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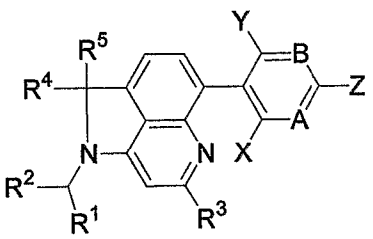
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(54) **Title:** 8-ARYL-4-ALKYLPYRROLO[2,3,4-DE]QUINOLIN-5(4H)-ONE AND 8-ARYL-4-ALKYL-4,5-DIHYDROPYRROLO[2,3,4-DE]QUINOLIN-5-OL DERIVATIVES



[I]

(57) **Abstract:** An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc. An 8-aryl-4-alkylpyrrolo[2,3,4-de]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-de]quinolin-5-ol derivative represented by the following formula [I], has a high affinity for CRF receptors, and is effective against diseases in which CRF is considered to be involved.

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DESCRIPTION

8-ARYL-4-ALKYLPYRROLO[2,3,4-*de*]QUINOLIN-5(4H)-ONE AND 8-ARYL-4-ALKYL-4,5-DIHYDROPYRROLO[2,3,4-*de*]QUINOLIN-5-OL DERIVATIVES

[DETAILED DESCRIPTION OF THE INVENTION]

[TECHNICAL FIELD]

The present invention relates to a therapeutic agent for diseases in which corticotropin releasing factor (CRF) is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

[DESCRIPTION OF THE PRIOR ART]

CRF is a hormone comprising 41 amino acids (Science, 213, 1394-1397, 1981; and J. Neurosci., 7, 88-100, 1987), and it is suggested that CRF plays a core role in biological reactions against stresses (Cell. Mol. Neurobiol., 14, 579-588, 1994; Endocrinol., 132, 723-728, 1994; and Neuroendocrinol. 61, 445-452, 1995). For CRF, there are the following two paths: a

path by which CRF acts on peripheral immune system or sympathetic nervous system through hypothalamus-pituitary-adrenal system, and a path by which CRF functions as a neurotransmitter in the central nervous system (in Corticotropin Releasing Factor: Basic and Clinical Studies of a Neuropeptide, pp. 29-52, 1990). Intraventricular administration of CRF to hypophysectomized rats and normal rats causes an anxiety-like symptom in both types of rats (Pharmacol. Rev., 43, 425-473, 1991; and Brain Res. Rev., 15, 71-100, 1990). That is, there are suggested the participation of CRF in hypothalamus-pituitary-adrenal system and the pathway by which CRF functions as a neurotransmitter in central nervous system.

The review by Owens and Nemeroff in 1991 summarizes diseases in which CRF is involved (Pharmacol. Rev., 43, 425-474, 1991). That is, CRF is involved in depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, inflammation, immunity-related diseases, etc. It has recently been reported that CRF is involved also in epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, and cephalic external wound (Brain Res. 545, 339-342, 1991; Ann. Neurol. 31, 48-498, 1992; Dev. Brain Res. 91, 245-251, 1996; and Brain Res. 744, 166-170, 1997). Accordingly, antagonists against CRF receptors are useful as

therapeutic agents for the diseases described above.

JP2002-308877 disclose 4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one derivatives as phosphodiesterase inhibitors. However none disclose the compounds provided in the present invention.

[PROBLEM(S) TO BE SOLVED BY INVENTION]

An object of the present invention is to provide an antagonist against CRF receptors which is effective as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, epilepsy, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

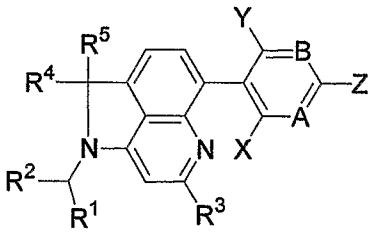
[MEANS FOR SOLVING PROBLEM]

The present inventors earnestly investigated 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one and 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivatives that have a high affinity for CRF receptors, whereby the present invention has been accomplished.

The present invention is 8-aryl-4-

alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one and 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivatives explained below.

An 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative represented by the following formula [I],



[I]

wherein R^1 and R^2 are the same or different, and independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, cyano, cyano-C_{1-6}alkyl or $R^6(R^7)N$-C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydroxyl and R^5 is hydrogen; or R^4 and R^5 are taken together to form a carbonyl group;

R^6 and R^7 are the same or different, and independently hydrogen or C_{1-3}alkyl; or R^6 and R^7 are taken together to form $-(CH_2)_s-R^8-(CH_2)_t-$;

R^8 is methylene, oxygen, NR^9 or a single bond;

R^9 is hydrogen or C_{1-3}alkyl;

s and t are the same or different, and independently an integer selected from 1, 2 or 3;

A and B are the same or different, and

independently N or CH;

X, Y and Z are the same or different, and independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkylthio, halogen, trifluoromethyl, trifluoromethoxy or $-N(R^{10})R^{11}$;

R^{10} and R^{11} are the same or different, and independently hydrogen or C_{1-3}alkyl; or pharmaceutically acceptable salts and hydrates thereof.

The terms used in the present specification have the following meanings.

The term "C_{1-6}alkyl" means a straight chain or branc hed chain alkyl group of 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, *sec*-butyl, pentyl, isopentyl, hexyl, isohexyl or the like.

The term "C_{3-7}cycloalkyl" means a cyclic alkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl.

The term "C_{3-7}cycloalkyl-C_{1-6}alkyl" means a substituted C_{1-6}alkyl group having the above-mentioned C_{3-7}cycloalkyl as the substituent, such as cyclopropylmethyl, cyclopropylethyl, cyclopentylethyl or the like.

The term "C_{1-6}alkoxy" means a straight chain or branched chain alkoxy group of 1 to 6 carbon atoms, such as methoxy, ethoxy, propoxy, isopropyloxy, butoxy, isobutyloxy, pentyloxy, isopentyloxy or the like.

The term "C_{1-6}alkoxy-C_{1-6}alkyl" means a

substituted C_{1-6}alkyl group having the above-mentioned C_{1-6}alkoxy group as the substituent, such as methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl or the like.

The term "hydroxy-C_{1-6}alkyl" means a substituted C_{1-6}alkyl group having hydroxy group, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 4-hydroxybutyl, 5-hydroxypentyl or the like.

The term "cyano-C_{1-6}alkyl" means a substituted C_{1-6}alkyl group having cyano group, such as cyanomethyl, 1-cyanoethyl, 2-cyanoethyl, 3-cyanopropyl, 4-cyanobutyl, 5-cyanopentyl or the like.

The term "halogen" means fluorine, chlorine, bromine or iodine atom.

The term "C_{1-3}alkylthio" means a straight chain or branched chain alkylthio group of 1 to 3 carbon atoms, such as methylthio, ethylthio, propylthio or the like.

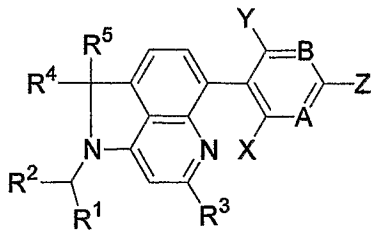
The "pharmaceutically acceptable salts" in the present invention include, for example, salts with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid or the like; salts with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid,

glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid or the like; salts with one or more metal ions such as lithium ion, sodium ion, potassium ion, calcium ion, magnesium ion, zinc ion, aluminium ion or the like; salts with amines such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine or the like.

In a compound of the present invention, isomers such as diastereomers, enantiomers, geometricisomers and tautomeric forms may exist. The compound of the present invention includes the individual isomers and the racemic and non-racemic mixtures of the isomers.

Preferable examples of the compound of the present invention are as follows.

That is, preferable are compounds represented by the formula [I],



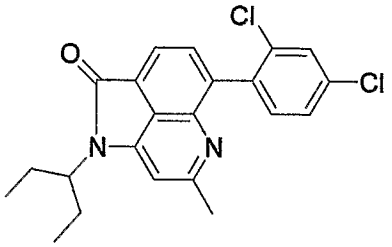
[I]

wherein R^1 and R^2 are the same or different, and independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, cyano, cyano-C_{1-6}alkyl or $R^6(R^7)N$-C_{1-6}alkyl; R^3 is

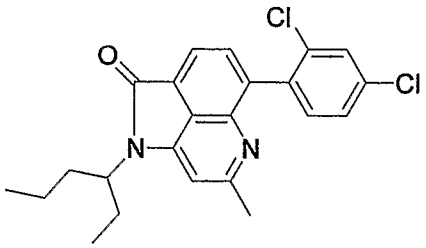
methyl; R^4 and R^5 are taken together to form a carbonyl group; R^6 and R^7 are the same or different, and independently hydrogen or C_{1-3}alkyl; A and B are the same or different, and independently N or CH; X, Y and Z are the same or different, and independently hydrogen, C_{1-3}alkyl, halogen or $-N(R^{10})R^{11}$. R^{10} and R^{11} are the same or different, and independently hydrogen or C_{1-3}alkyl; More preferable are compounds of formula [I], wherein R^1 and R^2 are the same or different, and independently are C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxy-C_{1-6}alkyl. R^3 is methyl; R^4 and R^5 are taken together to form a carbonyl group; A and B are the same or different, and independently N or CH; X, Y and Z are the same or different, and independently hydrogen, methyl, chloro or dimethylamino;

Especially preferable compounds of the present invention are:

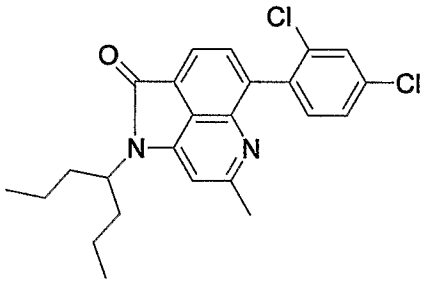
8-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



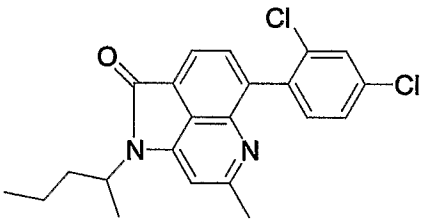
8-(2,4-dichlorophenyl)-4-(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



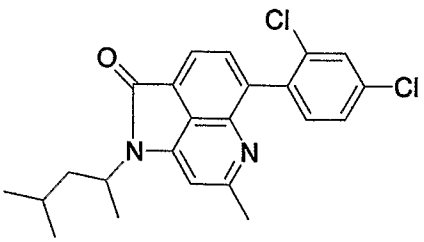
8-(2,4-dichlorophenyl)-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



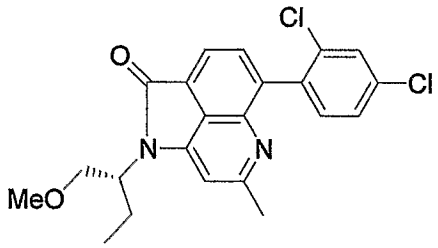
8-(2,4-dichlorophenyl)-2-methyl-4-(1-methylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



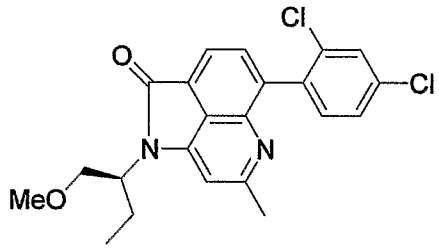
8-(2,4-dichlorophenyl)-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



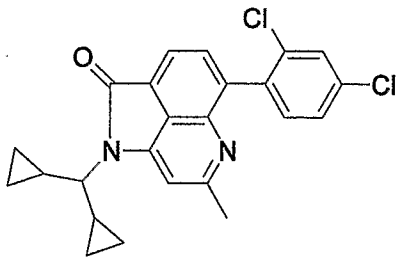
8-(2,4-dichlorophenyl)-4-[(1*R*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



8-(2,4-dichlorophenyl)-4-[(1*S*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

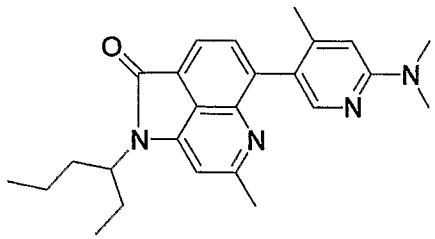


8-(2,4-dichlorophenyl)-4-(dicyclopropylmethyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

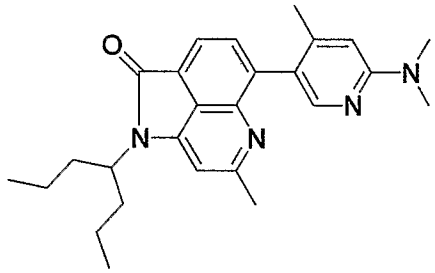


8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-

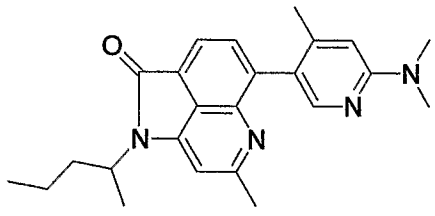
(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



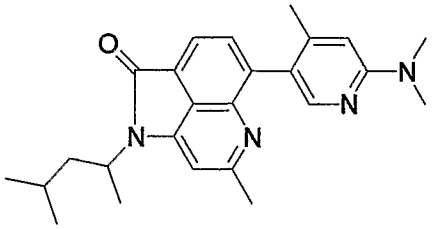
8-[6-(dimethylamino)-4-methylpyridin-3-yl]-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



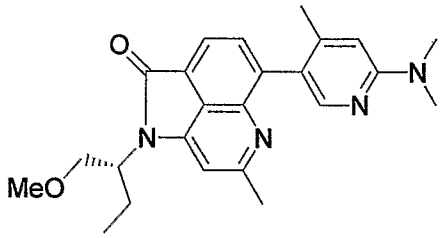
8-[6-(dimethylamino)-4-methylpyridin-3-yl]-2-methyl-4-(1-methylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



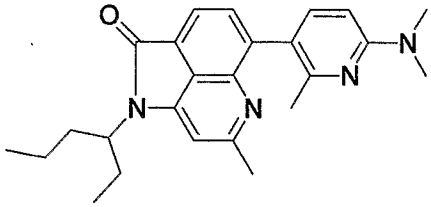
8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



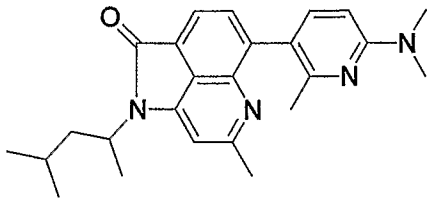
8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-[(1*R*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



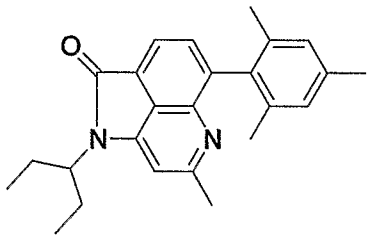
8-[6-(dimethylamino)-2-methylpyridin-3-yl]-4-(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



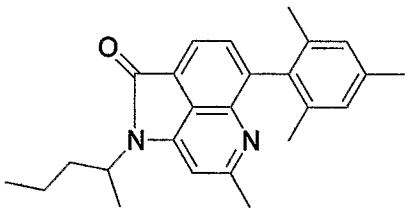
8-[6-(dimethylamino)-2-methylpyridin-3-yl]-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



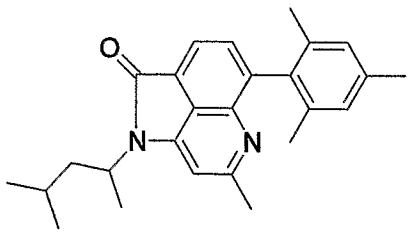
4-(1-ethylpropyl)-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



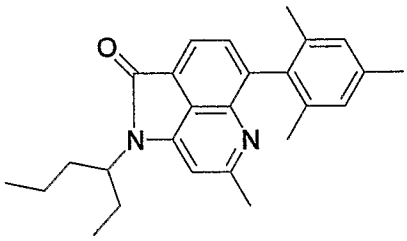
2-methyl-4-(1-methylbutyl)-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



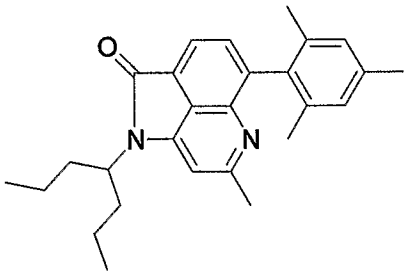
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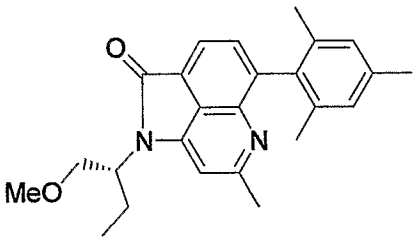
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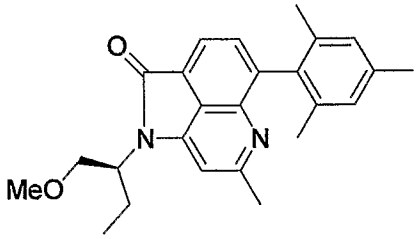
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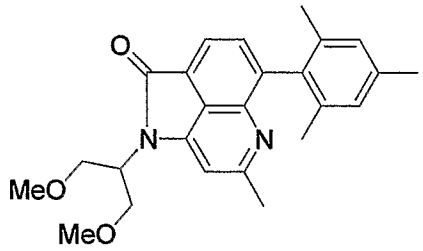
4-[(1*R*)-1-(methoxymethyl)propyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



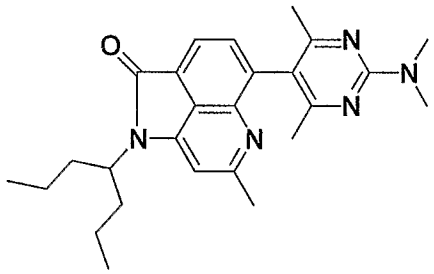
4-[(1*S*)-1-(methoxymethyl)propyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,



4-[2-methoxy-1-(methoxymethyl)ethyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one

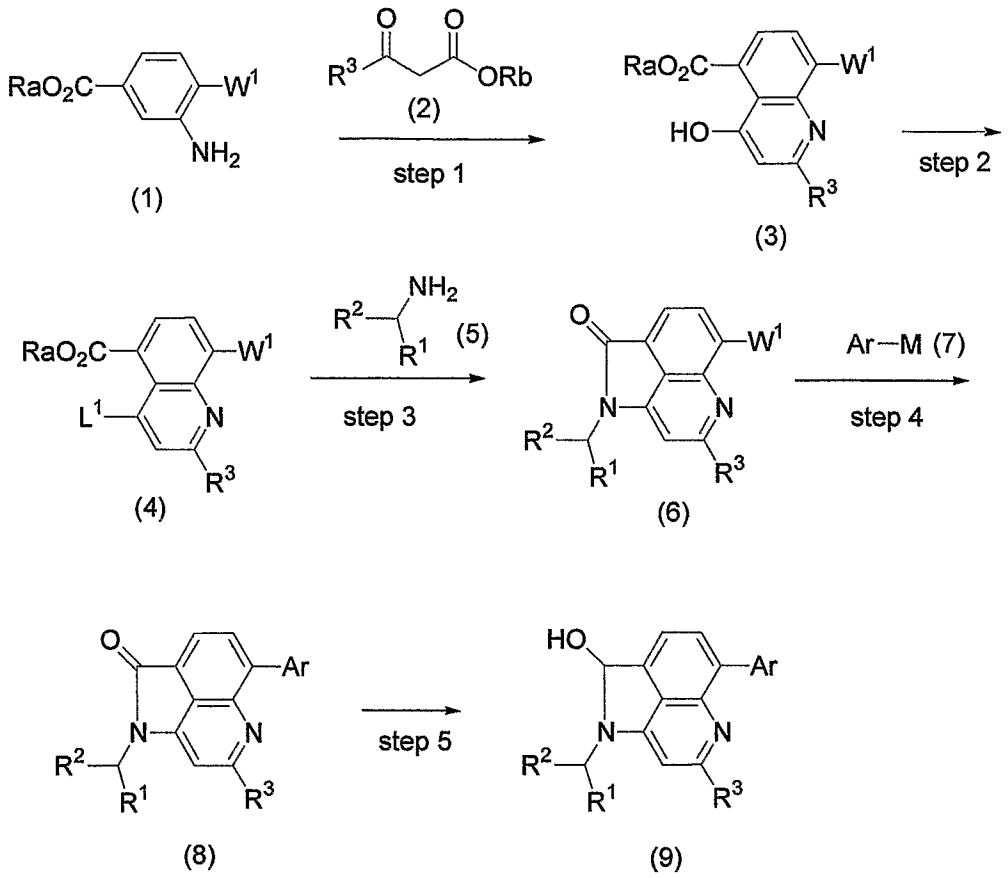


and 8-[2-(dimethylamino)-4,6-dimethylpyrimidin-5-yl]-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one.



The compounds represented by the formula [I] can be produced, for example, by the process shown in the following reaction scheme 1 or 2 (in the following reaction scheme, R^1, R^2, R^3, X, Y, Z, A and B are as defined above, L^1, L^2, W^1 and W^2 are the same or different, and independently chloro, bromo, iodo, methanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy or trifluoromethanesulfonyloxy group, Ra, Rb, Rc and Rd are the same or different, and independently C_{1-3}alkyl, M is an appropriate group such as $B(OH)_2$ or $SnBu_3$ for aryl coupling).

Reaction Scheme 1



Step1: Compound (1) can be converted to Compound (3) by reacting Compound (1) with beta-ketoester (2) in the presence or absence of an acid in an inert solvent or without any solvent. Herein, the acid includes, for example, organic acids such as formic acid, acetic acid, trifluoroacetic acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, trifluoromethanesulfonic acid or the like; inorganic acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, polyphosphoric

acid, nitric acid and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Step 2: Compound (3) can be converted to Compound (4) by reacting (3) with a halogenating reagent or a sulfonating reagent in the presence or absence of a base in an inert solvent or without any solvent. Herein, the halogenating reagent includes, for example, phosphoryl chloride, phosphoryl bromide, phosphorous pentachloride, phosphorous trichloride, phosphorous pentabromide, phosphorous tribromide, thionyl chloride, thionyl bromide, oxalyl chloride, oxalyl bromide and the like. The sulfonating reagent includes, for example, *p*-toluenesulfonyl chloride, methanesulfonyl chloride, *p*-toluenesulfonic anhydride, methansulfonic anhydride, trifluoromethanesulfonic anhydride, *N*-phenylbis(trifluoromethanesulfonimide) and the like. The base includes, for example, amines such as triethylamine, diisopropylethylamine, pyridine, *N,N*-

dimethylaniline, *N,N*-diethylaniline and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methyl magnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; dichloromethane; chloroform; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents. When L^1 is a sulfonyloxy group, L^1 can be converted to a halogen atom by reacting with a halogenating reagent in the presence or absence of a base in an inert solvent or without any solvent. Herein, the halogenating reagent includes, for example, potassium iodide, potassium bromide, sodium iodide, sodium bromide, sodium chloride and the like.

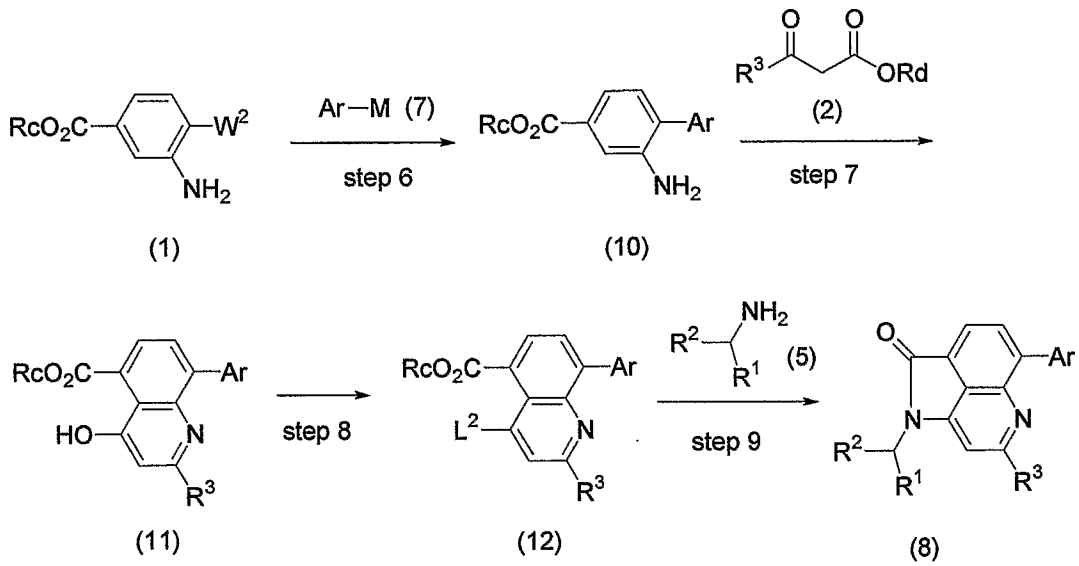
Step 3: Compound (4) can be converted to Compound (6) by reacting Compound (4) with the corresponding amine (5) in the presence or absence of a base in an inert solvent or without any solvent. Herein, the base includes, for example, amines such as triethylamine, *N,N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, potassium hydroxide, sodium hydroxide, lithium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; and metal amides such as sodium amide, lithium diisopropylamide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; amides such as *N,N*-dimethylformamide, *N*-methylpyrrolidone, *N,N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Step 4: Compound (8), a compound of the present invention, can be obtained by reacting Compound (6) with compound (7) in the presence or absence of a

catalyst in an inert solvent in the presence or absence of a base. Herein, the catalyst includes, for example, tetrakis(triphenylphosphine)palladium(0), dichlorobis(tri-*o*-tolylphosphine)palladium(II), palladium(II) acetate and the like; Herein, the base includes, for example, amines such as triethylamine, *N*,*N*-diisopropylethylamine, pyridine and the like; inorganic bases such as sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium hydride and the like; metal alcoholates such as sodium methoxide, sodium ethoxide, potassium *tert*-butoxide and the like; metal amides such as sodium amide, lithium diisopropylamide and the like; and Grignard reagents such as methylmagnesium bromide and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene, xylene and the like; esters such as ethyl acetate, ethyl formate and the like; amides such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, *N*,*N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; chloroform; dichloromethane; water; and mixtures of solvents selected from these inert solvents.

Step 5: Compound (9), a compound of the present invention, can be obtained by reduction of Compound (8) with a conventional reducing agent in an inert solvent. Herein, the reducing agent includes, for example, iron, zinc, lithium borohydride, sodium borohydride, calcium borohydride, lithium triethylborohydride, lithium tri-*sec*-butylborohydride, potassium tri-*sec*-butylborohydride, zinc borohydride, borane, lithium trimethoxyborohydride, lithium triacetoxyborohydride, tetramethylammonium borohydride, lithium aluminum hydride, sodium aluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, diisobutylaluminum hydride, trichlorosilane and the like. The reduction can be also carried out by hydrogenation using a catalyst such as palladium, platinum dioxide, Raney nickel and the like. The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; hydrocarbons such as benzene, toluene and the like; amides such as *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, *N*,*N*-dimethylacetamide and the like; acetonitrile; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

Reaction Scheme 2 -



Step 6: Compound (1) can be converted to Compound (10) by reacting Compound (1) with compound (7) in the same method as described in step 4.

Step 7: Compound (10) can be converted to Compound (11) by reacting Compound (10) with beta-ketoester (2) in the same method as described in step 1.

Step 8: Compound (11) can be converted to Compound (12) by reacting (11) with a halogenating reagent or a sulfonating reagent in the same method as described in step 2.

Step 9: Compound (8), a compound of the present invention, can be obtained by reacting Compound (12) with the corresponding amine (5) in the same method as described in step 3.

The compound of the present invention can be converted to a salt with an inorganic acid such as sulfuric acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid and the like; with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, citric acid, benzenesulfonic acid, methanesulfonic acid, *p*-toluenesulfonic acid, benzoic acid, camphorsulfonic acid, ethanesulfonic acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, malic acid, malonic acid, mandelic acid, galactaric acid, naphthalene-2-sulfonic acid and the like; with an inorganic base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, aluminium hydroxide and the like; or with an organic base such as ammonia, arginine, lysine, piperazine, choline, diethylamine, 4-phenylcyclohexylamine, 2-aminoethanol, benzathine and the like in an inert solvent.

The inert solvent includes, for example, alcohols such as methanol, ethanol, isopropyl alcohol, ethylene glycol and the like; ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; esters such as ethyl acetate, ethyl formate and the like; ketones such as acetone, methylethylketone and the like; hydrocarbons such as benzene, toluene and the like; amides such as

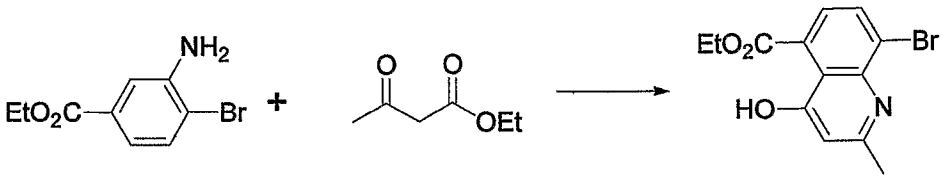
N,*N*-dimethylformamide, *N*-methylpyrrolidone, *N*,*N*-dimethylacetamide and the like; acetonitrile; dichloromethane; chloroform; dimethyl sulfoxide; pyridine; water; and mixtures of solvents selected from these inert solvents.

The compound of the present invention is useful as a therapeutic or prophylactic agent for diseases in which CRF is considered to be involved. For this purpose, the compound of the present invention can be formulated into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections and the like by a conventional preparation technique by adding conventional fillers, binders, disintegrators, pH-adjusting agents, solvents, etc.

The compound of the present invention can be administered to an adult patient in a dose of 0.1 to 500 mg per day in one portion or several portions orally or parenterally. The dose can be properly increased or decreased depending on the kind of a disease and the age, body weight and symptom of a patient.

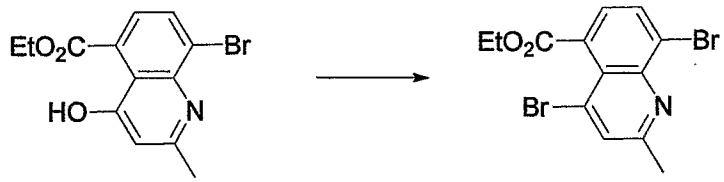
Example 1

(1) Ethyl 8-bromo-4-hydroxy-2-methylquinoline-5-carboxylate



A mixture of ethyl 3-amino-4-bromobenzoate (89 g, 0.36 mol) and ethyl 3-oxobutanoate (141 g, 1.08 mol) was added to polyphosphoric acid (445 g) at 110-120 °C over 1 h. After additional stirring at 120 °C for 10 min, the mixture was cooled to 60 °C. After water, aq. NaOH and $CHCl_3$ were added to the mixture, the mixture was filtered through celite. The filtrate was separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, $CHCl_3$ / MeOH = 70 / 1 ~ 40 / 1) to give the title compound (35.5 g, 32 %) as a solid.

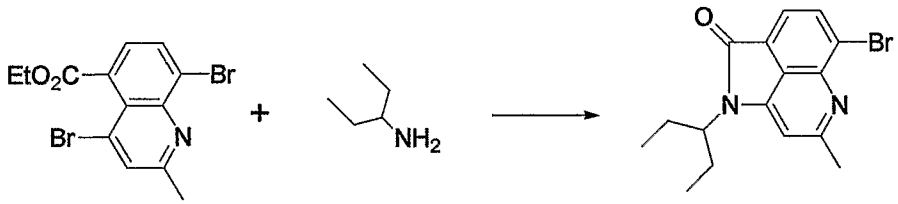
(2) Ethyl 4,8-dibromo-2-methylquinoline-5-carboxylate



To a mixture of ethyl 8-bromo-4-hydroxy-2-methylquinoline-5-carboxylate (92.2 g, 311 mmol) and triethylamine (62.9 g, 622 mmol) in MeCN (1.2 L) was added trifluoromethanesulfonic anhydride (62.8 mL, 373 mmol) at -18 °C over 1 h. The mixture was stirred at the same temperature for 4 h, and poured into ice. The aqueous layer was extracted with $CHCl_3$, and the organic layer was washed with saturated aq. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. To a mixture of the above residue in DMSO (750 mL) and

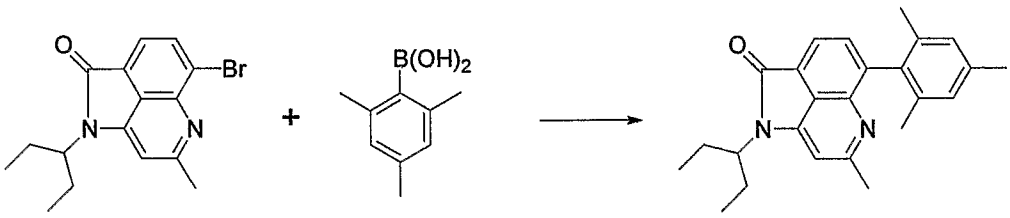
THF (250 mL) was added NaBr (48.0 g, 467 mmol), and the mixture was stirred at 130 °C for 3 h. After cooling to room temperature, water was added to the mixture. The aqueous layer was extracted with hexane-EtOAc (1:1), and the organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, hexane / EtOAc = 5 / 1 ~ 2 / 1) to give the title compound (65.8 g, 57 %) as a solid.

(3) 8-Bromo-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one



A mixture of ethyl 4,8-dibromo-2-methylquinoline-5-carboxylate (3.9 g, 11 mmol) and pentan-3-amine (4.8 g, 55 mmol) in *N*-methylpyrrolidone (8 mL) was stirred at 100 °C for 7 h. After cooling to room temperature, the mixture was partitioned between hexane-EtOAc (1:2) and water. The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, hexane / EtOAc = 10/ 1 ~ 5 / 1) to give the title compound (3.4 g, 98 %) as a solid.

(4) 4-(1-Ethylpropyl)-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one (1-36)

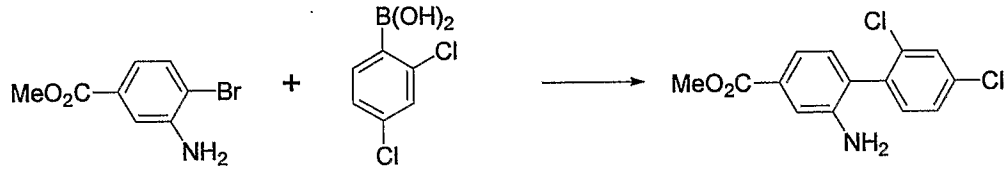


A mixture of 8-bromo-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one (220 mg, 0.660 mmol), (2,4,6-trimethylphenyl)boronic acid (162 mg, 0.990 mmol) and $Pd(PPh_3)_4$ (76 mg, 0.066 mmol) in EtOH (1.5 mL), toluene (5 mL) and 2 M aq. Na_2CO_3 (1.5 mL) was refluxed for 11 h. After cooling to room temperature, the mixture was partitioned between EtOAc and saturated aq. NH_4Cl. The separated organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, hexane / EtOAc = 10/1 ~ 4 / 1). Furthermore, a suspension of the above product in diisopropyl ether (1 mL) was refluxed for 1 h, and stirred at room temperature for 15 h. The resulting precipitate was collected by filtration to give the title compound (185 mg, 75 %) as a solid.

Example 2

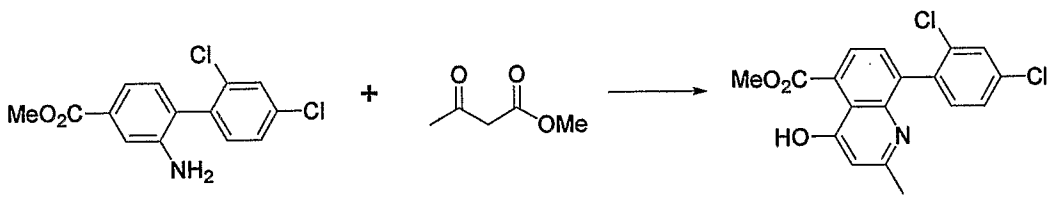
(1) Methyl 2-amino-2',4'-dichlorobiphenyl-4-

carboxylate



A mixture of methyl 3-amino-4-bromobenzoate (15.0 g, 65.6 mmol), (2,4-dichlorophenyl)boronic acid (13.8 g, 72.2 mmol) and $Pd(PPh_3)_4$ (7.58 g, 6.56 mmol) in EtOH (101 mL), toluene (347 mL) and 2 M aq. Na_2CO_3 (101 mL) was refluxed for 6 h. After cooling to room temperature, the mixture was separated. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, hexane / EtOAc = 5/1 ~ 4/1) to give the title compound (19.3 g, 99 %) as a solid.

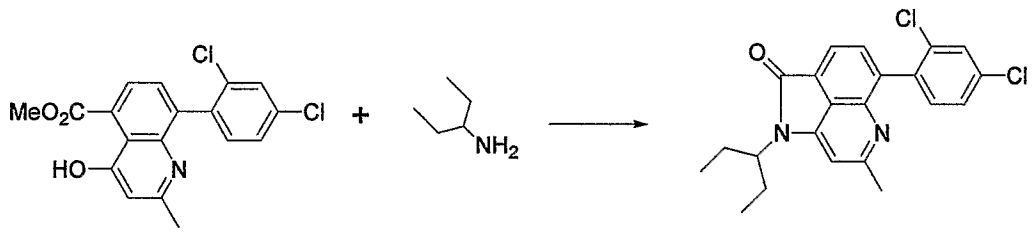
(2) Methyl 8-(2,4-dichlorophenyl)-4-hydroxy-2-methylquinoline-5-carboxylate



To a mixture of methyl 2-amino-2',4'-dichlorobiphenyl-4-carboxylate (19.3 g, 65.2 mmol) and methyl 3-oxobutanoate (8.33 g, 71.7 mmol) in benzene

(97 mL) was added *p*-toluenesulfonic acid monohydrate (62 mg). After the mixture was refluxed for 1 h, Ph_2O (58 mL) was added. After benzene was distilled away, the mixture was stirred at 230 °C for 20 min and cooled to room temperature. The above mixture was purified by flush column chromatography (silica gel C-200, $CHCl_3$ / MeOH = 50/1 ~ 40/1) to give the title compound (6.89 g, 29 %) as a solid.

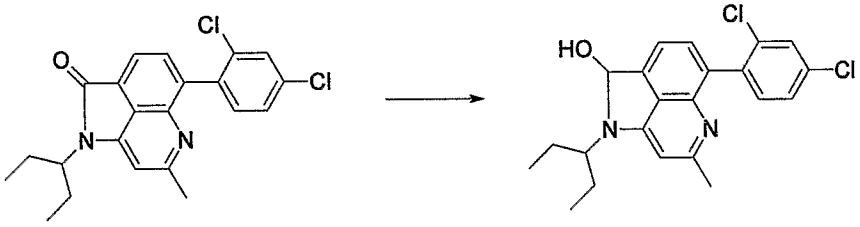
(3) 8-(2,4-Dichlorophenyl)-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one (1-04)



A mixture of methyl 8-(2,4-dichlorophenyl)-4-hydroxy-2-methylquinoline-5-carboxylate (6.83 g, 18.9 mmol) in *N*-methylpyrrolidone (41 mL) was added to NaH (60% in oil) (905 mg, 22.6 mmol), and the mixture was stirred at room temperature for 30 mim. After additional stirring at 50 °C for 15 min, the mixture was cooled in ice-water bath. *N*-Phenyl-bis(trifluoromethanesulfonimide) (8.08 g, 22.6 mmol) was added, and the mixture was stirred at room temperature for 1 h. Pentan-3-amine (9.86 g, 113 mmol) was added, and the mixture was stirred at 70 °C for 1 h.

After cooling to room temperature, the mixture was poured into hexane / EtOAc (1/4) and water. The mixture was separated, and the aqueous layer was extracted with hexane / EtOAc (1/4). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (silica gel C-200, hexane / EtOAc = 15/1 ~ 13/1). Furthermore, a suspension of the above product in hexane (6 mL) was refluxed for 30 min, stirred at room temperature for 30 min and stirred in ice water bath for 4 h. The resulting precipitate was collected by filtration to give the title compound (1.97 g, 26 %) as a solid.

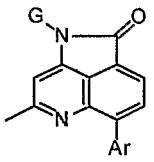
(4) 8-(2,4-Dichlorophenyl)-4-(1-ethylpropyl)-2-methyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol (2-01)



To a mixture of lithium aluminum hydride (76 mg) in THF (4 mL) was added a solution of 8-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one (800 mg, 2.00 mmol) in THF (4 mL) in ice-water bath over 5 min. After additional stirring at room temperature for 4 h, 2 M aq. NaOH was added to the mixture in ice-water

bath. After 2 M aq. NaOH was added to the mixture, the aqueous layer was extracted with EtOAc. The organic layer was washed with saturated aq. NH_4Cl, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flush column chromatography (Chromatorex NH, hexane / EtOAc = 10 / 1 ~ 2 / 1). Furthermore, a suspension of the above product in Et_2O (5 mL) was refluxed for 1 h, and stirred at room temperature for 15 h. The resulting precipitate was collected by filtration to give the title compound (377 mg, 47 %) as a solid.

Table1*[1]



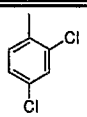
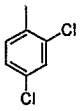
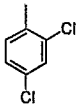
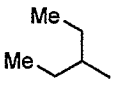
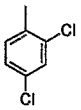
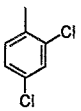
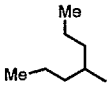
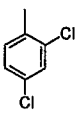
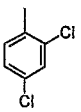
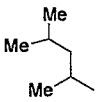
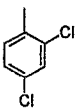
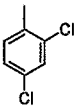
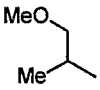
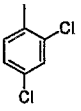
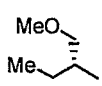
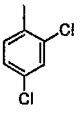
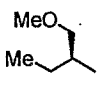
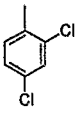
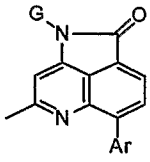
Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
1-01	2	n-Pr		137-139 (AcOEt/IPE)
1-02	2			129-131 (hexane)
1-03	2			136-137 (hexane)
1-04	2			
1-05	2			
1-06	2			
1-07	2			
1-08	2			
1-09	2			188-190 (AcOEt)
1-10	2			116-118 (hexane/IPE)
1-11	2			
1-12	2			

Table1[*1](Cont'd)



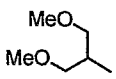
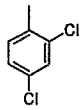
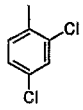
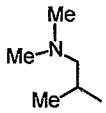
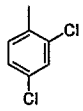
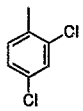
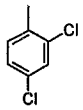
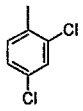
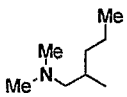
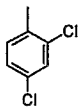
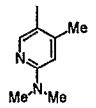
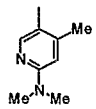
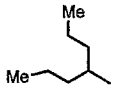
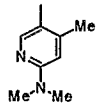
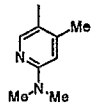
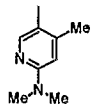
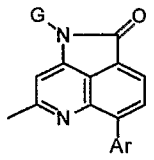
Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
1-13	2			123-125 (hexane/IPE)
1-14	2			143-145 (IPE)
1-15	2			183-185 (IPE)
1-16	1			
1-17	1			146-148 (IPE)
1-18	1			189-191 (IPE)
1-19	1			145-147 (hexane)
1-20	1			amorphous*2
1-21	1			amorphous*2
1-22	1			
1-23	1			amorphous*2
1-24	1			amorphous*2

Table1*1(Cont'd)



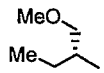
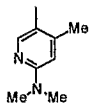
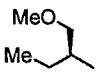
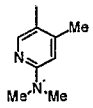
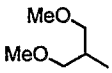
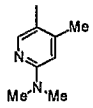
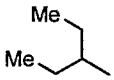
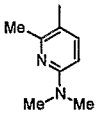
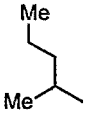
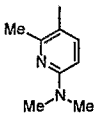
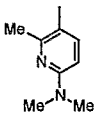
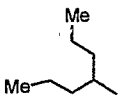
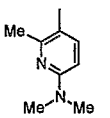
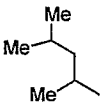
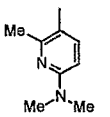
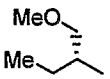
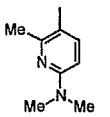
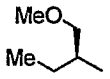
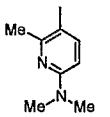
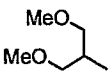
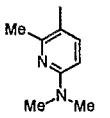
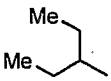
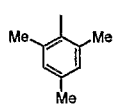
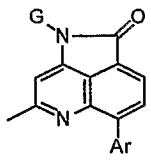
Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
1-25	1			amorphous*2
1-26	1			amorphous*2
1-27	1			139-140 (hexane)
1-28	1			154-156 (hexane/IPE)
1-29	1			135-137 (hexane)
1-30	1			
1-31	1			141-142 (hexane)
1-32	1			
1-33	1			119-121 (hexane)
1-34	1			132-133 (hexane)
1-35	1			168-170 (hexane)
1-36	1			

Table1*1(Cont'd)



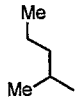
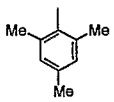
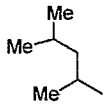
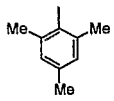
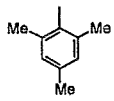
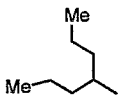
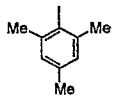
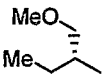
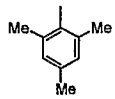
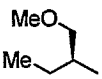
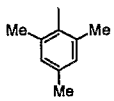
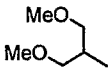
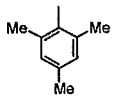
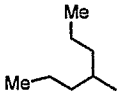
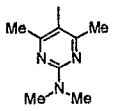
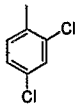
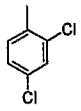
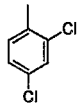
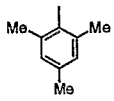
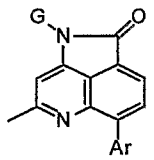
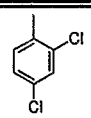
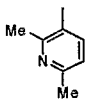
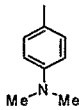
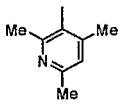
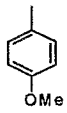
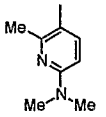
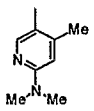
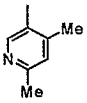
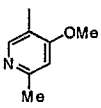
Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
1-37	1			
1-38	1			
1-39	1			
1-40	1			
1-41	1			
1-42	1			
1-43	1			
1-44	1			
1-45	1 or 2			
1-46	1 or 2			
1-47	1 or 2			
1-48	1 or 2			

Table1*1(Cont'd)



Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
1-49	1 or 2			
1-50	1 or 2			
1-51	1 or 2			
1-52	1 or 2			
1-53	1 or 2			
1-54	1 or 2			
1-55	1 or 2			
1-56	1 or 2			
1-57	1 or 2			

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization: EtOAc = ethyl acetate, IPE = diisopropyl ether, Et_2O = diethylether

*2: 2 HCl salt

*3: The crystal was obtained after standing the compound purified by flush column chromatography.

Analytical data are described below.

1-04

MS (ES, Pos): 399 $(M + 1)^+$, 421 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (6 H, t, J=7.3 Hz), 1.43 - 1.63 (2 H, m), 1.71 - 2.16 (3 H, m), 2.68 (3 H, s), 4.11 - 4.43 (1 H, m), 6.79 (1 H, s), 7.31 - 7.52 (1 H, m), 7.57 (1 H, d, J=1.8 Hz), 7.77 (1 H, d, J=7.0 Hz), 8.00 (1 H, d, J=7.0 Hz).

1-05

MS (ES, Pos): 413 $(M + 1)^+$, 435 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.77 - 1.03 (6 H, m), 1.19 - 1.50 (2 H, m), 1.50 - 1.63 (2 H, m), 1.60 - 2.21 (3 H, m), 2.68 (3 H, s), 4.21 - 4.67 (1 H, m), 6.80 (1 H, s), 7.30 - 7.50 (1 H, m), 7.57 (1 H, d, J=2.2 Hz), 7.77 (1 H, d, J=7.5 Hz), 7.99 (1 H, d, J=7.0 Hz).

1-06

MS (ES, Pos): 427 $(M + 1)^+$, 449 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.76 - 1.07 (6 H, m), 1.16 - 1.43 (4 H,

m), 1.63 - 1.87 (2 H, m), 1.89 - 2.20 (2 H, m), 2.69 (3 H, s), 4.33 - 4.70 (1 H, m), 6.80 (1 H, s), 7.30 - 7.51 (2 H, m), 7.57 (1 H, d, J=1.8 Hz), 7.72 - 7.84 (1 H, m), 7.99 (1 H, d, J=7.0 Hz).

1-07

MS (ES, Pos): 399 $(M + 1)^+$, 421 $(M + Na)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 - 1.03 (6 H, m), 1.16 - 1.42 (1 H, m), 1.47 - 1.60 (2 H, m), 1.67 - 1.88 (1 H, m), 1.89 - 2.20 (1 H, m), 2.69 (3 H, s), 4.51 - 4.84 (1 H, m), 6.82 (1 H, s), 7.41 (1 H, q, J=8.2 Hz), 7.57 (1 H, d, J=1.8 Hz), 7.76 (1 H, d, J=7.0 Hz), 7.99 (1 H, d, J=7.5 Hz).

1-08

MS (ES, Pos): 413 $(M + 1)^+$, 435 $(M + Na)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 - 1.09 (6 H, m), 1.30 - 1.77 (6 H, m), 1.84 - 2.15 (1 H, m), 2.69 (3 H, s), 4.61 - 4.95 (1 H, m), 6.82 (1 H, s), 7.41 (1 H, q, J=8.2 Hz), 7.57 (1 H, d, J=1.8 Hz), 7.76 (1 H, d, J=7.0 Hz), 7.99 (1 H, d, J=7.0 Hz).

1-11

MS (ES, Pos): 437 $(M + Na)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (3 H, t, J=7.3 Hz), 1.41 - 1.61 (2 H, m), 1.79 - 2.19 (1 H, m), 2.68 (3 H, s), 3.35 (3 H, s), 3.55 - 3.75 (1 H, m), 3.81 - 4.03 (1 H, m), 6.87 (1 H, s), 7.30 - 7.50 (2 H, m), 7.57 (1 H, s), 7.67 - 7.85 (1 H,

m), 8.00 (1 H, d, J=7.0 Hz).

1-12

MS (ES, Pos): 437 $(M + Na)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (3 H, t, J=7.3 Hz), 1.44 - 1.64 (2 H, m), 1.77 - 2.34 (1 H, m), 2.68 (3 H, s), 3.35 (3 H, s), 3.52 - 3.78 (1 H, m), 3.83 - 4.03 (1 H, m), 4.44 - 4.67 (1 H, m), 6.87 (1 H, s), 7.29 - 7.50 (2 H, m), 7.57 (1 H, d, J=2.2 Hz), 7.69 - 7.85 (1 H, m), 8.00 (1 H, d, J=7.0 Hz).

1-16

MS (ES, Pos): 423 $(M + 1)^+$, 445 $(M + Na)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.19 - 0.65 (6 H, m), 0.67 - 0.92 (2 H, m), 1.39 - 1.72 (2 H, m), 2.70 (3 H, s), 3.14 (1 H, t, J=9.2 Hz), 6.95 (1 H, s), 7.32 - 7.51 (2 H, m), 7.58 (1 H, d, J=1.8 Hz), 7.77 (1 H, d, J=7.3 Hz), 7.99 (1 H, d, J=7.3 Hz).

1-20

MS (ES, Pos): 389 $(M + 1)^+$, 411 $(M + Na)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (6 H, t, J = 7.31 Hz), 1.90-2.10 (4 H, m), 2.35 (3 H, s), 3.23 (3 H, s), 3.47 (6 H, s), 4.25-4.38 (1 H, m), 6.88 (1 H, s), 7.00 (1 H, s), 7.86 (1 H, d, J = 7.31 Hz), 8.07 (1 H, br.s), 8.21 (1 H, d, J = 7.31 Hz).

1-21

MS (ES, Pos): 403 $(M + 1)^+$, 425 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88-0.97 (6 H, m), 1.32-1.42 (2 H, m), 1.68-2.07 (4 H, m), 2.23 (3 H, s), 2.69 (3 H, s), 3.16 (6 H, s), 4.32-4.45 (1 H, m), 6.50 (1 H, s), 6.78 (1 H, s), 7.64 (1 H, d, J = 7.20 Hz), 7.97 (1 H, d, J = 7.20 Hz), 8.18 (1 H, s).

1-22

MS (ES, Pos): 417 $(M + 1)^+$, 439 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.79 - 1.02 (6 H, m), 1.18 - 1.46 (4 H, m), 1.50 - 1.63 (2 H, m), 1.65 - 1.84 (2 H, m), 1.91 - 2.12 (1 H, m), 2.22 (3 H, s), 2.70 (3 H, s), 3.16 (6 H, s), 6.50 (1 H, s), 6.78 (1 H, s), 7.64 (1 H, d, J=7.5 Hz), 7.96 (1 H, d, J=7.0 Hz), 8.18 (1 H, s).

1-23

MS (ES, Pos): 389 $(M + 1)^+$, 411 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (3 H, t, J = 7.31 Hz), 1.20-1.90 (7 H, m), 2.32 (3 H, s), 3.23 (3 H, s), 3.47 (6 H, s), 4.57-4.76 (1 H, m), 6.87 (1 H, s), 7.00 (1 H, s), 7.84 (1 H, d, J = 7.15 Hz), 8.07 (1 H, br.s), 8.18 (1 H, d, J = 7.15 Hz).

1-24

MS (ES, Pos): 403 $(M + 1)^+$, 425 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84-1.03 (6 H, m), 1.20-1.90 (5 H, m), 1.93-2.12 (1 H, m), 2.33 (3 H, s), 3.23 (3 H, s), 3.47 (6 H, s), 4.68-4.82 (1 H, m), 6.89 (1 H, s), 7.06 (1 H,

br.s), 7.78-7.92 (1 H, m), 7.96-8.14 (1 H, m), 8.19 (1 H, br.s).

1-25

MS (ES, Pos): 405 $(M + 1)^+$, 427 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3 H, t, J = 7.39 Hz), 1.96-2.22 (2 H, m), 2.32 (3 H, s), 3.24 (3 H, s), 3.35 (3 H, s), 3.47 (6 H, s), 3.68 (1 H, dd, J = 3.24, 6.68 Hz), 3.90 (1 H, dd, J = 3.42, 6.68 Hz), 4.51-4.62 (1 H, m), 6.88 (1 H, s), 7.20 (1 H, s), 7.85 (1 H, d, J = 7.15 Hz), 8.04-8.10 (1 H, m), 8.20 (1 H, d, J = 7.15 Hz).

1-26

MS (ES, Pos): 405 $(M + 1)^+$, 427 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (3 H, t, J = 7.46 Hz), 1.95-2.20 (2 H, m), 2.33 (3 H, s), 3.19 (3 H, s), 3.35 (3 H, s), 3.47 (6 H, s), 3.62-4.71 (1 H, m), 3.83-4.93 (1 H, m), 4.50-4.63 (1 H, m), 6.87 (1 H, s), 7.18 (1 H, s), 7.83 (1 H, d, J = 7.16 Hz), 8.04-8.10 (1 H, m), 8.18 (1 H, d, J = 7.16 Hz).

,

1-30

MS (ES, Pos): 425 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 - 1.03 (6 H, m), 1.19 - 1.44 (1 H, m), 1.44 - 1.65 (6 H, m), 2.37 (3 H, s), 2.69 (3 H, s), 3.16 (6 H, s), 6.49 (1 H, d, J=8.4 Hz), 6.78 (1 H, s), 7.44 - 7.73 (2 H, m), 7.95 (1 H, d, J=7.5 Hz).

1-32

MS (ES, Pos): 403 $(M + 1)^+$, 425 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (6 H, m), 1.37 - 1.74 (9 H, m), 2.35 (2 H, s), 2.70 (2 H, s), 3.16 (6 H, s), 6.49 (1 H, d, *J*=8.4 Hz), 6.81 (2 H, s), 7.43 - 7.73 (1 H, m), 7.83 - 8.09 (1 H, m).

1-36

MS (ES, Pos): 373 $(M + 1)^+$, 395 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (6 H, t, *J*=7.3 Hz), 1.77 - 2.16 (10 H, m), 2.38 (3 H, s), 2.64 (3 H, s), 4.06 - 4.48 (1 H, m), 6.77 (1 H, s), 7.00 (2 H, s), 7.55 (1 H, d, *J*=7.3 Hz), 7.98 (1 H, d, *J*=7.3 Hz).

1-37

MS (ES, Pos): 373 $(M + 1)^+$, 395 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (3 H, t, *J*=7.3 Hz), 1.17 - 2.17 (13 H, m), 2.38 (3 H, s), 2.64 (3 H, s), 4.67 (1 H, m), 6.80 (1 H, s), 7.01 (2 H, s), 7.54 (1 H, d, *J*=7.3 Hz), 7.97 (1 H, d, *J*=7.3 Hz).

1-38

MS (ES, Pos): 387 $(M + 1)^+$, 409 $(M + Na)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 - 1.02 (6 H, m), 1.48 - 1.64 (5 H, m), 1.94 (3 H, s), 1.97 (3 H, s), 2.00 - 2.12 (1 H, m), 2.38 (3 H, s), 2.65 (3 H, s), 4.68 - 4.80 (1 H, m), 6.80 (1 H, s), 7.00 (2 H, s), 7.54 (1 H, d, *J*=7.2 Hz), 7.96 (1 H, d, *J*=7.2 Hz).

1-39

MS (ES, Pos): 409 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (6 H, t, *J*=7.5 Hz), 1.27 - 1.43 (2 H, m), 1.50 - 1.71 (2 H, m), 1.74 - 2.11 (8 H, m), 2.38 (3 H, s), 2.64 (3 H, s), 4.30 - 4.57 (1 H, m), 6.77 (1 H, s), 7.00 (2 H, s), 7.54 (1 H, d, *J*=7.0 Hz), 7.97 (1 H, d, *J*=7.5 Hz).

1-40

MS (ES, Pos): 401 $(M + 1)^+$, 423 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 - 1.08 (6 H, m), 1.17 - 1.48 (4 H, m), 1.53 - 2.21 (10 H, m), 2.38 (3 H, s), 2.65 (3 H, s), 4.08 - 4.91 (1 H, m), 6.78 (1 H, s), 7.01 (2 H, s), 7.54 (1 H, d, *J*=7.0 Hz), 7.97 (1 H, d, *J*=7.0 Hz).

1-41

MS (ES, Pos): 389 $(M + 1)^+$, 411 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (3 H, d, *J*=14.9 Hz), 1.58 (2 H, s), 1.81 - 2.48 (10 H, m), 2.63 (3 H, s), 3.37 (3 H, s), 3.55 - 4.15 (2 H, m), 6.84 (1 H, s), 7.00 (2 H, s), 7.54 (1 H, d, *J*=7.0 Hz), 7.98 (1 H, d, *J*=7.0 Hz).

1-42

MS (ES, Pos): 389 $(M + 1)^+$, 411 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (3 H, t, *J*=7.3 Hz), 1.47 - 2.21 (8 H, m), 2.38 (3 H, s), 2.63 (3 H, s), 3.37 (3 H, s), 3.55 - 3.83 (1 H, m), 3.79 - 4.14 (1 H, m), 4.33 - 4.83 (1 H,

m), 6.84 (1 H, s), 7.00 (2 H, s), 7.54 (1 H, d, J=7.5 Hz), 7.98 (1 H, d, J=7.5 Hz).

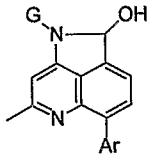
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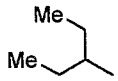
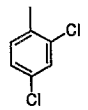
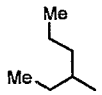
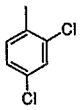
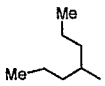
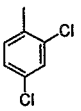
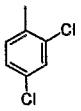
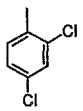
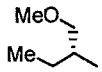
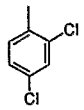
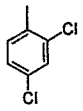
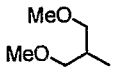
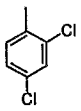
MS (ES, Pos): 405 $(M + 1)^+$, 427 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 1.95 (6 H, br s), 2.38 (3 H, s), 2.64 (3 H, s), 3.38 (6 H, s), 3.59 - 4.17 (4 H, m), 4.57 - 5.16 (1 H, m), 6.92 (1 H, s), 7.00 (2 H, s), 7.40 - 7.74 (1 H, m), 7.98 (1 H, d, J=7.5 Hz).

1-44

MS (ES, Pos): 432 $(M + 1)^+$, 454 $(M + Na)^+$; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 - 1.04 (6 H, m), 1.21 - 1.42 (2 H, m), 1.57 (3 H, s), 1.64 - 1.86 (1 H, m), 1.87 - 2.20 (10 H, m), 2.66 (3 H, s), 3.26 (3 H, s), 6.78 (1 H, s), 7.26 (2 H, s), 7.48 - 7.68 (1 H, m), 7.95 (1 H, d, J=7.0 Hz).

Table 2 *1



Com.No.	Ex. No.	G	Ar	Melting Point (°C) (solvent for crystallization)
2-01	2			146-148 (Et_2O)
2-02	2			140-142 (IPE)
2-03	2			130-132 (hexane)
2-04	2			141-143 (IPE)
2-05	2			135-137 (IPE)
2-06	2			125-127 (IPE)
2-07	2			125-127 (IPE)
2-08	2			121-123 (IPE)

*1: Com. No. = compound number, Ex. No. = example number, solvent for crystallization: IPE = diisopropyl ether, Et_2O = diethylether

Test Example 1 [CRF receptor binding test]

The membranes of COS-7 cells expressing monkey CRF_1 were used as a receptor preparation.

^{125}I-CRF was used as ^{125}I-labeled ligand.

Binding reaction using the ^{125}I-labeled ligand was carried out by the following method described in The Journal of Neuroscience, 7, 88 (1987).

Preparation of receptor membranes:

COS-7 cells expressing monkey CRF_1 was homogenized in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA and centrifuged at 48,000 x g for 20 min, and the precipitate was washed once with Tris-HCl buffer. The washed precipitate was suspended in 50 mM Tris-HCl buffer (pH 7.0) containing 10 mM $MgCl_2$, 2 mM EDTA, 0.1% bovine serum albumin and 100 kallikrein units/ml aprotinin, to obtain a membrane preparation.

CRF receptor binding test:

The membrane preparation (150-250 μg protein/ml), ^{125}I-CRF (0.2 nM) and a test drug were reacted at 25°C or room temperature for 2 hours. After completion of the reaction, the reaction mixture was filtered by suction through a glass filter (GF/C) treated with 0.3% polyethylene imine, and the glass filter was washed three times with phosphate-buffered saline containing 0.01% Triton X-100. After the washing, the radioactivity of the filter paper was measured in a gamma counter.

The amount of ^{125}I-CRF bound when the reaction was carried out in the presence of 1 μM CRF was taken as the degree of nonspecific binding of ^{125}I-CRF, and the difference between the total degree of ^{125}I-CRF binding and the degree of nonspecific ^{125}I-CRF binding was taken as the degree of specific ^{125}I-CRF binding. An inhibition curve was obtained by reacting a definite concentration (0.2 nM) of ^{125}I-CRF with various concentrations of each test drug under the conditions described above. A concentration of the test drug at which binding of ^{125}I-CRF is inhibited by 50% (IC_{50}) was determined from the inhibition curve.

As a result, it was found that compounds 1-04, 1-05, 1-06, 1-07, 1-08, 1-11, 1-12, 1-16, 1-21, 1-22, 1-23, 1-24, 1-25, 1-30, 1-32, 1-36, 1-37, 1-38, 1-39, 1-40, 1-41, 1-42, 1-43, 1-44 can be exemplified as typical compounds having an IC_{50} value of 50 nM or less.

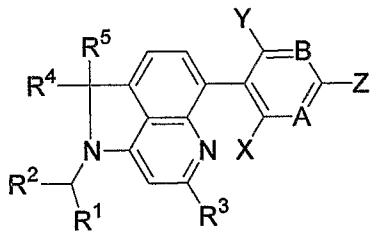
[EFFECT OF THE INVENTION]

According to the present invention, compounds having a high affinity for CRF receptors have been provided. These compounds are effective against diseases in which CRF is considered to be involved, such as depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia,

cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia, pain, etc.

CLAIMS

1. An 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative represented by the following formula [I],



[I]

wherein R^1 and R^2 are the same or different, and independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, cyano, cyano-C_{1-6}alkyl or $R^6(R^7)N$-C_{1-6}alkyl;

R^3 is hydrogen or C_{1-6}alkyl;

R^4 is hydroxyl and R^5 is hydrogen; or R^4 and R^5 are taken together to form a carbonyl group;

R^6 and R^7 are the same or different, and independently hydrogen or C_{1-3}alkyl; or R^6 and R^7 are taken together to form $-(CH_2)_s-R^8-(CH_2)_t-$;

R^8 is methylene, oxygen, NR^9 or a single bond;

R^9 is hydrogen or C_{1-3}alkyl;

s and t are the same or different, and independently an integer selected from 1, 2 or 3;

A and B are the same or different, and independently N or CH;

X, Y and Z are the same or different, and independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-}

$_3$alkylthio, halogen, trifluoromethyl, trifluoromethoxy or $-N(R^{10})R^{11}$;

R^{10} and R^{11} are the same or different, and independently hydrogen or C_{1-3}alkyl; or pharmaceutically acceptable salts and hydrates thereof.

2. The 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one derivative according to claim 1, wherein R^1 and R^2 are the same or different, and independently are hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, cyano, cyano-C_{1-6}alkyl or $R^6(R^7)N$-C_{1-6}alkyl;

R^3 is methyl;

R^4 and R^5 are taken together to form a carbonyl group;

R^6 and R^7 are the same or different, and independently hydrogen or C_{1-3}alkyl;

A and B are the same or different, and independently N or CH;

X, Y and Z are the same or different, and independently hydrogen, C_{1-3}alkyl, halogen or $-N(R^{10})R^{11}$;

R^{10} and R^{11} are the same or different, and independently hydrogen or C_{1-3}alkyl; or pharmaceutically acceptable salts and hydrates thereof.

3. The 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one derivative according to claim 1,

wherein R^1 and R^2 are the same or different, and independently are C_{1-6}alkyl, C_{3-7}cycloalkyl or C_{1-6}alkoxy-C_{1-6}alkyl;

R^3 is methyl;

R^4 and R^5 are taken together to form a carbonyl group;

A and B are the same or different, and independently N or CH;

X, Y and Z are the same or different, and independently hydrogen, methyl, chloro or dimethylamino; or pharmaceutically acceptable salts and hydrates thereof.

4. The 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative according to claim 1, selected from the group consisting of

8-(2,4-dichlorophenyl)-4-(1-ethylpropyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-2-methyl-4-(1-methylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-[(1*R*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-[(1*S*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-

de]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-[1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-(2,4-dichlorophenyl)-4-(dicyclopropylmethyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-2-methyl-4-(1-methylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-[(1*R*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-[(1*S*)-1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-4-methylpyridin-3-yl]-4-[1-(methoxymethyl)propyl]-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-2-methylpyridin-3-yl]-4-(1-ethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

8-[6-(dimethylamino)-2-methylpyridin-3-yl]-4-(1,3-dimethylbutyl)-2-methylpyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-(1-ethylpropyl)-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

2-methyl-4-(1-methylbutyl)-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-(1,3-dimethylbutyl)-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-(1-ethylbutyl)-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

2-methyl-4-(1-propylbutyl)-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-[(1*R*)-1-(methoxymethyl)propyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-[(1*S*)-1-(methoxymethyl)propyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-[(1-(methoxymethyl)propyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one,

4-[2-methoxy-1-(methoxymethyl)ethyl]-2-methyl-8-(2,4,6-trimethylphenyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one and

8-[2-(dimethylamino)-4,6-dimethylpyrimidin-5-yl]-2-methyl-4-(1-propylbutyl)pyrrolo[2,3,4-*de*]quinolin-5(4*H*)-one

, or pharmaceutically acceptable salts and hydrates thereof.

5. A pharmaceutical composition which comprises an 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative, or pharmaceutically acceptable salts and hydrates thereof according to any one of claims 1 to 4, as an active ingredient, and a pharmaceutical acceptable carrier.

6. A therapeutic method for the treatment of depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia or pain in a mammal, said method comprising the step of administering to said mammal an effective amount of an 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative, or pharmaceutically acceptable salts and hydrates thereof according to any one of claims 1 to 4.

7. A therapeutic method for the treatment of

depression, anxiety or irritable bowel syndrome in a mammal, said method comprising the step of administering to said mammal an effective amount of an 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative, or pharmaceutically acceptable salts and hydrates thereof according to any one of claims 1 to 4.

8. Use of an 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative, or pharmaceutically acceptable salts and hydrates thereof according to any one of claims 1 to 4, for the manufacture of a medicament for the treatment of depression, anxiety, Alzheimer's disease, Parkinson's disease, Huntington's chorea, eating disorder, hypertension, gastrointestinal diseases, drug dependence, cerebral infarction, cerebral ischemia, cerebral edema, cephalic external wound, inflammation, immunity-related diseases, alopecia, irritable bowel syndrome, sleep disorders, epilepsy, dermatitides, schizophrenia or pain.

9. Use of an 8-aryl-4-alkylpyrrolo[2,3,4-*de*]quinolin-5(4H)-one or 8-aryl-4-alkyl-4,5-dihydropyrrolo[2,3,4-*de*]quinolin-5-ol derivative, or pharmaceutically acceptable salts and hydrates thereof according to any one of claims 1 to 4, for the manufacture of a medicament for the treatment of depression, anxiety or irritable bowel syndrome.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2008/062877

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/235011 A1 (RUBAS LADISLAV [NO] ET AL) 25 December 2003 (2003-12-25) claims 1,20	1-9
A	WO 03/008412 A (GLAXO GROUP LTD [GB]; DI FABIO ROMANO [IT]; MICHELI FABRIZIO [IT]; ST-) 30 January 2003 (2003-01-30) claim 13; examples 1,2	1-9
A	WO 2006/001511 A (TAISHO PHARMA CO LTD [JP]; NAKAZATO ATSURO [JP]; OKUBO TAKETOSHI [JP];) 5 January 2006 (2006-01-05) claims 1,15	1-9
A	JP 2002 308877 A (NIPPON SODA CO) 23 October 2002 (2002-10-23) cited in the application	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2008	06/11/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/JP2008/062877

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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