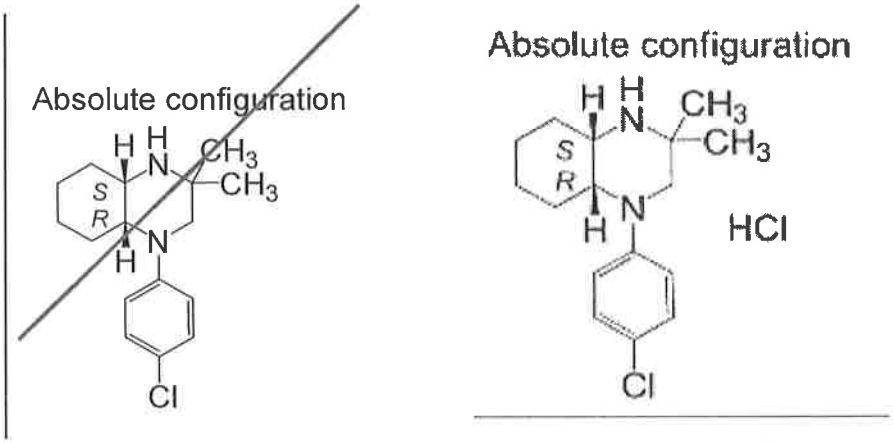
^{1}H-NMR ($CDCl_3$) δppm : 1.0-1.45 (11H, m), 1.6-1.8 (3H, m), 1.8-1.95 (1H, m), 2.70 (1H, d, J = 11.3Hz), 3.04 (1H, d, J = 11.3Hz), 3.50 (1H, ddd, J = 3.8, 3.8, 12.1Hz), 3.55-3.65 (1H, m), 6.47 (1H, dd, J = 3.4, 8.6Hz), 6.84 (1H, dd, J = 2.5, 2.5Hz), 6.89 (1H, dd, J = 8.6, 10.4Hz), 7.60 (1H, d, J = 2.2Hz).

[0275]

Example 106

Production of (4aS,8aR)-1-(4-chlorophenyl)-3,3-dimethyldecahydroquinoxaline hydrochloride



A toluene (10 ml) suspension of (4aR,8aS)-2,2-dimethyldecahydroquinoxaline (252 mg, 1.50 mmol), 1-bromo-4-chlorobenzene (345 mg, 1.80 mmol), $Pd(OAc)_2$ (16.8 mg, 0.0748 mmol), t-$Bu_3P.HBF_4$ (21.8 mg, 0.0751 mmol), and NaOt-Bu (202 mg, 2.10 mmol) was stirred for 5 hours under reflux in a nitrogen atmosphere. The reaction solution was cooled to room temperature. Then, water (0.5 mL) and AcOEt (10 mL) were added thereto, and the mixture was stirred. $MgSO_4$ was further added thereto, and the mixture was stirred. Then, insoluble matter was filtered through celite. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by basic silica gel column chromatography (Hex-AcOEt). The obtained oil was dissolved in 1 N HCl-EtOH (3 mL), and the solvent was distilled off under reduced pressure. The deposited crystal was recrystallized from ethanol/acetone to obtain (4aS,8aR)-1-(4-chlorophenyl)-3,3-dimethyldecahydroquinoxaline hydrochloride (262 mg, yield: 55%) in a white powder form.

^{1}H-NMR (DMSO-d_6) δppm : 1.2-1.45 (6H, m), 1.51 (3H, s), 1.6-2.1 (5H, m), 2.93 (1H, d, J = 13.6Hz), 3.40 (1H, d, J = 13.8Hz), 3.65-3.85 (1H, m), 3.9-4.1 (1H, m), 6.8-7.05 (2H, m), 7.1-7.35 (2H, m), 8.14 (1H, br), 9.77 (1H, br).

[0276]

Example 112

Production of (4aS,8aR)-1-(3-chloro-4-fluorophenyl)-3,3-dimethyldecahydroquinoxaline hydrochloride

(168 mg, 0.998 mmol), 5-bromo-1-methyl-1H-indole-2-carbonitrile (259 mg, 1.10 mmol), $Pd(OAc)_2$ (11.2 mg, 0.0499 mmol), t-$Bu_3P.HBF_4$ (14.5 mg, 0.0500 mmol), and NaOt-Bu (135 mg, 1.40 mmol) was stirred for 4 hours under reflux in a nitrogen atmosphere. The reaction solution was cooled to room temperature. Then, water (0.5 mL) and AcOEt (10 mL) were added thereto, and the mixture was stirred. $MgSO_4$ was further added thereto, and the mixture was stirred. Insoluble matter was filtered through celite, and the residue was washed with CH_2Cl_2:MeOH (3:1) (5 mL×2). Then, the filtrate was concentrated under reduced pressure. The obtained residue was purified by basic silica gel column chromatography (Hex-AcOEt) to obtain a colorless oil. This oil was crystallized from hexane (1 mL) to obtain ~~(4aS,8aR)-1-(7-fluorobenzofuran-4-yl)-3,3-dimethyldecahydroquinoxaline~~ 5-((4aR,8aS)-3,3-dimethyldecahydroquinoxalin-1-yl)-1-methyl-1H-indole-2-carbonitrile (148 mg, yield: 46%) in a pale yellow powder form.

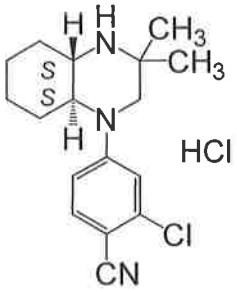
^{1}H-NMR ($CDCl_3$) δppm : 0.7-2.3 (15H, m), 2.7-3.2 (2H, m), 3.5-3.8 (2H, m), 3.85 (3H, s), 6.95-7.05 (2H, m), 7.15-7.3 (2H, m).

[0278]

Example 237

Production of (4aS,8aS)-1-(3-chloro-4-cyanophenyl)-3,3-dimethyldecahydroquinoxaline hydrochloride

Absolute configuration



A toluene (10 ml) suspension of (4aS,8aS)-2,2-dimethyldecahydroquinoxaline (400 mg, 2.38 mmol), 4-bromo-2-chlorobenzonitrile (669 mg, 3.09 mmol), $Pd(OAc)_2$ (53 mg, 0.24 mmol), t-$Bu_3P.HBF_4$ (70 mg, 0.24 mmol), and t-BuONa (320 mg, 3.33 mmol) was stirred for 5 hours under reflux in a nitrogen atmosphere. The reaction solution was cooled. Then, insoluble matter was filtered through celite, and the filtrate was concentrated. The obtained residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH) to obtain an orange amorphous solid. This amorphous solid was dissolved in ethyl acetate (5 mL). A crystal deposited by the addition of 4 N HCl/AcOEt (0.6 mL) was collected by filtration and dried under reduced pressure to obtain (4aS,8aS)-1-(3-chloro-4-cyanophenyl)-

3,3-dimethyldecahydroquinoxaline hydrochloride (304 mg~~m~~, 48%) in a pale orange powder form.

^{1}H-NMR ($CDCl_3$) δppm : 1.05-1.20 (1H, m), 1.23-1.44 (2H, m), 1.54-2.10 (4H, m), 1.63 (3H,

column chromatography (AcOEt/hexane=1/10→1/1) to obtain a product (370 mg, 1.30 mmol) in an oil form. This oil was dissolved in ethanol (5 mL). To this solution, an ethanol (5 mL) solution of fumaric acid (151 mg) was added, and ethanol was removed under reduced pressure. The obtained solid was recrystallized from ethanol/ethyl acetate to obtain ~~5-((4aS,8aS)-3,3-dimethyldecahydroquinoxalin-1-yl)-1H-indole-2-carbonitrile~~ (4aS,8aS)-3,3-dimethyl-1-(1H-pyrrolo[2,3-b]pyridin-4-yl)decahydroquinoxaline fumarate (246 mg, yield: 63%) in a white powder form.

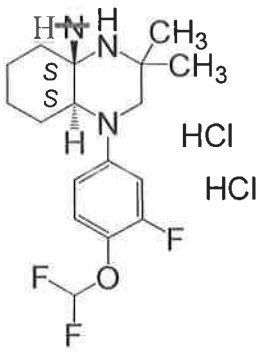
^{1}H-NMR (DMSO-d_6) δppm : 0.94-1.09 (1H, m), 1.20 (3H, s), 1.26-1.55 (7H, m), 1.68-1.78 (1H, m), 1.85-2.04 (2H, m), 2.81-2.93 (1H, m), 2.95-3.23 (3H, m), 6.36-6.42 (1H, m), 6.49 (2H, s), 6.71 (1H, d, J = 5.2 Hz), 7.32-7.38 (1H, m), 8.09 (1H, d, J = 5.2 Hz), 8.50-11.20 (1H, br), 11.59 (1H, s).

[0287]

Example 587

Production of (4aS,8aS)-1-(4-(difluoromethoxy)-3-fluorophenyl)-3,3-dimethyldecahydroquinoxaline dihydrochloride

Absolute configuration



A toluene (5 mL) suspension of (4a~~R~~S,8aS)-2,2-dimethyldecahydroquinoxaline (200 mg, 1.19 mmol), 4-bromo-1-difluoromethoxy-2-fluorobenzene (315 mg, 1.31 mmol), $Pd(OAc)_2$ (13.3 mg, 0.0594 mmol), $tBu_3P.HBF_4$ (17.2 mg, 0.0594 mmol), and t-BuONa (137 mg, 1.43 mmol) was stirred at 100°C for 4 hours. Insoluble matter was filtered through celite, and the filtrate was concentrated. The obtained residue was purified by basic silica gel column chromatography (AcOEt/hexane). The solvent was removed under reduced pressure. The obtained residue was dissolved in ethyl acetate. To this solution, 1 N hydrochloric acid-ethanol was added, and the deposited crystal was collected by filtration. The obtained crystal was dried under reduced pressure to obtain (4aS,8aS)-1-(4-difluoromethoxy-3-fluorophenyl)-3,3-dimethyldecahydroquinoxaline dihydrochloride (193 mg, yield: 40%) in a white powder form.

^{1}H-NMR (DMSO-d_6) δppm :1.01-1.39 (6H, m), 1.49-1.67 (6H, m), 1.67-1.77 (1H, m), 1.96-2.05 (1H, m), 2.81-2.95 (2H, m), 3.02 (1H, d, J = 12.5 Hz), 3.10-3.23 (1H, m), 4.30-4.80 (1H, br),

6. The heterocyclic compound represented by the general formula (1) or a salt thereof according to claim 5, which is selected from
(4a*S*,8a*R*)-1-(4-chlorophenyl)-3,3-dimethyldecahydroquinoxaline,
2-chloro-4-((4a*S*,8a*S*)-3,3-dimethyloctahydroquinoxalin-1(2*H*)-yl)benzonitrile,
(4a*S*,8a*R*)-1-(3-chloro-4-fluorophenyl)-3,3-dimethyldecahydroquinoxaline,
(4a*S*,8a*R*)-1-(7-fluorobenzofuran-4-yl)-3,3-dimethyldecahydroquinoxaline,
5-((4a*R*,8a*S*)-3,3-dimethyloctahydroquinoxalin-1(2*H*)-yl)-1-methyl-1*H*-indole-2-carbonitrile,
(4a'*R*,8a'*S*)-4'-(7-methoxybenzofuran-4-yl)octahydro-1'*H*-spiro[cyclobutane-1,2'-quinoxaline],
(4a*S*,8a*R*)-1-(6,7-difluorobenzofuran-4-yl)-3,3-dimethyldecahydroquinoxaline,
5-((4a*S*,8a*S*)-3,3-dimethyloctahydroquinoxalin-1(2*H*)-yl)-1*H*-indole-2-carbonitrile,
(4a*S*,8a*R*)-1-(7-chloro-2,3-dihydro-1*H*-inden-4-yl)-3,3-dimethyldecahydroquinoxaline,
6-((4a*S*,8a*S*)-3,3-dimethyloctahydroquinoxalin-1(2*H*)-yl)-2-naphthonitrile,
(4a*S*,8a*S*)-3,3-dimethyl-1-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)decahydroquinoxaline, ~~and~~
(4a*S*,8a*S*)-1-(4-(difluoromethoxy)-3-fluorophenyl)-3,3-dimethyldecahydroquinoxaline,
(4aS,8aS)-1-(4-(difluoromethoxy)phenyl)-3,3-dimethyldecahydroquinoxaline, and
(4aR,8aR)-1-(4-(difluoromethoxy)-3-fluorophenyl)-3,3-dimethyldecahydroquinoxaline.

7. A pharmaceutical composition comprising a heterocyclic compound represented by the general formula (1) or a salt thereof according to claim 1 as an active ingredient and a pharmaceutically acceptable carrier.

8. A prophylactic and/or therapeutic agent for disorders caused by reduced neurotransmission of serotonin, norepinephrine or dopamine, comprising as an active ingredient a heterocyclic compound of general formula (1) or a salt thereof according to claim 1.

9. A prophylactic and/or therapeutic agent according to claim 8, wherein the disorder is selected from the group consisting of depression, depression status caused by adjustment disorder, anxiety caused by adjustment disorder, anxiety caused by various diseases, generalized anxiety disorder, phobia, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, acute stress disorder, hypochondria, dissociative amnesia, avoidant personality disorder, body dysmorphic disorder, eating disorder, obesity, chemical dependence, pain, fibromyalgia, Alzheimer's disease, memory deficit, Parkinson's disease, restless leg syndrome, endocrine disorder, vasospasm, cerebellar ataxia, gastrointestinal

disorder, negative syndrome of schizophrenia, premenstrual syndrome, stress urinary incontinence, Tourette's disorder, attention deficit hyperactivity disorder (ADHD), autism, Asperger syndrome, impulse control disorder, trichotillomania, kleptomania, gambling disorder, cluster headache, migraine,