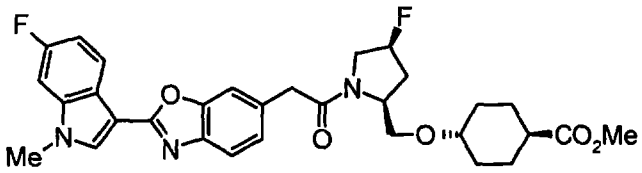


To methyl (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetate (889 mg, 2.63 mmol) were added THF (25 ml) and 0.25N NaOH (15.8 ml, 3.95 mmol). The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was poured in 1N HCl (30 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (741 mg, 87%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.71 (s, 2H), 3.94 (s, 3H), 7.18 (td, J=9.5,2.5Hz, 1H), 7.23 (d, 1H, J=7.8Hz, 1H), 7.59-7.64 (m, 3H), 7.97 (dd, J=9.5,2.5Hz, 1H), 8.39 (s, 1H), 12.35 (broad s, 1H).

MS (ESI) m/z 325 (M^++1).

(Step 5) Synthesis of methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



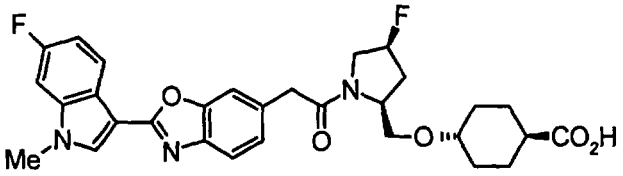
To (2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (200 mg, 0.62 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (160 mg, 0.62 mmol),

HOBt (17.0 mg, 0.12 mmol), and DMAP (15.0 mg, 0.12 mmol) were added DMF (6.0 ml) and EDC HCl (142 mg, 0.74 mmol). The resulting mixture was stirred at room temperature for 21 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 ethyl acetate eluate fractions, methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (355 mg, 99%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.16-1.32 (m, 2H), 1.38-1.51 (m, 2H), 1.95-2.48 (m, 7H), 3.24 (m, 1H), 3.34 and 3.49 (each m, total 1H), 3.62 and 3.65 (each s, total 3H), 3.83 (s, 3H), 3.90-4.06 (m, 2H), 4. 25 and 4.37 (each m, total 1H), 5.23 (m, 1H), 7.04-7.10 (m, 2H), 7.17 and 7.18 (each dd, J=7.8,1.4Hz, total 1H), 7.46 and 7.47 (each d, J=1.4Hz, 2H), 7.61 and 7.63 (each d, J=7.8Hz, 1H), 7.87 (s, 1H), 8.35 (dd, J=8.5, 5.3Hz, 1H).

MS (ESI) m/z 566 (M^++1).

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



To methyl trans-4-(1-((2-(6-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (355 mg, 0.63 mmol) were added THF (6.5 ml) and 0.25N NaOH (3.77 ml, 0.94 mmol). The resulting mixture was stirred at room temperature for 15 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 (294 mg, 85%) as a yellow solid.

IR (ATR) ν 2938, 1712, 1616, 1577, 1434 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.39 (m, 4H), 1.84-1.93 (m, 4H), 2.06-2.44 (m, 3H), 3.16-3.99 (m, 10H), 4.13 and 4.33 (each m, total 1H), 5.30 and 5.36 (each m, total 1H), 7.12-7.21 (m, 2H), 7.49 (dd, J=9.8,2.2Hz, 1H), 7.51 and 7.53 (each s, total 1H), 7.60 and 7.61 (each d, J=8.1Hz, total 2H), 8.28 (dd, J=8.1,5.6Hz, 1H), 8.30 and 8.31 (each s, total 1H), 12.03 (broad s, 1H).

MS (ESI) m/z 553 (M^++2);

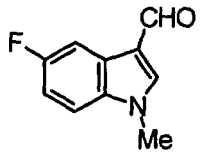
Anal. Calcd for $C_{30}H_{31}ClFN_3O_5$ 0.5H_2O: C, 64.28; H, 5.75; N, 7.50.

Found: C, 64.59; H, 5.77; N, 7.44.

Example 100

trans-4-(1-((2-(5-Fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 5-fluoro-1-methylindole-3-carbaldehyde

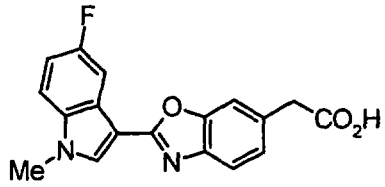


In DMF (60 ml) was dissolved 5-fluoroindole-3-carbaldehyde (5.00 g, 30.6 mmol). Under stirring at 0°C, sodium hydride (60% in oil, 1.35 g, 33.7 mmol) was added in portions. After the reaction mixture was stirred at the same temperature for 1 hour, methyl iodide (5.72 ml, 91.9 mmol) was added thereto. The resulting mixture was stirred further at 0°C for 2 hours. A saturated aqueous solution of ammonium chloride was added to the reaction mixture to neutralize the same, 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 ethyl acetate eluate fractions, 5-fluoro-1-methylindole-3-carbaldehyde (5.42 g, 100%) was obtained as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ: 3.88 (s, 3H), 7.09 (m, 1H), 7.29 (d, J=9.3,4.2Hz, 1H), 7.71 (s, 1H), 7.98 (dd, J=9.3,2.4Hz, 1H), 9.96 (s, 1H).

MS (ESI) m/z 178 (M^++1).

(Step 2) Synthesis of (2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid



In ethanol (25 ml), 5-fluoro-1-methylindole-3-carbaldehyde (989 mg, 5.58 mmol) and methyl 4-amino-3-hydroxyphenylacetate (1.27 g, 6.99 mmol) were stirred at room temperature for 9 hours. Iodobenzene diacetate (2.16 g, 6.69 mmol) was added and the mixture was stirred further at room temperature for 18 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. The residue thus obtained was purified by chromatography on a silica gel column, whereby from n-hexane-ethyl acetate (1:2, v/v) eluate fractions, a mixture (933 mg) of methyl (2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetate and 5-fluoro-1-methylindole-3-carboxaldehyde was obtained as a red solid.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.77 (s, 2H), 3.89 (s, 3H) 7.10 (m, 1H), 7.22-7.28 (m, 2H), 7.50 (m, 1H), 7.65 (d, J=8.1Hz, 1H), 7.92 (s, 1H), 8.11 (dd, J=9.3, 2.4Hz, 1H).

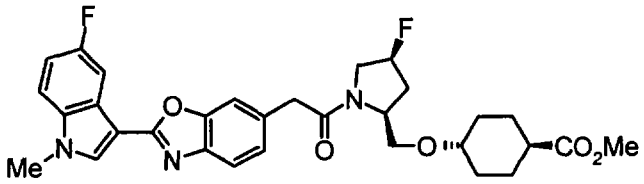
MS (ESI) m/z 339 (M^++1).

To the mixture (933 mg) were added THF (30 ml) and 0.25N NaOH (16.6 ml, 4.15 mmol) and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured in 1N HCl (30 ml). The crystals thus precipitated were collected by filtration under reduced pressure, washed with water, and dried under reduced pressure to give (2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (434 mg, 24%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.72 (s, 2H), 3.90 (s, 3H), 7.15 (td, J=9.8,2.2Hz, 1H), 7.23 (dd, J=8.1,1.2Hz, 1H), 7.50 (dd, J=9.8,2.2Hz, 1H), 7.59 (d, J=1.2Hz, 1H), 7.62 (d, J=8.1Hz, 1H), 8.29 (dd, J=8.8,5.4Hz, 1H), 8.33 (s, 1H), 12.37 (broad s, 1H).

MS (ESI) m/z 325 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



To (2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (200 mg, 0.62 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound

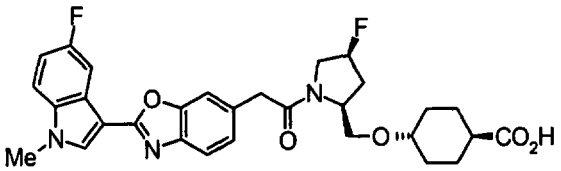
synthesized in (Step 3) of Example 21) (160 mg, 0.62 mmol), HOBt (17.0 mg, 0.12 mmol), and DMAP (15.0 mg, 0.12 mmol) were added DMF (6.0 ml) and EDC HCl (142 mg, 0.74 mmol). The resulting mixture was stirred at room temperature for 15 hours. Water was added to the reaction mixture, followed by extraction 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 ethyl acetate eluate fractions, methyl trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (346 mg, 99%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 1.17-1.34 (m, 2H), 1.39-1.53 (m, 2H), 1.97-2.51 (m, 7H), 3.26 (m, 1H), 3.35 and 3.51 (each m, total 1H), 3.64 and 3.67 (each s, total 3H), 3.90 (s, 3H), 3.91-4.13 (m, 2H), 4.26 and 4.40 (each m, total 1H), 5.24 (m, 1H), 7.09 (m, 1H), 7.19 and 7.20 (each dd, J=7.8,1.5Hz, total 1H), 7.48 and 7.50 (each d, J=1.5Hz, 2H), 7.63 and 7.65 (each d, J=7.8Hz, 1H), 7.94 (s, 1H), 8.12 (dd, J=9.5,2.4Hz, 1H).

MS (ESI) m/z 566 (M^++1).

(Step 4) Synthesis of trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To methyl trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (346 mg, 0.61 mmol) were added THF (6.5 ml) and 0.25N NaOH (3.67 ml, 0.92 mmol). The resulting mixture was stirred at room temperature for 15 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 (254 mg, 75%) as a yellow solid.

IR (ATR) ν 2938, 1716, 1616, 1631, 1577, 1484, 1434 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.09-1.39 (m, 4H), 1.84-1.97 (m, 4H), 2.03-2.28 (m, 3H), 3.15-4.00 (m, 7H), 3.93 (s, 3H), 4.15 and 4.34 (each m, total 1H), 5.30 and 5.36 (each m, total 1H), 7.16-7.21 (m, 2H), 7.52 and 7.54 (each s, total 1H), 7.61-7.64 (m, 2H), 7.97 (dd, J=9.8,2.9Hz, 1H), 8.36 and 8.37 (each s, total 1H), 12.03 (broad s, 1H).

MS (ESI) m/z 553 (M^++1);

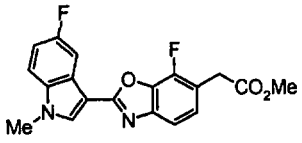
Anal. Calcd for $C_{30}H_{31}ClFN_3O_5$ 0.5H_2O: C, 64.28; H, 5.75; N, 7.50.

Found: C, 64.54; H, 5.75; N, 7.44.

Example 101

trans-4-(1-((2-(5-Fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetate



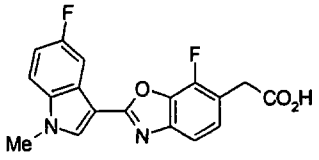
In ethanol (15 ml), Molecular Sieves 4A (1.20 g) was added to 5-fluoro-1-methylindolyl-3-carbaldehyde (515 mg, 2.91 mmol) and methyl 4-amino-2-fluoro-3-hydroxyphenylacetate (690 mg, 3.47 mmol) and the resulting mixture was stirred at room temperature for 18 hours. Iodobenzene diacetate (1.35 g, 4.10 mmol) was then added, and the resulting mixture was stirred further at room temperature for 1 hour. 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 (1/1) eluate fractions, methyl (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetate (279 mg, 27%) was obtained as a brown crystalline powder.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.81 (s, 2H), 3.90 (s, 3H), 7.10 (dt, J=2.4,8.8Hz, 1H), 7.17 (dd, J=6.4,8.0Hz, 1H), 7.31 (dd, J=4.4,8.8Hz, 1H), 7.44 (d, J=8.4Hz, 1H), 7.98 (s,

1H), 8.11 (dd, J=2.4,9.6Hz, 1H).

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

(Step 2) Synthesis of (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetic acid

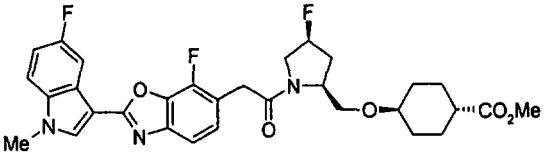


To methyl (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetate (279 mg, 0.78 mmol) were added THF/methanol (1/1, 20 ml) and 0.25N NaOH (9.4 ml, 2.35 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in 1N HCl to acidify the mixture therewith, 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. The crystals thus obtained were collected by filtration under reduced pressure, washed with hexane, and dried under reduced pressure to give (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetic acid (208 mg, 78%) as a brown crystalline powder.

^{1}H-NMR (DMSO-d_6) δ: 3.78 (s, 2H), 3.95 (s, 3H), 7.19-7.24 (m, 1H), 7.29 (d, J=8.0Hz, 1H), 7.50 (d, J=8.4Hz, 1H), 7.66 (dd, J=4.4,8.8Hz, 1H), 7.94 (brd, J=9.6Hz, 1H), 8.50 (brs, 1H), 12.52 (brs, 1H).

MS (ESI) m/z 342 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



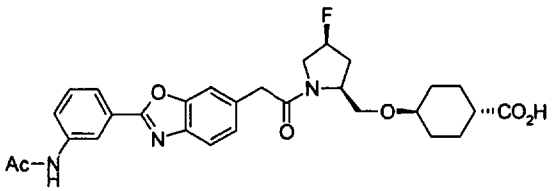
In DMF (15 ml), HOBt (16.0 mg, 0.12 mmol) was added to (2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetic acid (202 mg, 0.59 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy) cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (153 mg, 0.59 mmol) and EDC-HCl (124 mg, 0.65 mmol). The resulting mixture was stirred at room temperature for 17 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 hexane/ethyl acetate (1/5) eluate fractions, methyl trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (295 mg, 86%) was obtained as a colorless amorphous substance.

^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.20-1.31 (m, 2H), 1.39-1.55 (m, 2H), 1.99-2.55 (series of m, 8H), 3.22-4.42

(series of m, 7H), 3.64 and 3.67 (s, total 3H), 3.90 (s, 3H), 5.19-5.40 (m, 1H), 7.08-7.13 (m, 1H), 7.20 (dd, J=8.8, 15.2Hz, 1H), 7.32 (dd, J=4.0,8.8Hz, 1H), 7.45 (t, J=8.0Hz, 1H), 7.98 (s, 1H), 8.11 (dd, J=2.4,9.6Hz, 1H).

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

(Step 4) Synthesis of trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid



To trans-4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-7-fluoro-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (288 mg, 0.49 mmol) were added THF/methanol (1/1, 20 ml) and 0.25N NaOH (9.9 ml, 2.45 mmol). The resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was poured in 1N HCl to acidify the mixture therewith, 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. The residue was purified by chromatography on a silica gel column, whereby from chloroform/methanol (10/1) eluate fractions, the title compound (296 mg, 100%) was obtained as a colorless amorphous substance.

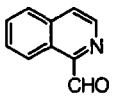
^{1}H-NMR ($CDCl_3$), mixture of rotamars, δ: 1.21-1.36 (m, 2H), 1.42-1.56 (m, 2H), 2.00-2.50 (series of m, 8H), 2.20 (s, 3H), 3.22-4.45 (series of m, 7H), 3.89 and 3.93 (s, total 3H), 5.20-5.40 (m, 1H), 7.10 (t, J=8.8Hz, 1H), 7.20 (dd, J=8.0, 14.4Hz, 1H), 7.30-7.32 (m, 1H), 7.46 (t, J=8.0Hz, 1H), 7.99 (s, 1H), 8.10 (dd, J=2.0,9.2Hz, 1H).

MS (ESI) m/z 570 (M^++1).

Example 102

trans-4-(1-(2-(1-Isoquinolinyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of 1-isoquinolinecarbaldehyde



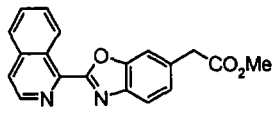
In 1,4-dioxane (20 ml) was dissolved 1-methylisoquinoline (300 mg, 2.10 mmol). To the resulting solution was added selenium dioxide (323 mg, 2.91 mmol), followed by heating under reflux for 1.5 hours under a nitrogen gas stream. After cooling to room temperature, the reaction mixture was filtered through Celite. 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, v/v) eluate fractions, 1-isoquinolinecarbaldehyde (252 mg, 77%) was obtained as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 7.73-7.79 (m, 2H), 7.88-7.93 (m, 2H),

8.74-8.76 (m, 1H), 9.30-9.33 (m, 1H), 10.39 (s, 1H).

MS (ESI) m/z 158 (M^++1).

(Step 2) Synthesis of methyl (2-(1-isoquinolinyl)-6-benzoxazolyl)acetate

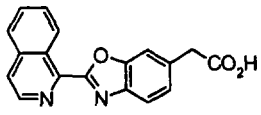


In ethanol (5 ml), 1-isoquinolinecarbaldehyde (252 mg, 1.60 mmol) and methyl 4-amino-3-hydroxyphenylacetate (349 mg, 1.93 mmol) were stirred at room temperature for 12 hours. Iodobenzene diacetate (619 mg, 1.92 mmol) was added and the reaction mixture was stirred further at room temperature for 15 minutes. 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 (4:1 to 3:1, v/v) eluate fractions, methyl (2-(1-isoquinolinyl)-6-benzoxazolyl)acetate (166 mg, 33%) was obtained as a yellow amorphous substance.

^{1}H-NMR ($CDCl_3$) δ: 3.73 (s, 3H), 3.82 (s, 2H), 7.35-7.38 (m, 1H), 7.68 (m, 1H), 7.75-7.95 (m, 5H), 8.77-8.78 (m, 1H), 9.67-9.70 (m, 1H).

MS (ESI) m/z 319 (M^++1).

(Step 3) Synthesis of (2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid

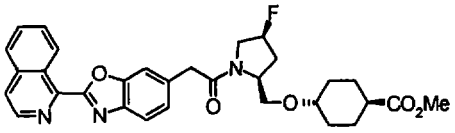


To methyl (2-(1-isoquinolinyl)-6-benzoxazolyl)acetate (166 mg, 0.52 mmol) were added THF (3 ml) and 0.5N NaOH (3.0 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was poured in ice-1N HCl to acidify therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid (138 mg, 87%) as a pale brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.82 (s, 2H), 7.41-7.43 (m, 1H), 7.82 (s, 1H), 7.88-7.95 (m, 3H), 8.13-8.17 (m, 2H), 8.76-8.78 (m, 1H), 9.53-9.55 (m, 1H), 12.45 (broad s, 1H).

MS (ESI) m/z 305 (M^++1).

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



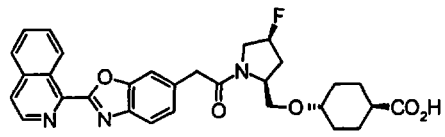
In DMF (10 ml), (2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid (138 mg, 0.45 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (118 mg, 0.46 mmol),

EDC·HCl (130 mg, 0.68 mmol), HOBt (92 mg, 0.68 mmol), and triethylamine (95 μl, 0.68 mmol) were stirred at room temperature for 15 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 toluene-acetone (4:1, v/v) eluate fractions, methyl trans-4-(1-(2-(1-isoquinolinyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (245 mg, 99%) was obtained as a pale yellow thick sticky liquid.

^{1}H-NMR ($CDCl_3$) δ: 1.21-1.53 (m, 4H), 1.97-2.52 (m, 7H), 3.24-3.37 and 3.50-3.54 (each m, total 2H), 3.64-4.14 (m, 8H), 4.25-4.28 and 4.39-4.41 (each m, total 1H), 5.18-5.19 and 5.31-5.33 (each m, total 1H), 7.15-7.24 (m, 1H), 7.33-7.36 (m, 1H), 7.64-7.93 (m, 5H), 8.75-8.77 (m, 1H), 9.66-9.68 (m, 1H).

MS (ESI) m/z 546.5 (M^++1).

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



To methyl trans-4-(1-(2-(1-isoquinolinyl)-6-

benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (245 mg, 0.45 mmol) were added THF (3.0 ml) and 0.5N NaOH (2.7 ml, 1.35 mmol). The resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured in ice-1N HCl to acidify the mixture. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give the title compound (175 mg, 73%) as a pale yellow solid.

^{1}H-NMR (DMSO-d_6) δ: 1.12-1.37 (m, 4H), 1.84-2.11 (m, 4H), 2.14-2.21 (m, 3H), 3.17-4.04 (m, 7H), 4.15 and 4.37-4.39 (each m, total 1H), 5.25-5.32 and 5.39-5.45 (each m, total 1H), 7.33-7.37 (m, 1H), 7.72-7.74 (m, 1H), 7.86-7.93 (m, 3H), 8.11-8.15 (m, 2H), 8.74-8.76 (m, 1H), 9.51-9.53 (m, 1H), 12.02 (broad s, 1H).

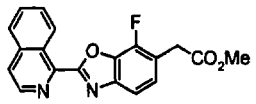
MS (ESI) m/z 532.5 (M^++1);

Anal. Calcd for $C_{30}H_{30}FN_3O_5 \cdot 1H_2O$: C, 65.56; H, 5.87; N, 7.65. Found: C, 65.39; H, 5.94; N, 7.51.

Example 103

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

(Step 1) Synthesis of methyl (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetate

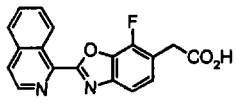


In ethanol (13 ml), isoquinoline-1-carbaldehyde (500 mg, 3.18 mmol) and methyl 4-amino-2-fluoro-3-hydroxyphenylacetate (632 mg, 3.17 mmol) were stirred at room temperature for 2 days. Iodobenzene diacetate (1.23 g, 3.82 mmol) was added, and the reaction mixture was stirred at room temperature for 10 minutes. 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 (3:1, v/v) eluate fractions, methyl (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetate (155 mg, 14%) was obtained as a red brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.74 (s, 3H), 3.87 (s, 2H), 7.30-7.33 (m, 1H), 7.66-7.94 (m, 5H), 8.78-8.79 (m, 1H), 9.58 (m, 1H).

MS (ESI) m/z 337 (M^++1).

(Step 2) Synthesis of (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid



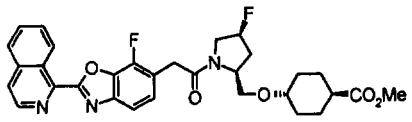
To methyl (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetate (155 mg, 0.46 mmol) were added THF (3 ml) and 0.5N NaOH (3.0 ml, 1.50 mmol). The resulting mixture was stirred at room temperature for 1 hour. The

reaction mixture was poured in ice-1N HCl to acidify the mixture therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid (116 mg, 78%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.86 (s, 2H), 7.44-7.48 (m, 1H), 7.78-7.80 (m, 1H), 7.88-7.93 (m, 2H), 8.15-8.16 (m, 2H), 8.77-8.79 (m, 1H), 9.48-9.50 (m, 1H), 12.63 (broad s, 1H).

MS (ESI) m/z 323 (M^++1).

(Step 3) Synthesis of methyl trans-4-(1-(7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



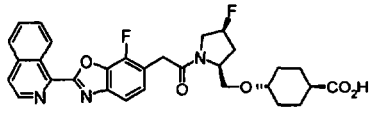
In DMF (5 ml), (7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolyl)acetic acid (116 mg, 0.36 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (93 mg, 0.36 mmol), EDC·HCl (103 mg, 0.54 mmol), HOBt (73 mg, 0.54 mmol), and triethylamine (75 µl, 0.54 mmol) were stirred at room temperature for 12 hours. The reaction mixture was poured in water. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and

dried under reduced pressure to give methyl trans-4-(1-(7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (192 mg, 95%) as a brown solid.

^{1}H-NMR ($CDCl_3$) δ: 1.25-1.54 (m, 4H), 1.97-2.51 (m, 7H), 3.26-3.38 and 3.54-3.58 (each m, total 2H), 3.64-4.09 (m, 8H), 4.37-4.39 (m, 1H), 5.21 and 5.34-5.39 (each m, total 1H), 7.33-7.40 (m, 1H), 7.66-7.71 (m, 1H), 7.80-7.82 (m, 2H), 7.86-7.87 (m, 1H), 7.95 (m, 1H), 8.79-8.80 (m, 1H), 9.58-9.59 (m, 1H).

MS (ESI) m/z 564.5 (M^++1).

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



To methyl trans-4-(1-(7-fluoro-2-(1-isoquinolinyl)-6-benzoxazolylacetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (192 mg, 0.34 mmol) were added THF (4.0 ml) and 0.25N NaOH (4.0 ml, 1.00 mmol). The resulting mixture was stirred at room temperature for 13 hours. The reaction mixture was poured into ice-1N HCl to acidify the mixture therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under

reduced pressure to give the title compound (158 mg, 84%) as a brown solid.

^{1}H-NMR (DMSO-d_6) δ: 1.13-1.41 (m, 4H), 1.84-2.32 (m, 7H), 3.16-4.45 (m, 7H), 5.26-5.35 and 5.40-5.49 (each m, total 1H), 7.32-7.39 (m, 1H), 7.75-7.78 (m, 1H), 7.87-7.93 (m, 2H), 8.14-8.16 (m, 2H), 8.77-8.78 (m, 1H), 9.48-9.50 (m, 1H), 12.02, (broad s, 1H).

MS (ESI) m/z 550.5 (M^++1);

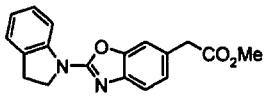
Anal. Calcd for $C_{30}H_{29}F_2N_3O_5 \cdot 1H_2O$: C, 63.48; H, 5.51; N, 7.40.

Found: C, 63.43; H, 5.48; N, 7.14.

Example 104

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

(Step 1) Synthesis of methyl (2-(1-indolinyl)-6-benzoxazolyl)acetate



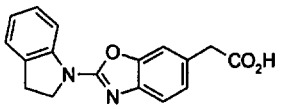
Indoline (0.34 ml, 3.0 mmol) was dissolved in THF (30 ml). To the resulting solution was added thiocarbonyldiimidazole (588 mg, 3.0 mmol), followed by stirring at room temperature for 3 hours. To the reaction mixture was added methyl 4-amino-3-hydroxyphenylacetate (544 mg, 3.0 mmol) and the resulting mixture was stirred at room temperature for 2 days. Mercuric oxide (yellow) (785

mg, 3.0 mmol) was added and the resulting mixture was stirred at 70°C for 6 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-(1-indolinyl)-6-benzoxazolyl)acetate (200 mg, 22%) was obtained as a brown solid.

^{1}H-NMR ($CDCl_3$) δ 3.30: (t, J=8.6Hz, 2H), 3.70 (s, 2H), 3.71 (s, 3H), 4.32 (t, J=8.3Hz, 2H), 7.00 (dt, J=7.3,1.0Hz, 1H), 7.13 (dd, J=8.1,6.4Hz, 1H), 7.23 (d, J=6.8Hz, 1H), 7.28 (d, J=7.3Hz, 1H), 7.36 (d, J=1.2Hz, 1H), 7.42 (d, J=8.1Hz, 1H), 7.97 (d, J=8.1Hz, 1H).

MS (ESI) m/z 309 (M^++1).

(Step 2) Synthesis of (2-(1-indolinyl)-6-benzoxazolyl)acetic acid



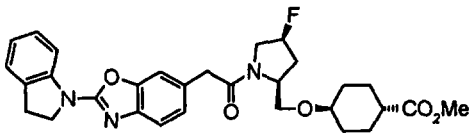
To methyl (2-(1-indolinyl)-6-benzoxazolyl)acetate (200 mg, 0.649 mmol) were added THF/methanol (6/3 ml) and 1N NaOH (3 ml). The resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was distilled under reduced pressure to remove the solvent. To the residue was added 1N HCl to acidify the residue

therewith. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (2-(1-indolinyl)-6-benzoxazolyl)acetic acid (161 mg, 84%) as a brown solid.

^{1}H-NMR (DMSO) δ: 3.27 (t, J=8.6Hz, 2H), 3.65 (s, 2H), 4.28 (t, J=8.3Hz, 2H), 7.00 (t, J=7.3Hz, 1H), 7.13 (dd, J=8.1,2.0Hz, 1H), 7.28 (t, J=6.9Hz, 2H), 7.38 (d, J=8.1Hz, 1H), 7.46 (s, 1H), 7.97 (d, J=7.8Hz, 1H), 12.32 (br, 1H).

MS (ESI) m/z 249 (M^++1).

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



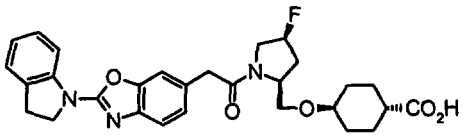
In DMF (5 ml), (2-(1-indolinyl)-6-benzoxazolyl)acetic acid (161 mg, 0.547 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (142 mg, 0.547 mmol), EDC HCl (157 mg, 0.821 mmol), HOBt (111 mg, 0.821 mmol) and triethylamine (0.38 ml, 2.74 mmol) were stirred at room temperature for 15 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 on a silica gel column, whereby from chloroform/acetone (10/1) eluate fractions, methyl trans-4-((4S)-fluoro-1-((2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (180 mg, 61%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.13-1.53 (m, 5H), 1.96-2.51 (m, 6H), 3.22-3.38 (m, 4H), 3.50 (t, J=8.1Hz, 1H), 3.64 and 3.66 (each s, total 3H, amide isomers), 3.68-4.03 (m, 4H), 4.24 and 4.34 (q and m, J=7.6Hz, total 1H, amide isomers), 4.31 (t, J=8.6Hz, 2H), 5.24 (dq, J=53.1,4.4Hz, 1H), 6.99 (t, J=7.3Hz, 1H), 7.10 (m, 1H), 7.23 (d, J=7.1Hz, 1H), 7.27 (t, J=7.6Hz, 1H), 7.36 (dd, J=8.3,1.2Hz, 1H), 7.40 and 7.42 (each d, each J=7.3Hz, total 1H, amide isomers), 7.96 (d, J=8.1Hz, 1H).

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

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



To methyl trans-4-((4S)-fluoro-1-((2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (180 mg, 0.336 mmol) were added THF/methanol (8/4 ml) and 1N NaOH (4 ml).

After stirring at room temperature for 17 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, washed with water and dried under reduced pressure to give the title compound (147 mg, 84%) as a colorless solid.

IR (ATR) ν 2937, 2860, 1722, 1635, 1601, 1570, 1487, 1439 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.19-1.39 (m, 5H), 1.83-2.21 (m, 7H), 3.17 (t, J=9.3Hz, 1H), 3.27 (t, J=8.6Hz, 1H), 3.40-3.94 (m, 5H), 4.13 and 4.33 (each m, total 1H, amide isomers), 4.28 (t, J=8.6Hz, 2H), 5.31 and 5.36 (dt and d, J=54.1, 4.4 and 54.1Hz, respectively, total 1H, amide isomers), 6.98 (t, J=7.3Hz, 1H), 7.09 (t, J=8.8Hz, 1H), 7.27 (t, J=7.8Hz, 1H), 7.29 (t, J=7.1Hz, 1H), 7.37 (t, J=4.2Hz, 1H), 7.40 and 7.42 (d and s, J=2.7Hz, total 1H, amide isomers), 7.97 (d, J=8.1Hz, 1H), 12.03 (s, 1H).

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

Anal. Calcd for $C_{29}H_{32}FN_3O_5 \cdot 0.4H_2O$: C, 65.87; H, 6.25; N, 7.95; F, 3.59.

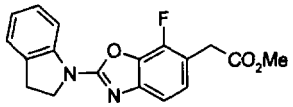
Found: C, 65.93; H, 6.27; N, 7.71; F, 3.45.

Example 105

trans-4-(1-((7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-

pyrrolidinylmethoxy)cyclohexanecarboxylic acid:

(Step 1) Synthesis of methyl (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetate



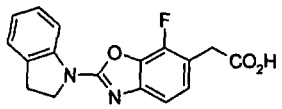
Indoline (0.49 ml, 4.36 mmol) was dissolved in THF (20 ml). To the resulting solution was added N,N'-thiocarbonyldiimidazole (863 mg, 4.36 mmol). The resulting mixture was stirred at room temperature for 14 hours. Methyl 4-amino-2-fluoro-3-hydroxyphenylacetate (1.0 g, 5.0 mmol) was added to the reaction mixture, followed by stirring at 70°C for 1 day. Mercuric oxide (yellow) (944 mg, 4.36 mmol) was added to the reaction mixture and the resulting mixture was heated at 70°C for 15 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 (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetate (330 mg, 23%) was obtained as a pale brown solid.

^{1}H-NMR ($CDCl_3$) δ: 3.31 (t, J=8.5Hz, 2H), 3.72 (s, 3H), 3.76 (s, 2H), 4.33 (t, J=8.3Hz, 2H), 7.02 (t, J=7.3Hz, 1H), 7.09 (t, J=6.6Hz, 1H), 7.23 (t, J=8.0Hz, 2H), 7.29 (d, J=8.3Hz,

1H), 7.99 (d, J=8.0Hz, 1H).

MS (ESI) m/z 327 (M^++1).

(Step 2) Synthesis of (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetic acid

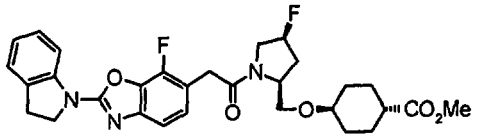


To methyl (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetate (330 mg, 1.01 mmol) were added THF/methanol (2:1, 12 ml) and 1N NaOH (4 ml). After stirring at room temperature for 14 hours, the reaction mixture was distilled under reduced pressure to remove the solvent. The residue was acidified with 1N HCl. The crystals thus precipitated were collected by filtration under reduced pressure, washed with water and dried under reduced pressure to give (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetic acid (284 mg, 90%) as a pale brown solid.

^{1}H-NMR (DMSO-d_6) δ: 3.28 (t, J=8.6Hz, 2H), 3.72 (s, 2H), 4.32 (d, J=8.6Hz, 2H), 7.03 (d, J=7.3Hz, 1H), 7.18(t, J=6.9Hz, 1H), 7.24 (d, J=8.1Hz, 1H), 7.27-7.32 (m, 2H), 7.95 (d, J=7.8Hz, 1H), 12.47 (br, 1H).

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

(Step 3) Synthesis of methyl trans-4-(1-((7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate



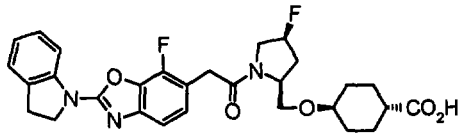
In DMF (4 ml), (7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetic acid (156 mg, 0.50 mmol), methyl trans-4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (the compound synthesized in (Step 3) of Example 21) (130 mg, 0.50 mmol), EDC HCl (144 mg, 0.75 mmol), HOBt (101 mg, 0.75 mmol) and triethylamine (0.35 ml, 2.50 mmol) were stirred at room temperature for 3 days. 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 thin layer plate, whereby from chloroform/acetone (10/1) eluate fractions, methyl trans-4-(1-((7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (279 mg, 100%) was obtained as a brown oil.

^{1}H-NMR ($CDCl_3$) δ: 1.19-1.58 (m, 4H), 1.97-2.53 (m, 7H), 3.25 (m, 1H), 3.30 (t, J=8.8Hz, 2H), 3.34 (m, 1H), 3.52-4.06 (m, 8H, including amide isomers and 3.69 s, 1H), 4.32 (t, J=8.5Hz, 2H), 4.37 (m, 1H), 5.26 and 5.30 (each dt, J=54.0, 4.4 and 53.2, 3.7Hz, total 1H, amide isomers), 7.01 (t, J=7.6Hz, 1H), 7.10 (q, J=7.3Hz, 1H), 7.22 (t, J=6.3Hz,

2H), 7.28 (t, J=7.8Hz, 1H), 7.98 (d, J=8.1Hz, 1H).

MS (ESI) m/z 566 (M^++1).

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



To methyl trans-4-(1-((7-fluoro-2-(1-indolinyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexanecarboxylate (279 mg, 0.50 mmol) were added THF/methanol (2:1, 15 ml) and 1N NaOH (5 ml). The resulting mixture was stirred 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 (210 mg, 78%) as a colorless solid.

IR (ATR) ν 2939, 2862, 1716, 1635, 1576, 1487, 1452, 1408 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 1.14-1.41 (m, 4H), 1.85-2.38 (m, 7H), 3.20 (t, J=9.8Hz, 1H), 3.29 (t, J=8.8Hz, 2H), 3.40-4.15 (m, 6H), 4.32 (t, J=8.3Hz, 2H), 4.37 (m, 1H), 5.33 and 5.41 (each d, J=54.9 and 53.5Hz, total 1H, amide isomers), 7.03 (t, J=7.3Hz, 1H), 7.08 and 7.11 (each d, each J=6.6Hz,

total 1H, amide isomers), 7.24 (dt, J=8.1, 1.9Hz, 1H), 7.29 and 7.31 (each d, each J=7.8Hz, total 2H, amide isomers), 7.96 (d, J=8.1Hz, 1H), 12.05 (br, 1H).

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

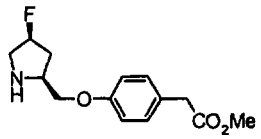
Anal. Calcd for $C_{29}H_{31}F_2N_3O_5$ $1H_2O$: C, 62.47; H, 5.97; N, 7.54; F, 6.81.

Found: C, 62.42; H, 5.87; N, 7.47; F, 6.88.

Example 106

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

(Step 1) Synthesis of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)phenylacetate



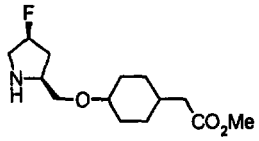
In THF (70 ml), diisopropyl azodicarboxylate (2.81 ml, 13.6 mmol) was added dropwise to N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethanol (2.48 g, 11.3 mmol), triphenylphosphine (3.56 g, 13.6 mmol) and methyl 4-hydroxyphenylacetate (1.88 g, 11.3 mmol) at room temperature. After completion of the dropwise addition, the reaction mixture was stirred at 70°C for 3 hours. The reaction mixture was cooled to room temperature and then, distilled under reduced pressure to remove the solvent. The residue was purified by chromatography on a silica gel column, whereby from hexane/ethyl acetate (2/1 to 4/1)

eluate fractions, methyl 4-(N-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)phenylacetate was obtained. The resulting compound was dissolved into methylene chloride (50 ml). To the resulting solution was added trifluoroacetic acid (20 ml). After the resulting mixture was stirred at room temperature for 1 hour, 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 (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 (10/1) eluate fractions, methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)phenylacetate (1.89 g, 63%) was obtained as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ: 1.90 (brs, 1H), 1.96-2.02 (m, 1H), 2.16-2.31 (m, 1H), 2.90-3.03 (m, 1H), 3.35 (dd, J=13.2, 20.8Hz, 1H), 3.52 (brs, 1H), 3.56 (s, 2H), 3.67 (s, 3H), 3.96-4.04 (m, 2H), 5.16-5.30 (m, 1H), 6.87 (d, J=8.4Hz, 2H), 7.18 (d, J=8.4Hz, 2H).

MS (ESI) m/z 268 (M^++1).

(Step 2) Synthesis of methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate

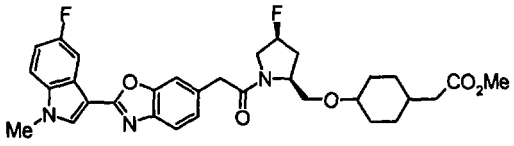


In ethanol/acetic acid (10/1, 55 ml), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)phenylacetate (1.89 g, 7.08 mmol) and rhodium-alumina (5%, 500 mg) were subjected to catalytic hydrogenation for 18 hours at room temperature under a hydrogen gas of 4 atm. From the reaction mixture, the catalyst was filtered off. The filtrate was distilled under reduced pressure to remove the solvent. The resulting oil was poured in a saturated aqueous solution of sodium bicarbonate to neutralize the oil therewith, 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 methyl ((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate (1.88 g, 97%) as a colorless oil.

^{1}H-NMR ($CDCl_3$), mixture of cis and trans isomers, δ: 1.23-2.16 (series of m, 10 H), 2.19-2.23 (m, 4H), 2.79-2.92 (m, 1H), 3.16-3.55 (series of m, 5H), 3.65 (s, 3H), 5.30 (d, J=54.8Hz, 1H).

MS (ESI) m/z 274 (M^++1).

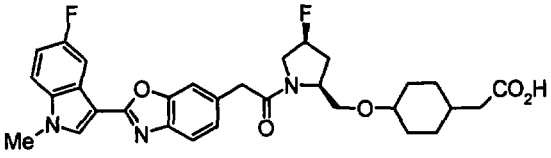
(Step 3) Synthesis of methyl 4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate



In DMF (10 ml), HOBt (18.0 mg, 0.14 mmol) was added to (2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetic acid (219 mg, 0.68 mmol), methyl 4-((4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate (185 mg, 0.68 mmol) and EDC-HCl (142 mg, 0.74 mmol). The resulting mixture was stirred at room temperature for 18 hours. 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 using thin layer silica gel, whereby from ethyl acetate eluate fractions, methyl 4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate (334 mg, 85%) was obtained as a colorless amorphous substance.

MS (ESI) m/z 579 (M^++1).

(Step 4) Synthesis of 4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetic acid



To methyl 4-(1-((2-(5-fluoro-1-methyl-3-indolyl)-6-

benzoxazolyl)acetyl)-(4S)-fluoro-(2S)-pyrrolidinylmethoxy)cyclohexylacetate (315 mg, 0.54 mmol) were added THF/methanol (1/1, 20 ml) and 0.25N NaOH (10.9 ml, 2.72 mmol). The resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was poured in 1N HCl to acidify the mixture therewith, 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 (10/1) eluate fractions, the title compound (260 mg, 85%) was obtained as a colorless amorphous substance.

^{1}H-NMR (DMSO-d_6), mixture of amide isomers, mixture of cis and trans isomers, δ: 1.53-2.60 (series of m, 14H), 3.44-4.67 (series of m, 6H), 4.24 (s, 3H), 3.22-4.45 (series of m, 7H), 5.55-5.74 (m, 1H), 7.45-7.56 (m, 2H), 7.83 (d, J=9.2Hz, 1H), 7.91-7.94 (m, 2H), 8.28 (dd, J=2.4, 9.6Hz, 1H), 8.66 (d J=2.8Hz, 1H), 12.23 (brs, 1H).

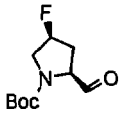
MS (ESI) m/z 566 (M^++1).

Example 107

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

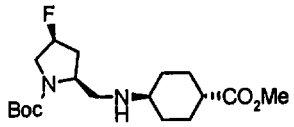
(Step 1) Synthesis of 1-tert-butoxycarbonyl-(4S)-

fluoroprolinal



To a solution of oxalyl chloride (0.4 ml, 4.605 mmol) in methylene chloride (4.0 ml), DMSO (0.65 ml, 9.209 mmol) was added dropwise in a nitrogen gas stream and the reaction mixture was stirred at the same temperature for 15 minutes. To the reaction mixture was added a solution of 1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethanol (504.8 mg, 2.302 mmol) in methylene chloride (5.0 ml) at -78°C by using a syringe. The reaction mixture was stirred at the same temperature for 1 hour. To the mixture was added diisopropylethylamine (2.0 ml, 11.51 mmol) at -78°C. After stirring at the same temperature for 30 minutes, the reaction mixture was warmed to room temperature and diluted with chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulfate, and distilled under reduced pressure to remove the solvent to give 1-tert-butoxycarbonyl-(4S)-fluoroprolinal as a pale yellow amorphous substance. The resulting compound was provided for the subsequent reaction without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.43, 1.46 (total 9H, s, t-Bu), 2.16-2.49 (2H, m), 3.44-3.70 (1H, m), 3.71-3.96 (1H, m), 4.17, 4.29 (total 1H, d, J=11.4Hz), 5.19 (1H, d, J=50.0Hz), 9.55 and 9.60 (total 1H, s, CHO).

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



In THF (16 ml), sodium triacetoxyborohydride (1.22 g, 5.756 mmol) was added to 1-tert-butoxycarbonyl-(4S)-fluoroprolinal and methyl trans-4-aminocyclohexanecarboxylate (362.0 mg, 2.302 mmol) under stirring at 0°C. After the reaction mixture was stirred for cyclohexylcarbon 1 hour, it was diluted with chloroform. A saturated aqueous solution of sodium bicarbonate was added, 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 hexane-ethyl acetate (1:1, v/v) to chloroform-methanol (10:1, v/v) eluate fractions, methyl trans-4-(N-(1-tert-butoxycarbonyl-(4S)-fluoro-(2S)-pyrrolidinylmethyl)amino)cyclohexanecarboxylate (776.1 mg, 94% for 2 steps) was obtained as a light brown oil.

^{1}H-NMR ($CDCl_3$) δ: 0.98-1.50 (total 13H, m, including 9H, s at δ 1.45), 1.88-2.12 (5H, m), 2.13-2.30 (2H, m), 2.35-3.07 (total 4H, series of m), 3.43-4.12 (total 6H, series of m,