

DESCRIPTION

QUINOLONE COMPOUND AND PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

The present invention relates to a quinolone compound
5 and a pharmaceutical composition.

BACKGROUND ART

Parkinson's disease is a chronic, progressive neurodegenerative disease that generally develops after middle age. Initial symptoms include unilateral resting tremor, akinesia
10 and rigidity. The tremors, akinesia, and rigidity are called the three major signs of Parkinson's disease, and each of them are caused by the selective death of dopaminergic neurons projected from the substantia nigra to the striatum. The etiology of the disease is still unknown; however, accumulated evidence suggests
15 that an impaired energy-generating system accompanied by abnormal mitochondrial function of nigrostriatal dopaminergic neurons triggers the neurodegenerative disorder of the disease. The mitochondrial dysfunction has been assumed to subsequently cause oxidative stress and failure of calcium homeostasis, thereby
20 resulting in neurodegeneration (Ann.N.Y.Acad.Sci.991:111-119(2003)).

Treatments of Parkinson's disease are roughly classified into medical management (medication) and surgical management (stereotaxic operation). Of these, medication is an
25 established therapy and regarded as a basic treatment. In the medication, a symptomatic therapeutic agent is used to compensate for the nigrostriatal dopaminergic neuronal function denatured by Parkinson's disease. L-dopa exhibits the most remarkable therapeutic effects. It is said that no agent exceeds the
30 effectiveness of L-dopa. Currently, L-dopa is used together with a dopa decarboxylase inhibitor to prevent the metabolism thereof in the periphery, and the desired clinical effects have been obtained.

However, one disadvantage of the L-dopa treatment is
35 that after several years of usage, the decrement of the

durability and stability of the drug's efficacy results in the recurrence of movement disorders such as dyskinesia and daily fluctuation. Moreover, digestive side effects such as nausea and vomiting brought on by the excess release of dopamine, circulatory organ problems such as orthostatic hypotension, tachycardia and arrhythmia, and neurological manifestations such as hallucinations, delusions and distractions have been a cause for concern.

Thus, in order to decrease the L-dopa preparation dosage and thereby reducing the side effects, multidrug therapies, in which dopamine receptor agonists, dopamine metabolism enzyme inhibitors, dopamine releaser, central anticholinergic agents and the like are used in combination, are employed. Such therapeutic advances remarkably improve prognoses; even now, however, there is no fundamental cure for Parkinson's disease and other neurodegenerative diseases. Medication must be taken for the rest of the patient's life, and the aforementioned drawbacks - decreased efficacy during long-term administration, side effects, and uncontrollable disease progression - can result from L-dopa monotherapy. In addition, it is difficult to expect dramatic effects, even during the employment of multidrug therapies.

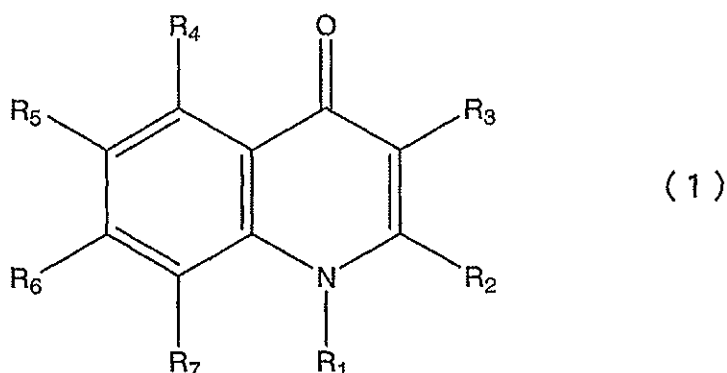
DISCLOSURE OF THE INVENTION

The present invention aims to provide a novel compound that has a functional improvement effect and suppresses of neurological dysfunction by inhibiting the chronic progression of Parkinson's disease or protecting dopamine neurons from the disease etiology, thereby prolonging the period before first L-dopa administration begins.

The present inventors carried out extensive research to accomplish the aforementioned object, and as a result, they succeeded in producing a compound represented by the following General Formula (1), which comprises protecting and improving mitochondrial functional activity, and protecting and repairing neuron activity. The present invention has been accomplished based on the above findings.

The present invention provides a quinolone compound , a pharmaceutical composition comprising said compound, a use of said compound, a method for treating or preventing a disorder, and a process for producing said compound, as described in Item 1 to 11 below.

Item 1. A quinolone compound represented by General Formula (1)



10

or a salt thereof,

wherein R_1 represents a hydrogen atom, a lower alkyl group, a cyclo C_{3-8} alkyl lower alkyl group, or a lower alkoxy lower alkyl group;

15

R_2 represents a hydrogen atom, a lower alkyl group, or a halogen-substituted lower alkyl group;

R_3 represents a phenyl group, a furyl group, a thienyl group, or a pyridyl group, each of the groups optionally being substituted with one or more groups selected from the group consisting of the following (1) to (16) on the aromatic or heterocyclic ring represented by the above R_3 :

- 20
- (1) lower alkyl groups,
 - (2) lower alkoxy groups,
 - (3) halogen-substituted lower alkoxy groups,
 - 25 (4) a phenoxy group,
 - (5) lower alkylthio groups,
 - (6) a hydroxy group,
 - (7) hydroxy lower alkyl groups,

- (8) halogen atoms,
- (9) lower alkanoyl groups,
- (10) lower alkoxy carbonyl groups,
- (11) amino groups optionally substituted with one or more lower
- 5 alkyl groups,
- (12) carbamoyl groups optionally substituted with one or more lower alkyl groups,
- (13) cyclo C₃₋₈ alkyl lower alkoxy groups,
- (14) pyrrolidinyl carbonyl groups,
- 10 (15) morpholinyl carbonyl groups, and
- (16) a carboxyl group;

R₄ represents a halogen atom;

R₅ represents a hydrogen atom or a halogen atom;

R₆ represents a hydrogen atom; and

- 15 R₇ represents any one of groups (1) to (15) below:

- (1) a hydroxy group,
- (2) a halogen atom,
- (3) a lower alkoxy group,
- (4) a halogen-substituted lower alkoxy group,
- 20 (5) a hydroxy lower alkoxy group,
- (6) a lower alkoxy lower alkoxy group,
- (7) an amino group optionally substituted with one or more members selected from the group consisting of lower alkyl groups, lower alkoxy lower alkyl groups, and cyclo C₃₋₈ alkyl groups,
- 25 (8) an amino lower alkoxy group optionally substituted on the amino group with one or more members selected from the group consisting of lower alkyl groups, lower alkanoyl groups, lower alkyl sulfonyl groups, and carbamoyl groups optionally substituted with one or more lower alkyl groups,
- 30 (9) a cyclo C₃₋₈ alkyloxy group,
- (10) a cyclo C₃₋₈ alkyl lower alkoxy group,
- (11) a tetrahydrofuryl lower alkoxy group,
- (12) a lower alkylthio group,
- (13) a heterocyclic group selected from the group consisting of
- 35 morpholinyl groups, pyrrolidinyl groups, furyl groups, thienyl

groups, and benzothienyl groups,

(14) a phenyl lower alkoxy lower alkoxy group, and

(15) a pyrrolidinyl carbonyl group.

5 Item 2. A quinolone compound of General Formula (1) or a salt thereof according to item 1,

 wherein R_1 represents a hydrogen atom or a lower alkyl group;

R_2 represents a hydrogen atom or a lower alkyl group;

10 R_3 represents a phenyl group or a pyridyl group, each of the groups optionally being substituted with one or two groups selected from the group consisting of the following (1), (2), (6), and (8) on the aromatic or heterocyclic ring represented by the above R_3 :

- 15 (1) lower alkyl groups,
 (2) lower alkoxy groups,
 (6) a hydroxy group, and
 (8) halogen atoms;

R_4 represents a halogen atom;

20 R_5 represents a hydrogen atom;

R_6 represents a hydrogen atom; and

R_7 represents any one of groups (3), (4), and (7)

below:

- (3) a lower alkoxy group,
25 (4) a halogen-substituted lower alkoxy group, and
 (7) an amino group optionally substituted with one or two lower alkyl groups

 Item 3. A quinolone compound of General Formula (1) or a
30 salt thereof according to item 2 selected from the group consisting of:

- 5-fluoro-3-(4-methoxyphenyl)-2-methyl-8-propoxy-1H-quinolin-4-one,
 5-fluoro-3-(4-methoxyphenyl)-1-methyl-8-propoxy-1H-quinolin-4-one,
 3-(2,4-dimethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one,
35 5-fluoro-8-isopropoxy-3-(4-methoxyphenyl)-1H-quinolin-4-one,

3-(2,4-dichlorophenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one,
8-ethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one,
5-fluoro-3-(4-methoxy-2-methylphenyl)-8-propoxy-1H-quinolin-4-one,
5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one,
5 5-fluoro-3-(2-fluoro-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one,
5-fluoro-3-(4-hydroxyphenyl)-8-propoxy-1H-quinolin-4-one,
8-cyclopropylmethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-
one,
5-fluoro-8-propoxy-3-pyridin-4-yl-1H-quinolin-4-one,
10 5-fluoro-3-(4-methoxyphenyl)-8-(N-methyl-N-propylamino)-1H-
quinolin-4-one, and
5-fluoro-3-(4-methoxyphenyl)-8-(4,4,4-trifluorobutoxy)-1H-
quinolin-4-one.

15 Item 4. A pharmaceutical composition comprising a
quinolone compound of General Formula (1) or a salt thereof
according to item 1 as an active ingredient and a
pharmaceutically acceptable carrier.

20 Item 5. A prophylactic and/or therapeutic agent for
neurodegenerative diseases, diseases induced by neurological
dysfunction, or diseases induced by deterioration of
mitochondrion function, comprising as an active ingredient a
quinolone compound of General Formula (1) or a salt thereof
25 according to item 1.

 Item 6. A prophylactic and/or therapeutic agent
according to item 5, wherein the neurodegenerative disease is
selected from the group consisting of Parkinson's disease,
30 Parkinson's syndrome, juvenile parkinsonism, striatonigral
degeneration, progressive supranuclear palsy, pure akinesia,
Alzheimer's disease, Pick's disease, prion disease, corticobasal
degeneration, diffuse Lewy body disease, Huntington's disease,
chorea-acanthocytosis, benign hereditary chorea, paroxysmal
35 choreoathetosis, essential tremor, essential myoclonus, Gilles de

la Tourette's syndrome, Rett's syndrome, degenerative ballism,
dystonia musculorum deformance, athetosis, spasmodic torticollis,
Meige syndrome, cerebral palsy, Wilson's disease, Segawa's
disease, Hallervorden-Spatz syndrome, neuroaxonal dystrophy,
5 pallidal atrophy, spino-cerebellar degeneration, cerebral
cortical atrophy, Holmes-type cerebellar atrophy,
olivopontocerebellar atrophy, hereditary olivopontocerebellar
atrophy, Joseph disease, dentatorubropallidoluysian atrophy,
Gerstmann-Straussler-Scheinker disease, Friedreich's Ataxia,
10 Roussy-Levy syndrome, May-White syndrome, congenital cerebellar
ataxia, hereditary episodic ataxia, ataxia telangiectasia,
amyotrophic lateral sclerosis, progressive bulbar palsy, spinal
progressive muscular atrophy, spinobulbar muscular atrophy,
Werdnig-Hoffmann disease, Kugelberg-Welander disease, hereditary
15 spastic paraparesis, syringomyelia, syringobulbia, Arnold-Chiari
malformation, Stiffman syndrome, Klippel-Feil syndrome, Fazio-
Londe syndrome, lower myelopathy, Dandy-Walker syndrome, spina
bifida, Sjogren-Larsson syndrome, radiation myelopathy, age-
related macular degeneration, and cerebral apoplexy selected from
20 the group consisting of cerebral infarction and cerebral
hemorrhage.

Item 7. A prophylactic and/or therapeutic agent
according to item 5, wherein the disease induced by neurological
25 dysfunction is selected from the group consisting of spinal cord
injury, chemotherapy-induced neuropathy, diabetic neuropathy,
radiation damage, and demyelinating diseases selected from the
group consisting of multiple sclerosis, acute disseminated
encephalomyelitis, transverse myelitis, progressive multifocal
30 leucoencephalopathy, subacute sclerosing panencephalitis, chronic
inflammatory demyelinating polyneuropathy and Guillain-Barre
syndrome.

Item 8. A prophylactic and/or therapeutic agent
35 according to item 5, wherein the disease induced by deterioration

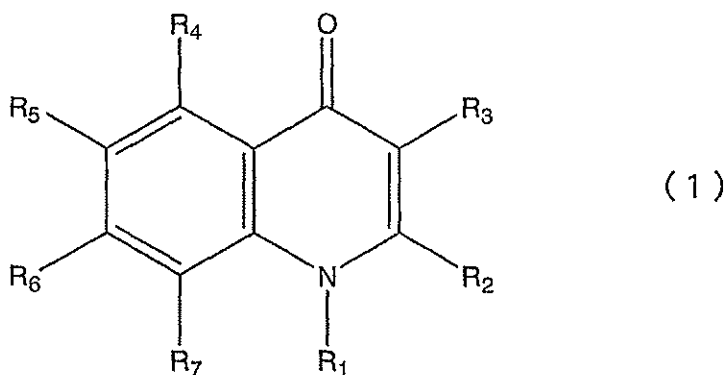
of mitochondrion function is selected from the group consisting of Pearson's syndrome, diabetes, deafness, malignant migraine, Leber's disease, MELAS, MERRF, MERRF/MELAS overlap syndrome, NARP, pure myopathy, mitochondrial cardiomyopathy, myopathy, dementia,
5 gastrointestinal ataxia, acquired sideroblastic anemia, aminoglycoside-induced hearing loss, complex III deficiency due to inherited variants of cytochrome b, multiple symmetrical lipomatosis, ataxia, myoclonus, retinopathy, MNGIE, ANTL disease, Twinkle disease, POLG disease, recurrent myoglobinuria, SANDO,
10 ARCO, complex I deficiency, complex II deficiency, optic nerve atrophy, fatal infantile complex IV deficiency, mitochondrial DNA deficiency, mitochondrial DNA deficiency syndrome, Leigh's encephalomyelopathy, chronic-progressive-external-ophthalmoplegia syndrome (CPEO), Kearns-Sayre syndrome, encephalopathy,
15 lactacidemia, myoglobinuria, drug-induced mitochondrial diseases, schizophrenia, major depression disorder, bipolar I disorder, bipolar II disorder, mixed episode, dysthymic disorders, atypical depression, seasonal affective disorders, postpartum depression, minor depression, recurrent brief depressive disorder,
20 intractable depression/chronic depression, double depression and acute renal failure.

Item 9. Use of a quinolone compound of General Formula (1) or a salt thereof according to item 1 as a drug.

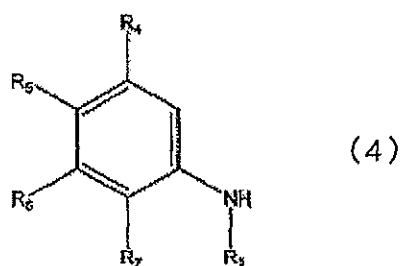
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Item 10. A method for treating or preventing neurodegenerative diseases, diseases induced by neurological dysfunction, or diseases induced by deterioration of mitochondrion function, comprising administering a quinolone
30 compound of General Formula (1) or a salt thereof according to item 1 to a human or an animal.

Item 11. A process for producing a quinolone compound of General Formula (1)

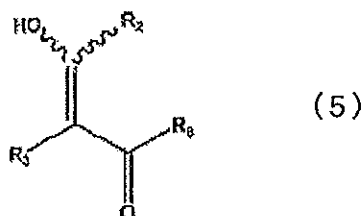


or a salt thereof, wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_7 are each defined above in item 1, comprising reacting a compound
5 represented by General Formula (4)



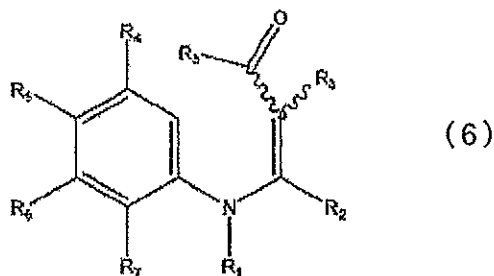
wherein R_1 , R_4 , R_5 , R_6 and R_7 are each defined above in item 1,
with a compound represented by General Formula (5)

10



wherein R_2 and R_3 are each defined above in item 1, and R_8 represents a lower alkoxy group, thereby giving an intermediate compound represented by General Formula (6)

15



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are each defined above; and
subjecting the resulting compound to a cyclization reaction.

5 Specific examples of groups in General Formula (1) are
as follows.

 Examples of lower alkyl groups include straight or
branched C_{1-6} (preferably C_{1-4}) alkyl groups such as methyl, ethyl,
n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-
10 pentyl, 1-ethylpropyl, isopentyl, neopentyl, n-hexyl, 1,2,2-
trimethylpropyl, 3,3-dimethylbutyl, 2-ethylbutyl, isohexyl, 3-
methylpentyl, etc.

 Examples of C_{3-8} cycloalkyl groups include cyclopropyl,
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.

15 Examples of cyclo C_{3-8} alkyl lower alkyl groups include
the lower alkyl groups substituted with one to three (preferably
one) cyclo C_{3-8} alkyl group(s) described above.

 Examples of lower alkoxy groups include straight or
branched C_{1-6} (preferably C_{1-4}) alkoxy groups such as methoxy,
20 ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy,
sec-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy, n-hexyloxy,
isohexyloxy, 3-methylpentyloxy, etc.

 Examples of lower alkoxy lower alkyl groups include the
lower alkyl groups substituted with one to three (preferably one)
25 lower alkoxy group(s) described above.

 Examples of halogen atoms include fluorine, chlorine,
bromine, and iodine.

 Examples of halogen-substituted lower alkyl groups

include the lower alkyl groups substituted with one to seven halogen atom(s), preferably one to three halogen atom(s). Examples thereof include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 5 bromomethyl, dibromomethyl, dichlorofluoromethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 2-fluoroethyl, 2-chloroethyl, 3,3,3-trifluoropropyl, heptafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoroisopropyl, 3-chloropropyl, 2-chloropropyl, 3-10 bromopropyl, 4,4,4-trifluorobutyl, 4,4,4,3,3-pentafluorobutyl, 4-chlorobutyl, 4-bromobutyl, 2-chlorobutyl, 5,5,5-trifluoropentyl, 5-chloropentyl, 6,6,6-trifluorohexyl, 6-chlorohexyl, perfluorohexyl, etc.

Examples of halogen-substituted lower alkoxy groups 15 include the lower alkoxy groups substituted with one to seven halogen atom(s), preferably one to three halogen atom(s). Examples thereof include fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, bromomethoxy, dibromomethoxy, 20 dichlorofluoromethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 2-chloroethoxy, 3,3,3-trifluoropropoxy, heptafluoropropoxy, heptafluoroisopropoxy, 3-chloropropoxy, 2-chloropropoxy, 3-bromopropoxy, 4,4,4-trifluorobutoxy, 4,4,4,3,3-pentafluorobutoxy, 4-chlorobutoxy, 4-bromobutoxy, 2-chlorobutoxy, 5,5,5-25 trifluoropentoxy, 5-chloropentoxy, 6,6,6-trifluorohexyloxy, 6-chlorohexyloxy, etc.

Examples of lower alkylthio groups include alkylthio groups wherein the alkyl moiety is the lower alkyl group mentioned above.

30 Examples of hydroxy lower alkyl groups include the above-mentioned lower alkyl groups substituted with one to three (preferably one) hydroxy group(s).

Examples of lower alkanoyl groups include straight or branched C₁₋₆ (preferably C₁₋₄) alkanoyl groups such as formyl, 35 acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-

butylcarbonyl, hexanoyl, etc.

Examples of lower alkoxy carbonyl groups include alkoxy carbonyl groups wherein the alkoxy moiety is the lower alkoxy group mentioned above.

5 Examples of amino groups optionally substituted with one or more lower alkyl groups include amino groups optionally substituted with one or two lower alkyl group(s) described above.

 Examples of carbamoyl groups optionally substituted with one or more lower alkyl groups include carbamoyl groups
10 optionally substituted with one or two lower alkyl group(s) described above.

 Examples of cyclo C₃₋₈ alkyl lower alkyl groups include the above-mentioned lower alkyl groups substituted with one to three (preferable one) cyclo C₃₋₈ alkyl group(s) described above.

15 Examples of hydroxy lower alkoxy groups include the above-mentioned lower alkoxy groups substituted with one to three (preferably one) hydroxy group(s).

 Examples of lower alkoxy lower alkoxy groups include the above-mentioned lower alkoxy groups substituted with one to
20 three (preferably one) lower alkoxy group(s) described above.

 Examples of amino groups optionally substituted with one or more members selected from the group consisting of lower alkyl groups, lower alkoxy lower alkyl groups, and cyclo C₃₋₈ alkyl groups include amino groups optionally substituted with one
25 or two members selected from the group consisting of the above-mentioned lower alkyl groups, the above-mentioned lower alkoxy lower alkyl groups, and the above-mentioned cyclo C₃₋₈ alkyl groups.

 Examples of lower alkyl sulfonyl groups include alkyl
30 sulfonyl groups wherein the alkyl moiety is the lower alkyl group mentioned above.

 Examples of amino lower alkoxy groups optionally substituted on an amino group with one or more members selected from the group consisting of lower alkyl groups, lower alkanoyl
35 groups, lower alkyl sulfonyl groups, and carbamoyl groups

optionally substituted with one or more lower alkyl groups include the lower alkoxy groups substituted with one to three (preferably one) amino group(s). Here, the amino lower alkoxy group is optionally substituted on an amino group with one or two
5 members selected from the group consisting of the above-mentioned lower alkyl groups, the above-mentioned lower alkanoyl groups, the above-mentioned lower alkyl sulfonyl groups, carbamoyl groups optionally substituted with one or more lower alkyl groups mentioned above.

10 Examples of cyclo C₃₋₈ alkyloxy groups include groups in which the cyclo C₃₋₈ alkyl group and an oxygen atom are bonded.

 Examples of tetrahydrofuryl lower alkoxy groups include the above-mentioned lower alkoxy groups substituted with one to three (preferably one) tetrahydrofuryl group(s).

15 Examples of lower alkylthio groups include alkylthio groups wherein the alkyl moiety is the lower alkyl group mentioned above.

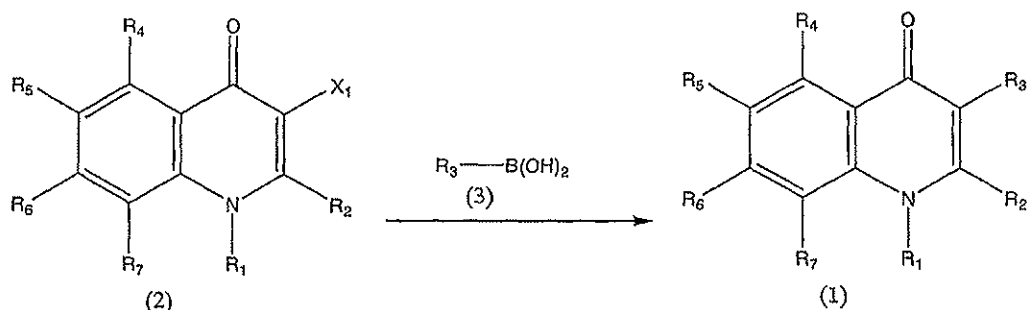
 Examples of phenyl lower alkoxy groups include the above-mentioned lower alkoxy groups substituted with one to three
20 (preferably one) phenyl group(s).

 Examples of phenyl lower alkoxy lower alkoxy groups include the above-mentioned lower alkoxy groups substituted with one to three phenyl lower alkoxy group(s) (preferably one) described above.

25 The process of producing the compound of the invention is described below in detail.

 The quinolone compound represented by General Formula (1) (hereinafter also referred to as Compound (1)) can be produced by various methods; for example, by a method according
30 to the following Reaction Scheme 1 or 2.

Reaction Scheme 1



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above, and X_1 represents a halogen atom.

5 Examples of halogen atoms represented by X_1 include fluorine, chlorine, bromine, and iodine.

 Preferable leaving groups in the reaction include halogen. Among these, iodine is particularly preferable.

 Compound (1) can be prepared by reacting the compound
 10 of General Formula (2) and the compound of General Formula (3) in an inert solvent or without using any solvents, in the presence or absence of a basic compound, in the presence of a palladium catalyst.

 Examples of inert solvents include water; ether-based
 15 solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents such as methanol, ethanol, and isopropanol; ketone-based solvents
 20 such as acetone and methyl ethyl ketone; and polar solvents such as *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

 Palladium compounds used in the reaction are not
 25 particularly limited, but include, for example, tetravalent palladium catalysts such as sodium hexachloropalladate (IV) tetrahydrate and potassium hexachloropalladate (IV); divalent palladium catalysts such as palladium (II) chloride, palladium (II) bromide, palladium (II) acetate, palladium (II)

acetylacetonato, dichlorobis(benzonitrile)palladium (II),
dichlorobis(acetonitrile)palladium (II),
dichlorobis(triphenylphosphine)palladium (II),
dichlorotetraammine palladium (II), dichloro(cycloocta-1,5-
5 diene)palladium (II), palladium (II) trifluoroacetate, and 1,1'-
bis(diphenylphosphino)ferrocene dichloropalladium (II)-
dichloromethane complex; zerovalent palladium catalysts such as
tris(dibenzylideneacetone)₂ palladium (0),
tris(dibenzylideneacetone)₂ palladium (0) chloroform complex, and
10 tetrakis(triphenylphosphine)palladium (0), etc. These palladium
compounds are used singly or in combinations of two or more.

In the reaction, the amount of the palladium catalyst
is not particularly limited, but is typically in the range from
0.000001 to 20 moles in terms of palladium relative to 1 mol of
15 Compound (2). The amount of the palladium catalyst is preferably
in the range from 0.0001 to 5 moles in terms of palladium
relative to 1 mol of Compound (2).

This reaction advantageously proceeds in the presence
of a suitable ligand. Examples of ligands of the palladium
20 catalyst include, for example, 2,2'-bis(diphenylphosphino)-1,1'-
binaphthyl(BINAP), tri-*o*-tolylphosphine,
bis(diphenylphosphino)ferrocene, triphenylphosphine, tri-*t*-
butylphosphine, and 9,9-dimethyl-4,5-
bis(diphenylphosphino)xanthene (XANTPHOS). These ligands are used
25 singly or in combinations of two or more.

The proportion of the palladium catalyst and ligand is
not particularly limited. The amount of the ligand is about 0.1
to about 100 moles per mole of the palladium catalyst, and
preferably about 0.5 to about 15 moles per mole of the palladium
30 catalyst.

Various known inorganic and organic bases can be used
as basic compounds.

Inorganic bases include, for example, alkali metal
hydroxides such as sodium hydroxide, potassium hydroxide, cesium
35 hydroxide, and lithium hydroxide; alkali metal carbonates such as

sodium carbonate, potassium carbonate, cesium carbonate, and lithium carbonate; alkali metal hydrogencarbonates such as lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and
5 potassium; phosphates such as sodium phosphate and potassium phosphate; amides such as sodium amide; and alkali metal hydrides such as sodium hydride and potassium hydride.

Organic bases include, for example, alkali metal lower alkoxides such as sodium methoxide, sodium ethoxide, sodium t-
10 butoxide, potassium methoxide, potassium ethoxide, and potassium t-butoxide, and amines such as triethylamine, tripropylamine, pyridine, quinoline, piperidine, imidazole, N-ethyldiisopropylamine, dimethylaminopyridine, trimethylamine, dimethylaniline, N-methylmorpholine,
15 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.

Such basic compounds can be used singly or in combinations of two or more. More preferable basic compounds used
20 in the reaction include alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, and lithium carbonate.

A basic compound is usually used in an amount of 0.5 to 10 moles per mole of Compound (2), and preferably 0.5 to 6 moles
25 per mole of Compound (2).

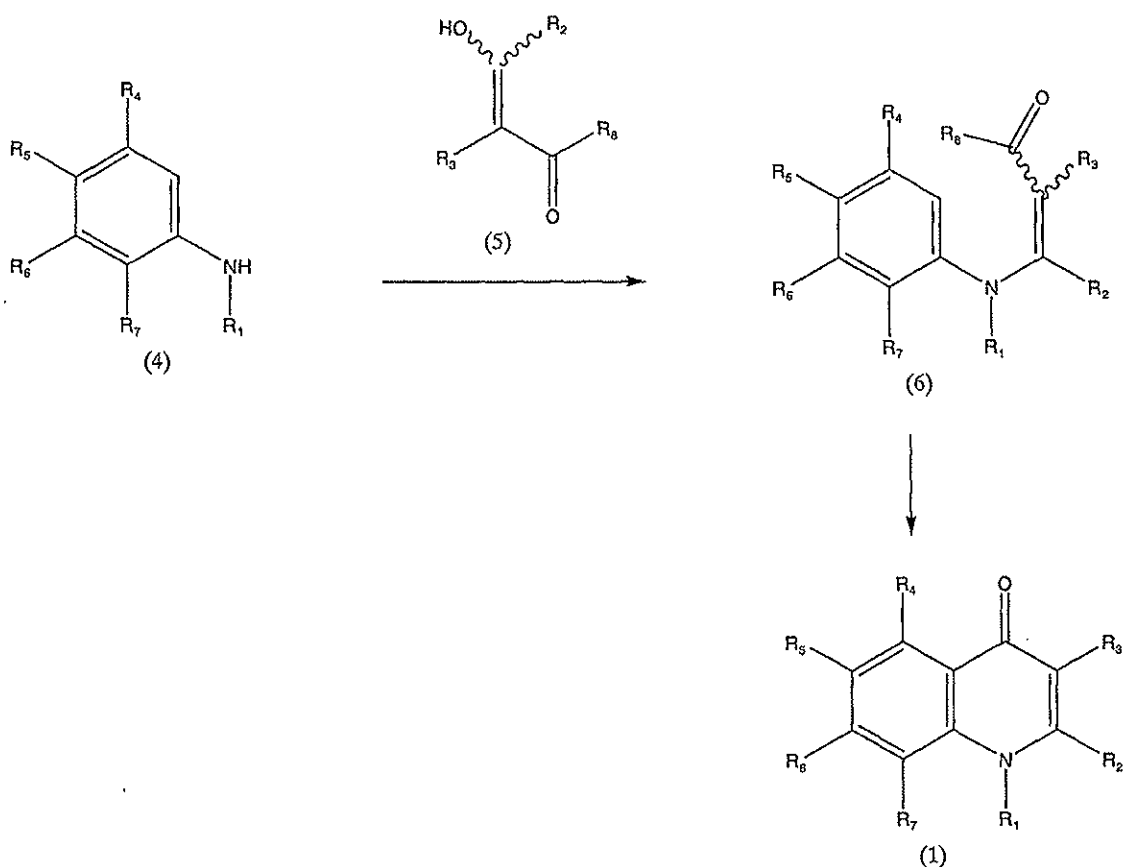
Compound (3) is usually used in an amount of at least about 1 mole per mole of Compound (2), and preferably about 1 to about 5 moles per mole of Compound (2).

The reaction can be conducted under normal pressure,
30 under inert gas atmospheres including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually at room temperature to 200°C, and preferably at room temperature to 150°C, and is usually completed in about 1 to about 30 hours. The reaction is also
35 achieved by heating at 100 to 200°C for 5 minutes to 1 hour using

a microwave reactor.

The compound represented by General Formula (3), which is used as a starting material in Reaction Scheme 1 is an easily available known compound. The compound represented by General
 5 Formula (2) includes a novel compound, and the compound is produced in accordance with Reaction Scheme 6 shown below.
 Reaction Scheme 2



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined
 10 above, and R_8 represents a lower alkoxy group.

The lower alkoxy group represented by R_8 in General Formula (5) has the same definition as described above.

The compounds represented by General Formulae (4) and (5) are reacted in an inert solvent or without using any solvents,
 15 in the presence or absence of an acid catalyst, thereby giving an intermediate compound represented by General Formula (6). Then, the resulting compound was cyclized to produce the compound represented by General Formula (1).

Examples of inert solvents include water; ether-based solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents such as methanol, ethanol, and isopropanol; and polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

Various kinds of known acid catalysts can be used, including toluenesulfonic acid, methanesulfonic acid, xylene sulfonic acid, sulfuric acid, glacial acetic acid, boron trifluoride, acidic ion exchangers, etc. These acid catalysts can be used singly or in combinations of two or more.

Among such acids, acidic ion exchangers are preferably used. Examples of acidic ion exchangers include polymeric cation exchangers available from the market such as Lewatit S100, Zeo-karb 225, Dowex 50, Amberlite IR120, or Amberlyst 15 and like styrene sulfonic acid polymers; Lewatit PN, Zeo-karb 215 or 315, and like polysulfonic acid condensates; Lewatit CNO, Duolite CS100, and like m-phenolic carboxylic acid resins; or Permutit C, Zeo-karb 226 or Amberlite IRC 50, and like polyacrylates. Of these, Amberlyst 15 is particularly preferred.

An oxide catalyst is usually used in an amount of 0.0001 to 100 moles per mole of Compound (4), and preferably 0.5 to 6 moles per mole of Compound (4).

In Reaction Scheme 2, Compound (5) is usually used in an amount of at least about 1 mole per mole of Compound (4), and preferably about 1 to about 5 moles per mole of Compound (4).

The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or under increased pressure.

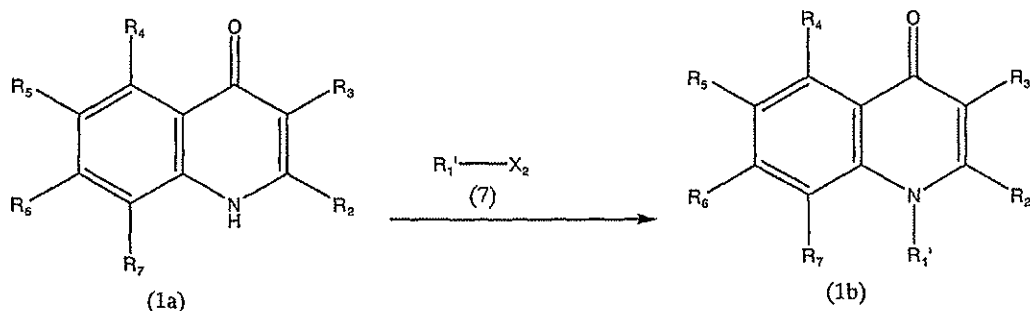
The reaction proceeds usually at room temperature to 200°C, and preferably at room temperature to 150°C. During the reaction, azeotropic removal of water is conducted until the

reaction water generation is completed. The reaction is usually finished in about 1 to about 30 hours.

The process of producing the compound of General Formula (1) via a cyclization reaction of the intermediate compound represented by General Formula (6) can be employed by heating the compound in a solvent such as diphenyl ether, or by heating the compound in the absence of a solvent. The reaction is conducted at 150 to 300°C for 5 minutes to 2 hours.

The compound represented by General Formula (4), used as a starting material in Reaction Scheme 2 described above is a known compound or can be produced easily using a known compound. The compound represented by General Formula (5) includes a novel compound, and the compound is manufactured in accordance with, for example, the methods shown in Reaction Scheme 4 and Reaction Scheme 5 described above.

Reaction Scheme 3



wherein R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above, and R_1' is a group represented by R_1 other than hydrogen, and X_2 represents a group that undergoes the same substitution reaction as that of a halogen or a halogen atom.

Halogens represented by X_2 in General Formula (1a) include the halogen atom described above. Groups that undergo the same substitution reaction as that of the halogen atoms represented by X_2 include lower alkyl sulfonyloxy groups, aryl sulfonyloxy groups, aralkyl sulfonyloxy groups, etc.

Examples of lower alkyl sulfonyloxy groups include straight or branched C_{1-6} alkyl sulfonyloxy groups, such as methane sulfonyloxy, ethane sulfonyloxy, n-propane sulfonyloxy,

isopropane sulfonyloxy, n-butane sulfonyloxy, tert-butane sulfonyloxy, n-pentane sulfonyloxy, and n-hexane sulfonyloxy.

Examples of aryl sulfonyloxy groups include naphthyl sulfonyloxy and phenyl sulfonyloxy optionally substituted on a phenyl ring with one to three group(s) selected from the group consisting of straight or branched C₁₋₆ alkyl groups, straight or branched C₁₋₆ alkoxy groups, nitro groups, and halogen atoms as a substituent. Examples of phenyl sulfonyloxy groups optionally substituted with the above substituent(s) include phenyl sulfonyloxy, 4-methylphenyl sulfonyloxy, 2-methylphenyl sulfonyloxy, 4-nitrophenyl sulfonyloxy, 4-methoxyphenyl sulfonyloxy, 2-nitrophenyl sulfonyloxy, 3-chlorophenyl sulfonyloxy, etc. Examples of naphthyl sulfonyloxy groups include α -naphthyl sulfonyloxy, β -naphthyl sulfonyloxy, etc.

Examples of aralkyl sulfonyloxy groups include phenyl-substituted straight or branched C₁₋₆ alkyl sulfonyloxy groups that may have, on the phenyl ring, one to three substituent(s) selected from the group consisting of straight or branched C₁₋₆ alkyl groups, straight or branched C₁₋₆ alkoxy groups, a nitro group and halogen atoms as a substituent, or naphthyl-substituted straight or branched C₁₋₆ alkyl sulfonyloxy groups. Examples of alkyl sulfonyloxy groups substituted with the above-mentioned phenyl group(s) include benzyl sulfonyloxy, 2-phenylethyl sulfonyloxy, 4-phenylbutyl sulfonyloxy, 4-methylbenzyl sulfonyloxy, 2-methylbenzyl sulfonyloxy, 4-nitrobenzyl sulfonyloxy, 4-methoxybenzyl sulfonyloxy, 3-chlorobenzyl sulfonyloxy, etc. Examples of alkyl sulfonyloxy groups substituted with the above-mentioned naphthyl group(s) include α -naphthylmethyl sulfonyloxy, β -naphthylmethyl sulfonyloxy, etc.

The compound represented by General Formula (1b) can be produced by the reaction of the compound represented by General Formula (1a) with the compound represented by General Formula (7) in an inert solvent or without using any solvents, in the presence or absence of a basic compound.

Examples of inert solvents include water; ether-based

solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents
5 such as methanol, ethanol, and isopropanol; ketone-based solvents such as acetone and methyl ethyl ketone; and polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

10 As a basic compound, various known inorganic bases and organic bases can be used.

Inorganic bases include, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as
15 sodium carbonate, potassium carbonate, cesium carbonate, and lithium carbonate; alkali metal hydrogen carbonates such as lithium hydrogen carbonate, sodium hydrogen carbonate, and potassium hydrogen carbonate; alkali metals such as sodium and potassium; amides such as sodium amide; and alkali metal hydrides
20 such as sodium hydride and potassium hydride.

Organic bases include, for example, alkali metal lower alkoxides such as sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium methoxide, potassium ethoxide, and potassium t-butoxide, and amines such as triethylamine, tripropylamine,
25 pyridine, quinoline, piperidine, imidazole, N-ethyl diisopropylamine, dimethylaminopyridine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.

30 Such basic compounds can be used singly or in combinations of two or more. More preferable basic compounds used in the reaction include inorganic bases such as sodium hydride and potassium hydride.

A basic compound is usually used in an amount of 0.5 to
35 10 moles per mole of Compound (1a), and preferably 0.5 to 6 moles

per mole of Compound (1a).

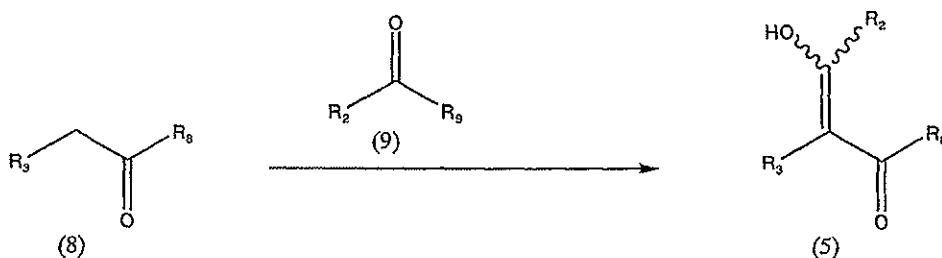
In Reaction Scheme 1, Compound (7) usually used in an amount of at least about 1 mole per mole of Compound (1a), and preferably about 1 to about 5 moles per mole of Compound (1a).

5 The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually at 0°C to 200°C, and preferably at room temperature to 150°C, and is usually completed
10 in about 1 to about 30 hours.

The compound represented by General Formula (7), which is used as a starting material in Reaction Scheme 3 is an easily available known compound.

Compound (5) and Compound (2), which are the starting
15 materials of the compound of the invention, include novel compounds, and can be produced by various methods; for example, by methods according to the following Reaction Schemes 4 to 6.
Reaction Scheme 4



20 wherein R₂, R₃, and R₈ are as defined above, and R₉ represents a lower alkoxy group.

The lower alkoxy group represented by R₉ in General Formula (9) has the same definition as described above.

The compound represented by General Formula (5) can be
25 produced by the reaction of the compound represented by General Formula (8) with the compound represented by General Formula (9) in an inert solvent or without using any solvents, in the presence or absence of a basic compound.

Examples of inert solvents include water; ether-based
30 solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-

dimethoxyethane, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents such as methanol, ethanol, and isopropanol; ketone-based solvents
5 such as acetone and methyl ethyl ketone; and polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

As a basic compound, various known inorganic bases and
10 organic bases can be used.

Inorganic bases include, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, and
15 lithium carbonate; alkali metal hydrogencarbonates such as lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; amides such as sodium amide; and inorganic bases of alkali metal hydrides such as sodium hydride and potassium
20 hydride.

Organic bases include, for example, alkali metal lower alkoxides such as sodium methoxide, sodium ethoxide, sodium t-butoxide; potassium methoxide, potassium ethoxide, and potassium t-butoxide; and amines such as triethylamine, tripropylamine,
25 pyridine, quinoline, piperidine, imidazole, N-ethyl-diisopropylamine, dimethylaminopyridine, trimethylamine, dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.

30 Such basic compounds can be used singly or in combinations of two or more. More preferable basic compounds used in the reaction include inorganic bases such as sodium hydride and potassium hydride.

A basic compound is usually used in an amount of about
35 1 to about 10 moles per mole of Compound (8), and preferably

5 The reaction can be conducted under normal pressure,
under inert gas atmospheres including nitrogen, argon, etc., or
under increased pressure.

The reaction proceeds usually at room temperature to 200°C, and preferably at room temperature to 150°C, and is usually
10 completed in about 1 to about 30 hours.

Reaction Scheme 5



The halogen atom represented by X_3 in General Formula (9') has the same definition as described above.

20 The compound represented by General Formula (5) can be
produced by the reaction of the compound represented by General
Formula (8') with the compound represented by General Formula
(9') in an inert solvent or without using any solvents, in the
presence of a basic compound such as cesium carbonate and a
25 copper catalyst such as copper iodide.

Examples of inert solvents include polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

The reaction may be conducted in the presence of amino acids such as L-proline.

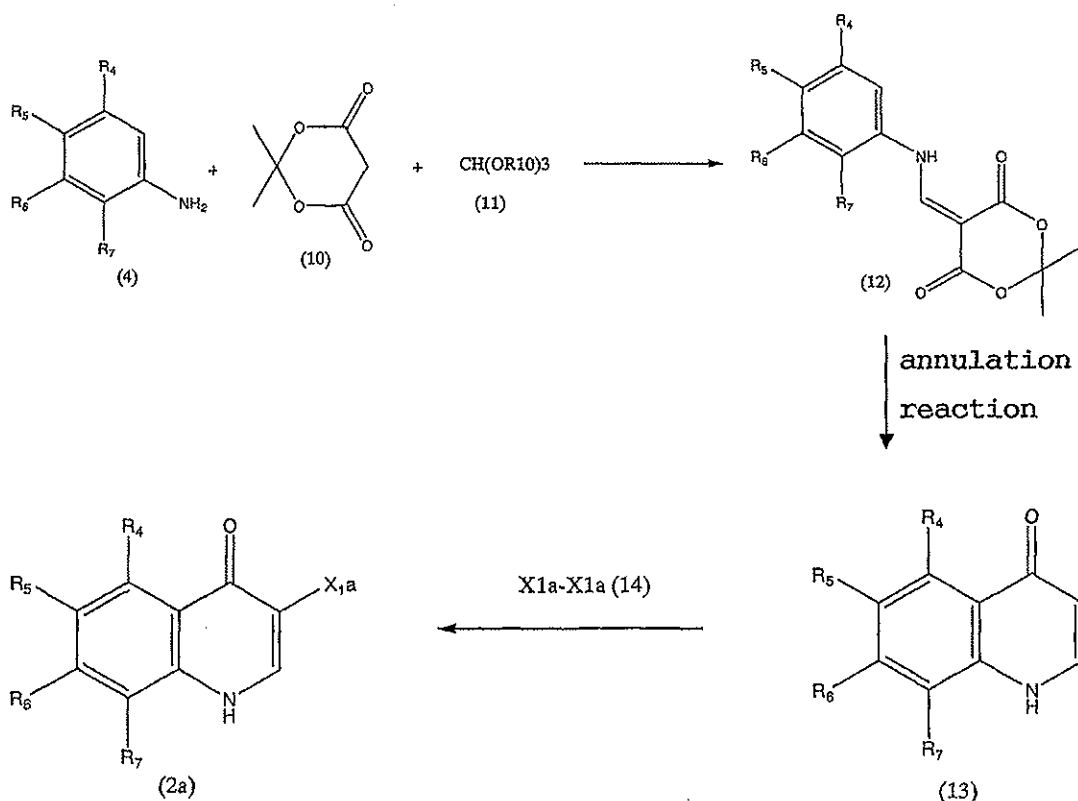
The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or
5 under increased pressure.

The reaction proceeds usually at room temperature to 200°C, and preferably at room temperature to 150°C, and is usually completed in about 1 to about 30 hours.

The above reaction is specifically shown in Reference
10 Example 58 below.

The compounds represented by General Formulae (8') and (9') used as starting materials in Reaction Scheme 5 described above are known compounds, or can be produced easily using known compounds.

15 Reaction Scheme 6



wherein R₄, R₅, R₆, and R₇ are as defined above, and X_{1a} represents a halogen atom. R₁₀ represents a lower alkyl group.

The lower alkyl group represented by R_{10} and a halogen atom represented by X_{1a} have the same definitions as described above.

The compound represented by General Formula (12) can be
5 produced by the condensation reaction of the compounds represented by General Formulae (4), (10), and (11) in an inert solvent or without using any solvents.

Examples of inert solvents include water; ether-based solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-
10 dimethoxyethane, diethylene glycol dimethyl ether, and ethylene glycol dimethyl ether; halogenated hydrocarbon-based solvents such as methylene chloride, chloroform, 1,2-dichloroethane, and carbon tetrachloride; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents such
15 as methanol, ethanol, and isopropanol; and polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. The compound represented by General Formula (11) can be used as a solvent in place of the solvents mentioned above. These inert solvents can
20 be used singly or in combinations of two or more.

In Reaction Scheme 6, Compound (10) is usually used in an amount of at least 1 mole per mole of Compound (4), and preferably about 1 to about 5 moles per mole of Compound (4).

An excess amount of Compound (11) is used relative to
25 Compound (10).

The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually at room temperature to
30 200°C, and preferably at room temperature to 150°C, and is usually completed in about 1 to about 30 hours.

The compound represented by General Formula (13) can be produced by an annulation reaction of the compound represented by General Formula (12) in an inert solvent or without using any
35 solvents.

Examples of inert solvents include ether-based solvents such as diphenyl ether.

The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or
5 under increased pressure.

The reaction proceeds usually at room temperature to 300°C, and preferably at 150 to 300°C, and is usually completed in about 1 to about 30 hours.

The compound represented by General Formula (2a) can be
10 produced by the reaction of the compound represented by General Formula (13) with the compound represented by General Formula (14) in an inert solvent or without using any solvents, in the presence or absence of a basic compound.

Examples of inert solvents include water; ether-based
15 solvents such as dioxane, tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane, diethylene-glycol dimethyl ether, and ethylene glycol dimethyl ether; aromatic hydrocarbon-based solvents such as benzene, toluene, and xylene; lower alcohol-based solvents such as methanol, ethanol, and isopropanol; ketone-based solvents
20 such as acetone and methyl ethyl ketone; polar solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric triamide, and acetonitrile. These inert solvents can be used singly or in combinations of two or more.

As a basic compound, various known inorganic bases and
25 organic bases can be used.

Inorganic bases include, for example, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, cesium hydroxide, and lithium hydroxide; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, and
30 lithium carbonate; alkali metal hydrogencarbonates such as lithium hydrogencarbonate, sodium hydrogencarbonate, and potassium hydrogencarbonate; alkali metals such as sodium and potassium; amides such as sodium amide; and alkali metal hydrides such as sodium hydride and potassium hydride

35 Organic bases include, for example, alkali metal

alkoxide-based solvents such as sodium methoxide, sodium ethoxide, sodium t-butoxide, potassium methoxide, potassium ethoxide, and potassium t-butoxide; and amines such as triethylamine, tripropylamine, pyridine, quinoline, piperidine, imidazole, N-ethyl-diisopropylamine, dimethylaminopyridine, trimethylamine, 5 dimethylaniline, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), etc.

Such basic compounds can be used singly or in combinations of two or more. More preferable basic compounds used 10 in the reaction include alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, and lithium carbonate, etc.

A basic compound is usually used in an amount of 0.5 to 15 10 moles per mole of Compound (13), and preferably 0.5 to 6 moles per mole of Compound (13).

In Reaction Scheme 6, Compound (14) is usually used in an amount of at least 0.5 moles per mole of Compound (13), and preferably about 0.5 to about 5 moles per mole of Compound (13).

20 The reaction can be conducted under normal pressure, under inert gas atmospheres including nitrogen, argon, etc., or under increased pressure.

The reaction proceeds usually at room temperature to 200°C, and preferably at room temperature to 150°C, and is usually 25 completed in about 1 to about 30 hours.

The compounds represented by General Formulae (10), (11) and (14), which are used as starting materials in Reaction Scheme 6, are easily available known compounds.

The raw material compounds used in each of the reaction 30 schemes described above may include suitable salts, and the objective compounds obtained via each of the reactions may form suitable salts. These preferable salts include the following preferable salts of Compound (1).

Suitable salts of Compound (1) are pharmacologically 35 allowable salts, including metal salts such as alkali metal salts

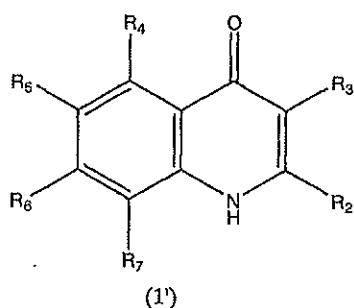
(e.g., sodium salts, potassium salts, and the like); alkaline earth metal salts (e.g., calcium salts, magnesium salts, and the like); ammonium salts; salts of inorganic bases such as alkali metal carbonates (e.g., lithium carbonate, potassium carbonate, sodium carbonate, cesium carbonate, and the like); alkali metal hydrogencarbonates (e.g., lithium hydrogencarbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, and the like); alkali metal hydroxides (e.g., lithium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, etc.); salts of organic bases such as tri(lower)alkylamine (e.g., trimethylamine, triethylamine, N-ethyl-diisopropylamine, and the like), pyridine, quinoline, piperidine, imidazole, picoline, dimethylaminopyridine, dimethylaniline, N-(lower)alkyl-morpholine (e.g., N-methylmorpholine, etc.), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and 1,4-diazabicyclo[2.2.2]octane (DABCO); inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, and phosphate; and organic acid salts such as formate, acetate, propionate, oxalate, malonate, succinate, fumarate, maleate, lactate, malate, citrate, tartrate, carbonate, picrate, methanesulfonate, ethanesulfonate, p-toluenesulfonate, and glutamate.

In addition, compounds in the form in which solvate (for example, hydrate, ethanolate, etc.) was added to the starting materials and objective compound shown in each of the reaction schemes are included in each of the general formulae. Preferable solvates include hydrate.

Each of the objective compounds obtained according to the above reaction schemes can be isolated and purified from the reaction mixture by, for example, after cooling the reaction mixture, performing an isolation procedure such as filtration, concentration, extraction, etc., to separate a crude reaction product, and then subjecting the crude reaction product to a usual purification procedure such as column chromatography, recrystallization, etc.

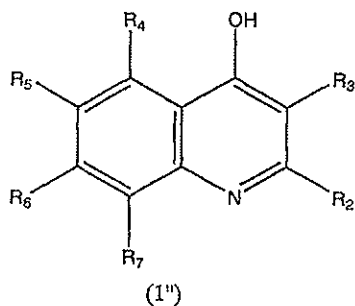
The compound of Formula (1) according to the present invention naturally includes geometrical isomers, stereoisomers, optical isomers, and like isomers.

5 The following points should be noted regarding the compound of General Formula (1) shown above. When R_1 of General Formula (1) represents a hydrogen atom, the compound includes a tautomer of the quinolone ring. That is, when R_1 represents a hydrogen atom (1') in the quinolone compound of General Formula (1),



10

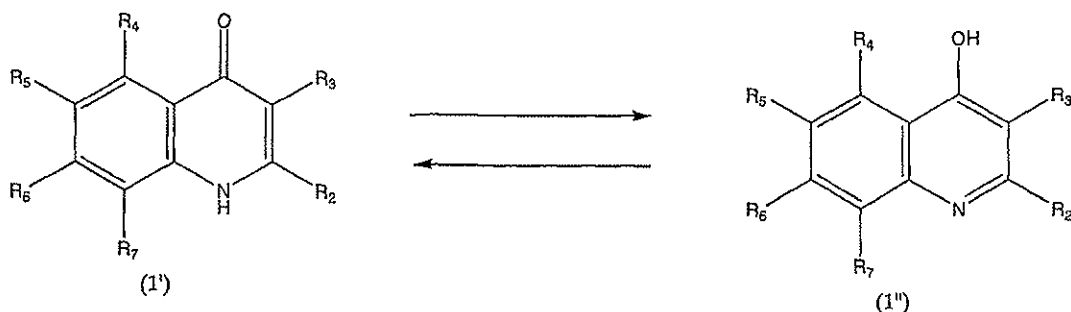
wherein R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above, the compound of the tautomer can be represented by Formula (1''),



15

wherein R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above.

That is, both of the compounds represented by Formulae (1') and (1'') are in the tautomeric equilibrium state represented by the following balance formula.



wherein R_2 , R_3 , R_4 , R_5 , R_6 , and R_7 are as defined above.

Such tautomerism between a 4-quinolone compound and a 4-hydroxyquinoline compound is technically known, and it is
5 obvious for a person skilled in the art that both of the above-described tautomers are balanced and mutually exchangeable.

Therefore, Compound (1) naturally includes the tautomers as mentioned above.

In the specification, the constitutional formula of a
10 4-quinolone compound is suitably used as a constitutional formula of the objective or starting material including compounds of such tautomers.

The compound of General Formula (1) and the salt thereof are used in the form of general pharmaceutical
15 preparations. The preparations are obtained using typically employed diluents or excipients such as fillers, extenders, binders, wetting agents, disintegrators, surfactants, lubricants, etc. The form of such pharmaceutical preparations can be selected according to the purpose of the therapy. Typical examples include
20 tablets, pills, powders, solutions, suspensions, emulsions, granules, capsules, suppositories, injections (solutions, suspensions, etc.) and the like.

To form tablets, any of various carriers conventionally known in this field can be used. Examples thereof include lactose,
25 white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and other excipients; water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethylcellulose, shellac, methylcellulose, potassium

phosphate, polyvinylpyrrolidone and other binders; dry starch, sodium alginate, agar powder, laminarin powder, sodium hydrogen carbonate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium lauryl sulfate, stearic acid monoglycerides, starch, lactose and other disintegrators; white sugar, stearin, cacao butter, hydrogenated oils and other disintegration inhibitors; quaternary ammonium bases, sodium lauryl sulfate and other absorption promoters; glycerol, starch and other wetting agents; starch, lactose, kaolin, bentonite, colloidal silicic acid and other adsorbents; purified talc, stearates, boric acid powder, polyethylene glycol and other lubricants; etc. Further, such tablets may be coated with typical coating materials as required, to prepare, for example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double- or multi-layered tablets, etc.

To form pills, any of various carriers conventionally known in this field can be used. Examples thereof include glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc and other excipients; gum arabic powder, tragacanth powder, gelatin, ethanol and other binders; laminarin, agar and other disintegrators; etc.

To form suppositories, any of various carriers conventionally known in this field can be used. Examples thereof include polyethylene glycol, cacao butter, higher alcohols, esters of higher alcohols, gelatin, semi synthetic glycerides, etc.

Capsules can be prepared by mixing the active principal compound with the above-mentioned carriers to enclose the former in a hard gelatin capsule, soft gelatin capsule or the like.

To form an injection, a solution, emulsion or suspension is sterilized and preferably made isotonic to blood. Any of the diluents widely used for such forms in this field can be employed to form the injection. Examples of such diluents include water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol,

fatty acid esters of polyoxyethylene sorbitan, etc.

In this case, the pharmaceutical preparation may contain sodium chloride, glucose or glycerol in an amount sufficient to prepare an isotonic solution, and may contain
5 typical solubilizers, buffers, analgesic agents, etc. Further, if necessary, the pharmaceutical preparation may contain coloring agents, preservatives, flavors, sweetening agents, etc., and/or other medicines.

The amount of the compound represented by the General
10 Formula (1) and the salt thereof included in the pharmaceutical preparation of the present invention is not limited, and can be suitably selected from a wide range. The proportion is generally about 0.1 to about 70 wt.%, preferably about 0.1 to about 30 wt.% of the pharmaceutical preparation.

15 The route of administration of the pharmaceutical preparation of the present invention is not particularly limited, and the preparation is administered by a route suitable to the form of the preparation, patient's age, sex and other conditions, and the status of the disease. For example, tablets, pills,
20 solutions, suspensions, emulsions, granules and capsules are administered orally. Injections are intravenously administered singly or as mixed with typical injection transfusions such as glucose solutions, amino acid solutions or the like, or singly administered intramuscularly, intracutaneously, subcutaneously or
25 intraperitoneally, as required. Suppositories are administered intrarectally.

The dosage of the pharmaceutical preparation of the invention is suitably selected according to the method of use, patient's age, sex and other conditions, and severity of the
30 disease. The amount of active principal compound is usually about 0.1 to about 10 mg/kg body weight/day. Further, it is desirable that the pharmaceutical preparation in each unit of the administration form contains the active principal compound in an amount of about 1 to about 200 mg.

35 The use of the compound of the present invention in

combination with L-dopa preparations, dopamine receptor agonists, dopamine metabolism enzyme inhibitors, dopamine release-rate-promoting preparations, central anticholinergic agents, and the like can achieve effects such as dosage reduction, improvement of
5 side effects, increased therapeutic efficacy, etc., which were not attained by known therapies.

EFFECT OF THE INVENTION

The compound of the present invention has protecting and improving mitochondrial functional activity and protecting
10 and repairing neuron activity, etc., and thus is effective in the treatment and prevention of neurodegenerative diseases, diseases relating to neurodegenerative disorder, and diseases relating to mitochondrial dysfunction.

Neurodegenerative diseases include Parkinson's disease,
15 Parkinson's syndrome, juvenile parkinsonism, striatonigral degeneration, progressive supranuclear palsy, pure akinesia, Alzheimer's disease, Pick's disease, prion disease, corticobasal degeneration, diffuse Lewy body disease, Huntington's disease, chorea-acanthocytosis, benign hereditary chorea, paroxysmal
20 choreoathetosis, essential tremor, essential myoclonus, Gilles de la Tourette's syndrome, Rett's syndrome, degenerative ballism, dystonia musculorum deformance, athetosis, spasmodic torticollis, Meige syndrome, cerebral palsy, Wilson's disease, Segawa's disease, Hallervorden-Spatz syndrome, neuroaxonal dystrophy,
25 pallidal atrophy, spino-cerebellar degeneration, cerebral cortical atrophy, Holmes-type cerebellar atrophy, olivopontocerebellar atrophy, hereditary olivopontocerebellar atrophy, Joseph disease, dentatorubropallidoluysian atrophy, Gerstmann-Straussler-Scheinker disease, Friedreich's Ataxia,
30 Roussy-Levy syndrome, May-White syndrome, congenital cerebellar ataxia, hereditary episodic ataxia, ataxia telangiectasia, amyotrophic lateral sclerosis, progressive bulbar palsy, spinal progressive muscular atrophy, spinobulbar muscular atrophy, Werdnig-Hoffmann disease, Kugelberg-Welander disease, hereditary
35 spastic paraparesis, syringomyelia, syringobulbia, Arnold-Chiari

malformation, Stiffman syndrome, Klippel-Feil syndrome, Fazio-Londe syndrome, lower myelopathy, Dandy-Walker syndrome, spina bifida, Sjogren-Larsson syndrome, radiation myelopathy, age-related macular degeneration and cerebral apoplexy (e.g.,
5 cerebral infarction, cerebral hemorrhage, etc.).

Diseases induced by neurological dysfunction include spinal cord injury, chemotherapy-induced neuropathy, diabetic neuropathy, radiation damage and demyelinating diseases (e.g., multiple sclerosis, acute disseminated encephalomyelitis,
10 transverse myelitis, progressive multifocal leucoencephalopathy, subacute sclerosing panencephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barre syndrome, etc.)

Diseases induced by deterioration of mitochondrion function include Pearson's syndrome, diabetes, deafness,
15 malignant migraine, Leber's disease, MELAS, MERRF, MERRF/MELAS overlap syndrome, NARP, pure myopathy, mitochondrial cardiomyopathy, myopathy, dementia, gastrointestinal ataxia, acquired sideroblastic anemia, aminoglycoside-induced hearing loss, complex III deficiency due to inherited variants of
20 cytochrome b, multiple symmetrical lipomatosis, ataxia, myoclonus, retinopathy, MNGIE, ANTI1 disease, Twinkle disease, POLG disease, recurrent myoglobinuria, SANDO, ARCO, complex I deficiency, complex II deficiency, optic nerve atrophy, fatal infantile complex IV deficiency, mitochondrial DNA deficiency,
25 mitochondrial DNA deficiency syndrome, Leigh's encephalomyelopathy, chronic-progressive-external-ophthalmoplegia syndrome (CPEO), Kearns-Sayre syndrome, encephalopathy, lactacidemia, myoglobinuria, drug-induced mitochondrial diseases, schizophrenia, major depression disorder, bipolar I disorder,
30 bipolar II disorder, mixed episode, dysthymic disorders, atypical depression, seasonal affective disorders, postpartum depression, minor depression, recurrent brief depressive disorder, intractable depression/chronic depression, double depression, acute renal failure.

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the present invention is described in more detail with reference to Reference Examples, Examples and Pharmacological Test Examples.

5 Reference Example 1

N-Cyclohexyl-4-fluoro-2-nitro-N-methylaniline

Potassium carbonate (6.0 g, 43.5 mmol) and N-methylcyclohexylamine (4.6 g, 40.6 mmol) were added to a N-methylpyrrolidone (NMP) solution (20 ml) of 2,5-
10 difluoronitrobenzene (5.0 g, 31.4 mmol), and stirred at 100°C for 3 hours. The reaction mixture was cooled to room temperature, water was added, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, and then dried over anhydrous magnesium sulfate. The resulting dry product
15 was concentrated under reduced pressure to thereby obtain 7.0 g of oily yellow N-cyclohexyl-4-fluoro-2-nitro-N-methylaniline (yield: 89%).

¹H-NMR (CDCl₃) δppm:

1.12-1.80 (10H, m), 2.67 (3H, s), 3.00-3.09 (1H, m), 7.07-7.20
20 (2H, m), 7.42-7.47(1H, m)

The compounds of the following Reference Examples 2 to 5 were prepared in the same manner as in the above Reference Example 1, using corresponding starting materials.

25

Reference Example 2

4-Fluoro-N-(2-methoxyethyl)-N-methyl-2-nitroaniline

¹H-NMR (CDCl₃) δppm:

2.85 (3H, s), 3.25-3.31 (5H, m), 3.52 (2H, t, J=5.6 Hz), 7.16-
30 7.20 (2H, m), 7.43-7.47 (1H, m)

Reference Example 3

4-Fluoro-N-isobutyl-N-methyl-2-nitroaniline

¹H-NMR (CDCl₃) δppm:

35 0.89 (3H, s), 0.91 (3H, s), 1.89-1.98 (1H, m), 2.81(3H,

s), 2.92 (2H, d, J=7.5 Hz), 7.15-7.20 (2H, m), 7.42-7.46 (1H, m)

Reference Example 4

4-Fluoro-N-isopropyl-N-methyl-2-nitroaniline

5 ¹H-NMR (CDCl₃) δppm:

1.16 (3H, s), 1.19 (3H, s), 2.67 (3H, s), 3.50-3.61 (1H, m), 7.15-7.20 (2H, m), 7.43-7.46 (1H, m)

Reference Example 5

10 4-Fluoro-N-methyl-2-nitro-N-propylaniline

¹H-NMR (CDCl₃) δppm:

0.84 (3H, t, J=7.5 Hz), 1.51-1.66 (2H, m), 2.77 (3H, s), 3.00 (2H, t, J=7.5 Hz), 7.05-7.20 (2H, m), 7.44 (1H, dd, J=2.75 Hz, J= 8.0 Hz)

15

Reference Example 6

4-Fluoro-2-nitro-1-propylsulfanylbenzene

Potassium carbonate (5.0 g, 36.2 mmol) and 1-propanethiol (2.7 g, 35.5 mmol) were added to a N-methylpyrrolidone (NMP) solution (15 ml) of 2,5-difluoronitrobenzene (5.0 g, 31.4 mmol), and the mixture obtained was stirred at 90°C for 2 hours. After the reaction mixture was cooled to room temperature, water (50ml) was added, and the reaction product was extracted with ethyl acetate (100ml). The organic layer was washed with water, and then dried over anhydrous magnesium sulfate. The resulting dry product was concentrated under reduced pressure to thereby obtain 6.7 g of powdery yellow 4-fluoro-2-nitro-1-propylsulfanylbenzene (yield: 99%).

25 30 ¹H-NMR (CDCl₃) δppm:

1.06 (3H, t, J=7.5 Hz), 1.68-1.83 (2H, m), 2.89 (2H, t, 7.5 Hz), 7.27-7.42 (2H, m), 7.89 (2H, dd, J=2.75 Hz, J=8.5 Hz)

Reference Example 7

35 1-tert-Butoxy-4-fluoro-2-nitrobenzene

A tetrahydrofuran (THF) solution (20 ml) of potassium tert-butoxide (3.55 g, 31.6 mmol) was cooled in an methanol-ice bath, and 4.2 g of 2,5-difluoronitrobenzene (26.4 mmol) was further added. The mixture was heated to room temperature, stirred for 96 hours, and further stirred at 60°C for 1 hour. Water (2 ml) and 2N-hydrochloric acid (2 ml) were added to the reaction mixture while cooling with an ice water bath, and subsequently water was added. The resulting mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was then purified using silica gel column chromatography (n-hexane : ethyl acetate = 19 : 1). The purified product was concentrated under reduced pressure to thereby obtain 4.5 g of oily orange 1-tert-butoxy-4-fluoro-2-nitrobenzene (yield: 80%).

¹H-NMR (CDCl₃) δppm:

1.38 (9H, s), 7.18-7.20 (2H, m), 7.47 (1H, d, J=7.1 Hz)

Reference Example 8

4-Fluoro-2-nitro-1-propoxybenzene

A N,N-dimethylformamide (DMF) solution (3 ml) of potassium carbonate (3.48 g, 25.2 mmol) and 1-iodopropane (3.95 g, 23.2 mmol) was added to a DMF solution (7 ml) of 4-fluoro-2-nitrophenol (3.3 g, 21.0 mmol). The mixture was stirred at room temperature for 48 hours. Water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated sodium chloride solution twice, and concentrated under reduced pressure. The residue was purified using silica gel column chromatography (n-hexane : ethyl acetate = 9 : 1). The purified product was concentrated under reduced pressure to thereby obtain 4.03 g of oily yellow 4-fluoro-2-nitro-1-propoxybenzene (yield: 96%).

¹H-NMR (CDCl₃) δppm:

1.06 (3H, t, J=7.4Hz), 1.78-1.92 (2H, m), 4.04 (2H, t, J=6.4Hz), 7.04 (1H, dd, J=4.3 Hz, J=9.2Hz), 7.21-7.29 (1H, m), 7.58 (1H, dd, J=3.1 Hz, J=7.8Hz)

The compounds of the following Reference Examples 9 to 16 were prepared in the same manner as the above Reference Examples 7 to 8, using corresponding starting materials.

5

Reference Example 9

4-Fluoro-1-isopropoxy-2-nitrobenzene

¹H-NMR (CDCl₃) δppm:

1.36 (3H, s), 4.54-4.63 (1H, m), 7.02-7.05 (1H, m),
10 7.18-7.26 (1H, m), 7.49 (1H, dd, J=3.0 Hz, J=7.5 Hz)

Reference Example 10

1-Ethoxy-4-fluoro-2-nitrobenzene

¹H-NMR (CDCl₃) δppm:

15 1.44 (3H, t, J=7.0 Hz), 4.08 (2H, q, J=7.0 Hz), 7.02
(1H, dd, J=4.25 Hz, J=9.25 Hz), 7.22-7.30 (1H, m), 7.56 (1H, dd,
J=3.25 Hz, J=7.75 Hz)

Reference Example 11

20 1-Cyclopropylmethoxy-4-fluoro-2-nitrobenzene

¹H-NMR (CDCl₃) δppm:

0.36-0.41 (2H, m), 0.61-0.69 (2H, m), 1.22-1.28 (1H, m),
3.95 (2H, d, J=6.8 Hz), 7.04 (1H, dd, J=4.4 Hz, J=9.2 Hz), 7.20-
7.27 (1H, m), 7.57 (1H, dd, J=3.1 Hz, J=7.8 Hz)

25

Reference Example 12

4-Fluoro-2-nitro-1-(4,4,4-trifluorobutoxy)benzene

¹H-NMR (CDCl₃) δppm:

2.04-2.16 (2H, m), 2.31-2.44 (2H, m), 4.14 (2H, t,
30 J=5.9 Hz), 7.04 (1H, dd, J=4.3 Hz, J=9.2 Hz), 7.24-7.32 (1H, m),
7.61 (1H, dd, J=3.2 Hz, J=7.8 Hz)

Reference Example 13

4-Fluoro-1-(2-methoxyethoxy)-2-nitrobenzene

35 ¹H-NMR (CDCl₃) δppm:

3.45 (3H, s), 3.78 (2H, t, J=4.8 Hz), 4.24 (2H, t, J=4.8 Hz), 7.12 (1H, dd, J=4.4 Hz, J= 9.2 Hz), 7.23-7.30 (1H, m), 7.59 (1H, dd, J=3.1 Hz, J= 7.8 Hz)

5 Reference Example 14

1-Cyclopentyloxy-4-fluoro-2-nitrobenzene

¹H-NMR (CDCl₃) δppm:

1.62-1.66 (2H, m), 1.83-1.94 (6H, m), 4.82-4.86 (1H, m),
7.04 (1H, dd, J=4.4 Hz, J=9.3 Hz), 7.19-7.27 (1H, m), 7.54 (1H,
10 dd, J=3.2 Hz, J=7.8 Hz)

Reference Example 15

1-Cyclobutylmethoxy-4-fluoro-2-nitrobenzene

¹H-NMR (CDCl₃) δppm:

1.90-2.02 (4H, m), 2.08-2.15 (2H, m), 2.77-2.81 (1H, m),
4.03 (2H, d, J=6.2 Hz), 7.04 (1H, dd, J=4.3 Hz, J=9.2 Hz), 7.21-
7.28 (1H, m), 7.58 (1H, dd, J=3.1 Hz, J=7.8 Hz)

Reference Example 16

20 2-(4-Fluoro-2-nitrophenoxy)methyl)tetrahydrofuran

¹H-NMR (CDCl₃) δppm:

1.88-2.12 (4H, m), 3.80-3.94 (2H, m), 4.11 (2H, d, J=4.0 Hz), 4.27-4.32 (1H, m), 7.10 (1H, dd, J=4.4 Hz, J=9.3 Hz), 7.22-7.30 (1H, m), 7.59 (1H, dd, J=3.1 Hz, J=7.8 Hz)

25

Reference Example 17

2-[3-(4-Fluoro-2-nitrophenoxy)propyl]isoindole-1,3-dione

Potassium carbonate (10.8 g, 78.1 mmol) and N-(3-bromopropyl)phthalimide (12.1 g, 45.1 mmol) were added to a N, N-dimethylformamide (DMF) solution (80 ml) of 4-fluoro-2-nitrophenol (6.0 g, 38.2 mmol), and the mixture was stirred at 60°C for 4 hours. After the reaction mixture was cooled to room temperature, water (200 ml) was added, and the reaction mixture was then cooled with ice. The precipitated insoluble matter was
35 collected by filtration. After being washed with water (50 ml ×

3), the substance remaining in the filter was air-dried, giving 13.2 g of powdery pale yellow 2-[3-(4-fluoro-2-nitrophenoxy)propyl]isoindole-1,3-dione (yield: 100%).

¹H-NMR (CDCl₃) δppm:

5 2.18-2.28 (2H, m), 3.93 (2H, t, J=6.5 Hz), 4.15 (2H, t, J=6.0 Hz), 7.04 (1H, dd, J=4.3 Hz, J=9.2 Hz), 7.23-7.28 (1H, m), 7.58 (1H, dd, J=3.1 Hz, J=7.8 Hz), 7.69-7.74 (2H, m), 7.81-7.85 (2H, m)

10 Reference Example 18

3-(4-Fluoro-2-nitrophenoxy)propylamine

6.5 g of 2-[3-(4-fluoro-2-nitrophenoxy)propyl]isoindole-1,3-dione was suspended in ethanol (140 ml), and hydrazine hydrate (3.0 ml) was added to the resulting suspension. The mixture was stirred for 3.5 hours while heating under reflux. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. 13 ml of 5N sodium hydroxide aqueous solution was added to the residue, and the resulting mixture was extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The resulting dry product was concentrated under reduced pressure to thereby obtain 4.03 g of oily red orange 3-(4-fluoro-2-nitrophenoxy)propylamine (yield: 100%).

25 ¹H-NMR (CDCl₃) δppm:

1.92-2.02 (2H, m), 2.94 (2H, t, J=6.5 Hz), 4.19 (2H, t, J=5.9 Hz), 7.07 (1H, dd, J=4.3 Hz, J= 9.2 Hz), 7.22-7.30 (1H, m), 7.59 (1H, dd, J=3.1 Hz, J= 7.8 Hz)

30 Reference Example 19

N-[3-(4-Fluoro-2-nitrophenoxy)propyl]acetamide

Pyridine (1.5 ml, 18.6 mmol) and acetic anhydride (0.97 g, 10.3 mmol) were added to a dichloromethane solution of 3-(4-fluoro-2-nitrophenoxy)propylamine (2.0 g, 9.33 mmol), while being cooled with ice, and then dichloromethane (4 ml) was further

added. The resulting mixture was stirred at room temperature for 15 hours. 2N-hydrochloric acid (9.5 ml) was added to the reaction mixture, and the mixture was stirred. Water was added to the mixture, and the resulting mixture was extracted with
5 dichloromethane. After being washed with a saturated sodium chloride aqueous solution, the organic layer was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (dichloromethane : methanol = 30 : 1 → 20 : 1). The purified product was concentrated under reduced
10 pressure to thereby obtain 2.13 g of oily yellow N-[3-(4-fluoro-2-nitrophenoxy)propyl]acetamide (yield: 89%).

¹H-NMR (CDCl₃) δppm:

2.04 (3H, s), 2.03-2.12 (2H, m), 3.48-3.55 (2H, m),
4.20 (2H, t, J=5.5 Hz), 6.56 (1H, brs), 7.08 (1H, dd, J=4.3 Hz,
15 J=9.3 Hz), 7.26-7.36 (1H, m), 7.70 (1H, dd, J=3.2 Hz, J=7.8 Hz)

Reference Example 20

N-[3-(4-Fluoro-2-nitrophenoxy)propyl]methanesulfonamide

Pyridine (1.5 ml, 18.6 mmol) and methanesulfonyl
20 chloride (0.8 ml, 10.3 mmol) were added, while being cooled with ice, to a dichloromethane solution of 3-(4-fluoro-2-nitrophenoxy)propylamine (2.0 g, 9.33 mmol), and dichloromethane (4 ml) was further added. The resulting mixture was stirred at room temperature for 24 hours, and methanesulfonyl chloride (0.12
25 ml, 1.5 mmol) was further added thereto, and then the mixture was stirred at room temperature for 15 hours. 2N hydrochloric acid (9.5 ml) was added to the reaction mixture, and the mixture was stirred. Water was added to the mixture, and the resulting mixture was extracted with dichloromethane. After being washed
30 with a saturated sodium chloride aqueous solution, the organic layer was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (n-hexane : ethyl acetate = 4 : 1 → 1 : 1). The purified product was concentrated under reduced pressure to thereby obtain 1.2 g of
35 oily yellow orange N-[3-(4-fluoro-2-

nitrophenoxy)propyl]methansulfonamide (yield: 44%).

¹H-NMR (CDCl₃) δppm:

2.09-2.18 (2H, m), 3.00 (3H, s), 3.39-3.46 (2H, m), 4.23 (2H, t, J=5.6 Hz), 5.00 (1H, brs), 7.09 (1H, dd, J=4.3 Hz, J=9.2 Hz),
5 7.26-7.35 (1H, m), 7.66 (1H, dd, J=3.1 Hz, J=7.8 Hz)

Reference Example 21

Phenyl [3-(4-Fluoro-2-nitrophenoxy)propyl]carbamate

Triethylamine (2.90 ml, 21.4 mmol) and phenyl
10 chlorocarbonate (2.52 ml, 20.0 mmol) were added to a dioxane
solution (43 ml) of 3-(4-fluoro-2-nitrophenoxy)propylamine (4.03
g, 18.8 mmol), while being cooled with ice, and the mixture was
stirred at room temperature for 0.5 hours. The reaction mixture
was concentrated under reduced pressure, and the residue was then
15 purified by silica gel column chromatography (dichloromethane :
ethyl acetate = 30 : 1). The purified product was concentrated to
dryness under reduced pressure to thereby obtain 5.92 g of
powdery yellow phenyl [3-(4-fluoro-2-
nitrophenoxy)propyl]carbamate (yield: 94%).

20 ¹H-NMR (CDCl₃) δppm:

2.09-2.18 (2H, m), 3.48-3.56 (2H, m), 4.21 (2H, t, J=5.7 Hz), 5.69 (1H, brs), 7.05-7.20 (4H, m), 7.26-7.37 (3H, m),
7.65 (1H, dd, J=3.1 Hz, J=7.8 Hz)

25 Reference Example 22

3-[3-(4-Fluoro-2-nitrophenoxy)propyl]-1,1-dimethyl urea

A 50% dimethylamine aqueous solution (2.5 ml) was added
to a DMF solution (25 ml) of phenyl [3-(4-fluoro-2-
nitrophenoxy)propyl]carbamate (5.89 g, 17.6 mmol), and the
30 mixture was stirred at room temperature for 24 hours. Water was
added to the reaction mixture, and the resulting mixture was
extracted with ethyl acetate. The organic layer was washed with a
saturated sodium chloride aqueous solution twice, and
concentrated under reduced pressure. The residue was then
35 purified by silica gel column chromatography (dichloromethane :

ethyl acetate = 19 : 1 → 4 : 1 → 2 : 1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 4.10 g of oily pale yellow 3-[3-(4-fluoro-2-nitrophenoxy)propyl]-1, 1-dimethyl urea (yield: 82%).

5 ¹H-NMR (CDCl₃) δppm:

2.03-2.12 (2H, m), 2.89 (6H, s), 3.42-3.49 (2H, m), 4.17 (2H, t, J=5.8 Hz), 4.85 (1H, brs), 7.09 (1H, dd, J=4.3 Hz, J=9.3 Hz), 7.24-7.32 (1H, m), 7.61 (1H, dd, J=3.2 Hz, J=7.8 Hz)

10 Reference Example 23

1-[3-(4-Fluoro-2-nitrophenoxy)propyl]-1,3,3-trimethylurea

Sodium hydride (55% in oil) (396 mg, 9.1 mmol) was added, while being cooled with ice, to a DMF solution (9 ml) of 2.0 g of 3-[3-(4-fluoro-2-nitrophenoxy)propyl]-1,1-dimethyl urea (7.0
15 mmol) and the mixture was stirred at room temperature for 5 minutes. Methyl iodide (0.735 ml, 11.8 mmol) was added to the mixture and the resulting mixture was stirred at room temperature for 48 hours. Water was added to the reaction mixture and extraction with ethyl acetate was performed. After being washed
20 with a saturated sodium chloride aqueous solution, the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane : ethyl acetate = 9 : 1 → 6 : 1). The purified product was concentrated under reduced pressure to thereby obtain 0.83 g of
25 oily pale yellow 1-[3-(4-fluoro-2-nitrophenoxy)propyl]-1,3,3-trimethylurea (yield: 40%).

¹H-NMR (CDCl₃) δppm:

2.04-2.14 (2H, m), 2.76 (6H, s), 2.83 (3H, s), 3.38 (2H, t, J=6.9 Hz), 4.09 (2H, t, J=5.9 Hz), 7.04 (1H, dd, J=4.3 Hz, J=9.3 Hz), 7.22-7.30 (1H, m), 7.60 (1H, dd, J=3.1 Hz, J=7.7 Hz)
30

Reference Example 24

5-Fluoro-2-propoxyaniline

4-Fluoro-2-nitro-1-propoxybenzene (2.0 g, 10.0 mmol) and
35 5% palladium carbon (750 mg) were added to ethanol (30 ml).

Catalytic reduction was conducted at room temperature and atmospheric pressure (normal pressure). The catalyst was removed by celite filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane, and dried over anhydrous magnesium sulfate. The resulting dry product was concentrated under reduced pressure to thereby obtain 1.45g of oily red orange 5-fluoro-2-propoxyaniline (yield: 86%).

¹H-NMR (CDCl₃) δppm:

1.04 (3H, t, J=7.4 Hz), 1.74-1.88 (2H, m), 3.89 (2H, brs), 3.90 (2H, t, J=6.5 Hz), 6.31-6.46 (2H, m), 6.66 (1H, dd, J=5.1 Hz, J=8.7 Hz)

The compounds of the following Reference Examples 25 to 42 were prepared in the same manner as the above Reference Example 24, using corresponding starting materials.

Reference Example 25

5-Fluoro-2-isopropoxyaniline

¹H-NMR (CDCl₃) δppm:

1.32 (3H, s), 1.35 (3H, s), 3.88 (2H, brs), 4.38-4.48 (1H, m), 6.31-6.46 (2H, m), 6.68-6.73 (1H, m)

Reference Example 26

2-Ethoxy-5-fluoroaniline

¹H-NMR (CDCl₃) δppm:

1.39 (3H, t, J=7.0 Hz), 3.90 (2H, brs), 3.97 (2H, q, J=7.0 Hz), 6.31-6.46 (2H, m), 6.63-6.68 (1H, m)

Reference Example 27

5-Fluoro-2-morpholin-4-ylaniline

¹H-NMR (CDCl₃) δppm:

2.83 (4H, t, J=4.6 Hz), 3.81 (4H, t, J=4.6 Hz), 4.13 (2H, brs), 6.38-6.45 (2H, m), 6.93-6.97 (1H, m)

Reference Example 28

5-Fluoro-2-pyrrolidin-1-ylaniline

¹H-NMR (CDCl₃) δppm:

1.88-1.94 (4H, m), 2.94-3.00 (4H, m), 4.03 (2H, brs),
6.35-6.46 (2H, m), 6.90-6.95 (1H, m)

5

Reference Example 29

2-Cyclopropylmethoxy-5-fluoroaniline

¹H-NMR (CDCl₃) δppm:

0.29-0.35 (2H, m), 0.58-0.65 (2H, m), 1.22-1.29 (1H, m),
10 3.77 (2H, d, J=6.9 Hz), 3.94 (2H, brs), 6.29-6.46 (2H, m), 6.64
(1H, dd, J=5.1 Hz, J=8.8 Hz)

Reference Example 30

N¹-Cyclohexyl-4-fluoro-N¹-methylbenzene-1, 2-diamine

15 ¹H-NMR (CDCl₃) δppm:

1.11-1.31 (4H, m), 1.55-1.82 (6H, m), 2.57-2.68 (4H, m), 4.18 (2H,
brs), 6.33-6.44 (2H, m), 6.92-6.98 (1H, m)

Reference Example 31

20 4-Fluoro-N¹-(2-methoxyethyl)-N¹-methylbenzene-1, 2-diamine

¹H-NMR (CDCl₃) δppm:

2.70 (3H, s), 2.96 (2H, t, J=5.4 Hz), 3.39 (3H, s), 3.45 (2H, t,
J=5.4 Hz), 4.38 (2H, brs), 6.33-6.43 (2H, m), 6.93-6.99 (1H, m)

25 Reference Example 32

4-Fluoro-N¹-isobutyl-N¹-methylbenzene-1, 2-diamine

¹H-NMR (CDCl₃) δppm:

0.92 (3H, s), 0.94 (3H, s), 1.62-1.83 (1H, m), 2.54-2.60 (5H, m),
6.30-6.49 (2H, m), 6.82-6.93 (1H, m)

30

Reference Example 33

4-Fluoro-N¹-isopropyl-N¹-methylbenzene-1, 2-diamine

¹H-NMR (CDCl₃) δppm:

1.05 (3H, s), 1.07 (3H, s), 2.55 (3H, s), 3.06-3.17 (1H, m), 4.16
35 (2H, brs), 6.34-6.45 (2H, m), 6.91-6.97 (1H, m)

Reference Example 34

4-Fluoro-N¹-methyl-N¹-propylbenzene-1, 2-diamine

¹H-NMR (CDCl₃) δppm: 0.86 (3H, t, J=7.4 Hz), 1.41-1.56 (2H, m),
5 2.57 (3H, s), 2.72 (2H, t, J=7.25 Hz), 4.18 (2H, brs), 6.35-6.44
(2H, m), 6.91-6.97 (1H, m)

Reference Example 35

N-[3-(2-Amino-4-fluorophenoxy)propyl]acetamide

10 ¹H-NMR (CDCl₃) δppm:
1.95-2.05 (2H, m), 1.97 (3H, s), 3.42-3.50 (2H, m), 3.92 (2H,
brs), 4.02 (2H, t, J=5.9 Hz), 5.83 (1H, brs), 6.32-6.47 (2H, m),
6.68 (1H, dd, J=5.0 Hz, J=8.8 Hz)

15 Reference Example 36

N-[3-(2-Amino-4-fluorophenoxy)propyl]methanesulfonamide

¹H-NMR (CDCl₃) δppm:
2.02-2.11 (2H, m), 2.94 (3H, s), 3.33-3.40 (2H, m), 3.91 (2H,
brs), 4.07 (2H, t, J=5.7 Hz), 4.76 (1H, brs), 6.32-6.46 (2H, m),
20 6.68 (1H, dd, J=5.0 Hz, J=8.8 Hz)

Reference Example 37

5-Fluoro-2-(4,4,4-trifluorobutoxy)aniline

¹H-NMR (CDCl₃) δppm:
25 2.01-2.12 (2H, m), 2.22-2.41 (2H, m), 3.87 (2H, brs),
4.01 (2H, t, J=6.0 Hz), 6.32-6.47 (2H, m), 6.65 (1H, dd, J=5.0 Hz,
J=8.8 Hz)

Reference Example 38

30 1-[3-(2-Amino-4-fluorophenoxy)propyl]-1,3,3-trimethylurea

¹H-NMR (CDCl₃) δppm:
1.99-2.10 (2H, m), 2.78 (6H, s), 2.84 (3H, s), 3.37 (2H, t, J=6.9
Hz), 3.94 (2H, brs), 3.97 (2H, t, J=6.1 Hz), 6.30-6.45 (2H, m),
6.65 (1H, dd, J=5.1 Hz, J=8.8 Hz)

Reference Example 39

5-Fluoro-2-(2-methoxyethoxy)aniline

¹H-NMR (CDCl₃) δppm:

3.43 (3H, s), 3.70-3.73 (2H, m), 3.99 (2H, brs), 4.07-4.10 (2H, m), 6.30-6.45 (2H, m), 6.72 (1H, dd, J=5.1 Hz, J=8.7 Hz)

Reference Example 40

2-Cyclopentyloxy-5-fluoroaniline

¹H-NMR (CDCl₃) δppm:

1.56-1.66 (2H, m), 1.75-1.87 (6H, m), 3.85 (2H, brs), 4.69-4.72 (1H, m), 6.30-6.45 (2H, m), 6.66 (1H, dd, J=5.1 Hz, J=8.8 Hz)

Reference Example 41

2-Cyclobutylmethoxy-5-fluoroaniline

¹H-NMR (CDCl₃) δppm:

1.86-1.96 (4H, m), 2.08-2.16 (2H, m), 2.74-2.80 (1H, m), 3.90 (2H, brs), 3.91 (2H, d, J=6.7 Hz), 6.31-6.45 (2H, m), 6.66 (1H, dd, J=5.1 Hz, J=8.8 Hz)

Reference Example 42

2-tert-Butoxy-5-fluoroaniline

¹H-NMR (CDCl₃) δppm:

1.37 (9H, s), 3.87 (2H, brs), 6.27-6.45 (2H, m), 6.85 (1H, dd, J=5.6 Hz, J=8.8 Hz)

Reference Example 43

5-Fluoro-2-propylsulfanylaniline

4-Fluoro-2-nitro-1-propylsulfanylbenzene (6.7 g, 31.1 mmol) was dissolved in a mixed solvent of ethanol (40 ml) and water (4 ml). Ammonium chloride (17 g, 0.32 mol) was added to the resulting mixture, and zinc powder (20 g, 0.31 mol) were added little by little. The resulting mixture was then stirred at room temperature for 1 hour. Insoluble matter was removed by filtration, and the filtrate was concentrated under reduced pressure to thereby obtain 5.8 g of oily brown 5-fluoro-2-

propylsulfanylaniline (yield: 93%).

¹H-NMR (CDCl₃) δppm:

0.96 (3H, t, J=7.3 Hz), 1.49-1.64 (2H, m), 2.62 (2H, t, J=7.4 Hz),
4.51 (2H, brs), 6.35-6.47 (2H, m), 7.32-7.38 (1H, m)

5

Reference Example 44

4,5-Difluoro-2-propoxyaniline

A toluene solution (20 ml) of benzophenone imine
(2.38 g, 13.1 mmol), tris(dibenzylidene acetone)dipalladium (275
10 mg, 0.3 mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene
(XANTPHOS) (347 mg, 0.6 mmol) and cesium carbonate(5.83 g, 17.9
mmol) were added to a toluene solution (60 ml) of 1-bromo-4,5-
difluoro-2-propoxybenzene (3.0 g, 11.9 mmol). The mixture was
stirred under a nitrogen atmosphere at 100°C for 23 hours. After
15 the reaction mixture was cooled to room temperature, water and a
saturated ammonium chloride aqueous solution were added. The
resulting mixture was extracted with ethyl acetate. The organic
layer was dried over anhydrous magnesium sulfate, and then
concentrated under reduced pressure. The residue was dissolved
20 with diethyl ether (60 ml), and concentrated hydrochloric acid
(10 ml) was added to the resulting solution, which was then
stirred for 2 hours. A 5N sodium hydroxide aqueous solution (24
ml) was added to the reaction mixture to get a pH =11, and
concentrated under reduced pressure. The residue was dissolved in
25 dichloromethane and washed with a saturated sodium chloride
aqueous solution. The organic layer was concentrated under
reduced pressure. The residue was then purified by silica gel
column chromatography (n-hexane : ethyl acetate = 9 : 1). The
purified product was concentrated under reduced pressure to
30 thereby obtain 850 mg of oily dark brown 4,5-difluoro-2-
propoxyaniline (yield: 38%).

¹H-NMR (CDCl₃) δppm:

1.04 (3H, t, J=7.4 Hz), 1.75-1.86 (2H, m), 3.71 (2H, brs), 3.88
(2H, t, J=6.5 Hz), 6.51 (1H, dd, J=8.0 Hz, 11.5 Hz), 6.60 (1H, dd,
35 J=7.3 Hz, J=11.8 Hz)

Reference Example 45

1-(2-Amino-4-fluorobenzoyl)pyrrolidine

A DMF solution (4 ml) of pyrrolidine (1.93 g, 27.1
5 mmol), a DMF solution (4 ml) of triethylamine (3.79 g, 37.5 mmol),
1-hydroxybenzotriazole (HOBt) (3.11 g, 23.0 mmol), and 1-(3-
dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC)
(3.91 g, 20.4 mmol) were added to a DMF solution (4 ml) of 4-
fluoroanthranilic acid (2.0 g, 12.8 mmol) in that order. The
10 mixture was stirred at room temperature for 14 hours. Water was
added to the reaction mixture and the resulting mixture was
extracted with ethyl acetate. The organic layer was washed with a
saturated sodium chloride aqueous solution, and then concentrated
under reduced pressure. The residue was then purified by silica
15 gel column chromatography (dichloromethane : methanol = 30 : 1).
The purified product was concentrated under reduced pressure to
thereby obtain 1.65 g of oily orange 1-(2-amino-4-
fluorobenzoyl)pyrrolidine (yield: 62%).

¹H-NMR (CDCl₃) δppm:

20 1.75-2.00 (4H, m), 3.40-3.75 (4H, m), 4.85 (2H, brs), 6.33-6.40
(2H, m), 7.14-7.21 (1H, m)

Reference Example 46

Ethyl α-(hydroxymethylene)-4-methoxyphenyl acetate

25 Sodium hydride (60% in oil) (467 mg, 11.7 mmol) was
added to a benzene solution (10 ml) of ethyl 4-methoxyphenyl
acetate (2.0 g, 10.3 mmol), while being cooled with ice. The
mixture was stirred at room temperature for 5 minutes. The
stirred mixture was cooled with ice again; ethyl formate (1.02 ml,
30 12.6 mmol) was added thereto, and stirred at room temperature for
3 hours. While being cooled with ice, water and ethyl acetate
were added to the reaction mixture, and then 2N hydrochloric acid
(6 ml) was added to separate the reaction mixture into two layers.
The organic layer was concentrated under reduced pressure, and
35 the residue was then purified by silica gel column chromatography

(n-hexane : ethyl acetate = 4 : 1). The purified product was concentrated under reduced pressure to thereby obtain 1.97 g of oily slightly reddish-brown ethyl α -(hydroxymethylene)-4-methoxyphenyl acetate (yield: 86%). The resultant compound
5 undergoes nitrogen substitution, and was stored in a freezer.

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.28 (3H, t, $J=7.1$ Hz), 3.81 (3H, s), 4.28 (2H, q, $J=7.1$ Hz), 6.87 (2H, d, $J=8.8$ Hz), 7.16-7.26 (3H, m), 12.02 (1H, d, $J=12.5$ Hz)

10

The compounds of the following Reference Examples 47 to 57 were prepared in the same manner as the above Reference Example 46, using corresponding starting materials.

15 Reference Example 47

Ethyl 2,4-dimethoxy- α -(hydroxymethylene)phenyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.21 (3H, t, $J=7.1$ Hz), 3.76 (3H, s), 3.81 (3H, s), 4.22 (2H, q, $J=7.1$ Hz), 6.43-6.49 (2H, m), 7.00 (1H, d, $J=8.9$ Hz),
20 7.12 (1H, d, $J=12.6$ Hz), 11.89 (1H, d, $J=12.6$ Hz)

Reference Example 48

Ethyl 2,4-dichloro- α -(hydroxymethylene)phenyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

25 1.15 (3H, t, $J=7.2$ Hz), 4.22 (2H, q, $J=7.2$ Hz), 7.11-7.26 (3H, m), 7.40-7.43 (1H, m), 12.00 (1H, d, $J=12.2$ Hz)

Reference Example 49

Ethyl α -(hydroxymethylene)-2-methoxyphenyl acetate

30 $^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.19 (3H, t, $J=7.1$ Hz), 3.79 (3H, s), 4.21 (2H, q, $J=7.1$ Hz), 6.86-7.68 (5H, m), 11.91 (1H, d, $J=12.3$ Hz)

Reference Example 50

35 Ethyl α -(hydroxymethylene)-2-isopropoxy-4-methoxyphenyl acetate

¹H-NMR (CDCl₃) δppm:

1.20-1.31 (9H, m), 3.80 (3H, s), 4.17 (2H, q, J=7.1 Hz), 4.43-4.47 (1H, m), 6.42-6.46 (2H, m), 6.90-7.12 (2H, m), 11.85 (1H, d, J=12.6 Hz)

5

Reference Example 51

Ethyl α-(hydroxymethylene)-4-methoxy-2-methylphenyl acetate

¹H-NMR (CDCl₃) δppm:

1.20 (3H, t, J=7.2 Hz), 2.19 (3H, s), 3.80 (3H, s), 4.22 (2H, q, J=7.2 Hz), 6.54-6.75 (2H, m), 7.02-7.26 (2H, m), 11.94 (1H, d, J=12.7 Hz)

10

Reference Example 52

Ethyl 2-fluoro-α-(hydroxymethylene)-4-methoxyphenyl acetate

15 ¹H-NMR (CDCl₃) δppm:

1.22 (3H, t, J=7.1 Hz), 3.80 (3H, s), 4.21 (2H, q, J=7.1 Hz), 6.61-6.69 (2H, m), 7.03-7.26 (2H, m), 12.05 (1H, d, J=12.3 Hz)

15

Reference Example 53

20 Ethyl 4-ethoxy-α-(hydroxymethylene)-2-methoxyphenyl acetate

¹H-NMR (CDCl₃) δppm:

1.19-1.45 (6H, m), 3.75 (3H, s), 4.00-4.26 (4H, m), 6.42-6.48 (2H, m), 6.97-7.26 (2H, m), 11.86 (1H, d, J=12.3 Hz)

20

25 Reference Example 54

Ethyl α-(hydroxymethylene)-4-isopropoxy-2-methoxyphenyl acetate

¹H-NMR (CDCl₃) δppm:

1.20-1.31 (9H, m), 3.75 (3H, s), 4.16 (2H, q, J=7.2 Hz), 4.43-4.47 (1H, m), 6.43-6.48 (2H, m), 6.99-7.22 (2H, m), 11.87 (1H, d, J=12.3 Hz)

30

Reference Example 55

Ethyl 4-cyclopropylmethoxy-α-(hydroxymethylene)phenyl acetate

¹H-NMR (CDCl₃) δppm:

35 0.35-0.37 (4H, m), 1.24 (3H, t, J=7.1 Hz), 3.81-3.83 (2H, m),

4.25 (2H, q, J=7.1 Hz), 6.85-6.91 (2H, m), 7.16-7.27 (3H, m),
12.02 (1H, d, J=12.5 Hz)

Reference Example 56

5 Ethyl α -(hydroxymethylene)-4-methylsulfanylphenyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.22 (3H, t, J=7.1 Hz), 2.47 (3H, s), 4.09 (2H, q, J=7.1 Hz),
6.85-6.94 (2H, m), 7.16-7.26 (3H, m), 11.99 (1H, d, J=12.3 Hz)

10 Reference Example 57

Ethyl 4-ethoxy- α -(hydroxymethylene)phenyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.23-1.47 (6H, m), 4.00-4.32 (4H, m), 6.85-6.88 (2H, m), 7.15-
7.27 (3H, m), 12.00 (1H, d, J=12.5 Hz)

15

Reference Example 58

Ethyl 4-methoxy- α -propionylphenyl acetate

L-Proline (980 mg, 8.52 mmol), copper (I) iodide (810
mg, 4.26 mmol), and cesium carbonate (27.7 g, 85.2 mmol) were
20 added to a dimethylsulfoxide (DMSO) solution (40 ml) of ethyl
propionyl acetate (3.8 g, 26.3 mmol) and 4-iodoanisole (5.0 g,
21.3 mmol) in that order. The mixture was stirred under a
nitrogen atmosphere at 40 to 45°C for 27 hours. The reaction
mixture was cooled to room temperature, and then water and
25 ammonium chloride aqueous solution were added. The resulting
mixture was extracted with ethyl acetate. The organic layer was
washed with a saturated sodium chloride aqueous solution twice,
and concentrated under reduced pressure. The residue was then
purified by silica gel column chromatography (n-hexane : ethyl
30 acetate = 19 : 1 $\rightarrow$ 8 : 1). The purified product was concentrated
under reduced pressure to thereby obtain 2.97 g of oily yellow
ethyl 4-methoxy- α -propionylphenyl acetate (yield: 56%).

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.01-1.11 (3H, m), 1.18-1.31 (3H, m), 2.52-2.61 (2H, m), 3.80 and
35 3.82 (3H, s), 4.15-4.24 (2H, m), 4.65 (0.6H, s), 6.84-7.28 (4H,

m), 13.13 (0.4H, s)

The compound of the following Reference Example 59 was prepared in the same manner as the above Reference Example 58,
5 using corresponding starting materials.

Reference Example 59

Ethyl α -acetyl-4-methoxyphenyl acetate

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

10 1.16-1.29 (3H, m), 1.85 (1.4H, s), 2.17 (1.6H, s), 3.80 and 3.82
(1.4 and 1.6H, s), 4.13-4.25 (2H, m), 4.62 (0.6H, s), 6.85-7.28
(4H, m), 13.09 (0.4H, s)

Reference Example 60

15 5-[(5-Fluoro-2-propoxyphenylamino)methylene]-2,2-dimethyl-
[1,3]dioxane-4,6-dione

Meldrum's acid (5.29g, 36.7 mmol) was added to methyl orthoformate (31 ml), and the mixture was stirred for 2 hours while heating under reflux. The resulting mixture was cooled to
20 50°C, and 5-fluoro-2-propoxyaniline (4.28 g, 25.3 mmol) and methyl orthoformate (3 ml) were added thereto. The resulting mixture was stirred for 6 hours while heating under reflux. The resulting reaction mixture was then cooled to room temperature, and concentrated under reduced pressure. The residue was
25 recrystallized from methanol to thereby obtain 7.61 g of powdery pale brown 5-[(5-fluoro-2-propoxyphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (yield: 93%).

$^1\text{H-NMR}$ (CDCl_3) δ ppm:

1.12 (3H, t, $J=7.4$ Hz), 1.75 (6H, s), 1.85-1.98 (2H, m), 4.02 (2H,
30 t, $J=6.3$ Hz), 6.86-6.91 (2H, m), 7.06-7.10 (1H, m), 8.60 (1H, d, $J=14.6$ Hz), 11.68 (1H, d, $J=14.8$ Hz)

The compound of the following Reference Example 61 was prepared in the same manner as the above Reference Example 60,
35 using corresponding starting materials.

Reference Example 61

5-[(2-Cyclopropylmethoxy-5-fluorophenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione

5 ¹H-NMR (CDCl₃) δppm:

0.39-0.43 (2H, m), 0.65-0.73 (2H, m), 1.31-1.37 (1H, m), 1.75 (6H, s), 3.92 (2H, d, J=6.9 Hz), 6.86-6.91 (2H, m), 7.07-7.11 (1H, m), 8.60 (1H, d, J=14.5 Hz), 11.69 (1H, d, J=14.3 Hz)

10 Reference Example 62

5-Fluoro-8-propoxy-1H-quinolin-4-one

5-[(5-Fluoro-2-propoxyphenylamino)methylene]-2,2-dimethyl-[1,3]dioxane-4,6-dione (7.6 g, 23.5 mmol) was added to diphenyl ether (15 ml), and the mixture was heated using a mantle
15 heater, and then kept under reflux for 2 hours. After the reaction mixture was cooled to room temperature, ethyl acetate (5 ml) and n-hexane (10 ml) were added. The resulting mixture was stirred and the resultant insoluble matter was collected by filtration. The filtrate was recrystallized from an ethyl
20 acetate-n-hexane mixed solvent to thereby obtain 3.15 g of powdery dark brown 5-fluoro-8-propoxy-1H-quinolin-4-one (yield: 61%).

¹H-NMR (DMSO-d₆) δppm:

1.03 (3H, t, J=7.3 Hz), 1.74-1.88 (2H, m), 4.07 (2H, t, J=6.4 Hz),
25 5.97 (1H, d, J=7.4 Hz), 6.87 (1H, dd, J=8.8 Hz, 11.9 Hz), 7.13 (1H, dd, J=4.0 Hz, J=8.8 Hz), 7.70 (1H, t, J=7.2 Hz), 11.07 (1H, brs)

The compound of the following Reference Example 63 was
30 prepared in the same manner as the above Reference Example 62, using corresponding starting materials.

Reference Example 63

8-Cyclopropylmethoxy-5-fluoro-1H-quinolin-4-one

35 ¹H-NMR (DMSO-d₆) δppm:

0.34-0.40 (2H, m), 0.55-0.61 (2H, m), 1.27-1.33 (1H, m), 3.98 (2H, d, J=7.0 Hz), 5.97 (1H, d, J=7.4 Hz), 6.86 (1H, dd, J=8.8 Hz, J=11.9 Hz), 7.13 (1H, dd, J=4.0 Hz, J= 8.8 Hz), 7.71 (1H, t, J=7.4 Hz), 11.10 (1H, brs)

5

Reference Example 64

5-Fluoro-2-methyl-8-propoxy-1H-quinolin-4-one

Amberlyst 15 (1.0 g, a product of Sigma Aldrich Corp.) was added to a benzene solution (200 ml) of 5-fluoro-2-propoxyaniline (10 g, 59 mmol) and ethyl acetoacetate (7.7 g, 59 mmol). The mixture was stirred while heating under reflux for 6 hours and using a Dean-Stark trap. The reaction mixture was cooled to room temperature, the resin was removed by filtration, and the filtrate was concentrated under reduced pressure.

15 Diphenyl ether (20ml) was added to the residue. The mixture was heated using a mantle heater and stirred under reflux for 2 hours. After the reaction mixture was cooled to room temperature, insoluble matter obtained by the addition of n-hexane-ethyl acetate (2 : 1) was collected by filtration. The substance

20 remaining on the filter was washed with n-hexane-ethyl acetate (2 : 1), and dried to thereby obtain 6.0 g of powdery pale yellow 5-fluoro-2-methyl-8-propoxy-1H-quinolin-4-one (yield: 43%).

¹H-NMR (DMSO-d₆) δppm:

0.97 (3H, t, J=7.3 Hz), 1.77-1.87 (2H, m), 2.34 (3H, s), 4.08 (2H, t, J=6.4 Hz), 5.84 (1H, s), 6.79-6.88 (1H, m), 7.10-7.14 (1H, m), 10.58 (1H, brs)

25

Reference Example 65

5-Fluoro-3-iodo-8-propoxy-1H-quinolin-4-one

30 5-Fluoro-8-propoxy-1H-quinolin-4-one (1.0 g, 4.52 mmol) was suspended in DMF (11 ml), and potassium carbonate (0.7 g, 5.06 mmol) and iodide (1.27 g, 5.00 mmol) were added to the suspension. The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into a sodium

35 thiosulfate (3.94 g, 25 mmol) aqueous solution (45 ml). The

mixture was stirred for 5 minutes. Ethyl acetate was added to the resulting reaction mixture and stirred, thereby collecting insoluble matter by filtration. The filtrate was separated, and the organic layer was washed with a saturated sodium chloride aqueous solution, and then concentrated under reduced pressure. The residue and the collected insoluble matter were combined, and then purified by silica gel column chromatography (dichloromethane : methanol = 50 : 1 → 40 : 1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 1.25 g of powdery pale dark brown 5-fluoro-3-iodo-8-propoxy-1H-quinolin-4-one (yield: 80%).

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.78-1.86 (2H, m), 4.09 (2H, t, J=6.5 Hz), 6.97 (1H, dd, J=8.8 Hz, J= 11.9 Hz), 7.19 (1H, dd, J=4.0 Hz, J=8.8 Hz), 8.19 (1H, s), 11.44 (1H, brs)

The compounds of the following Reference Examples 66 and 67 were prepared in the same manner as the above Reference Example 65, using corresponding starting materials.

20

Reference Example 66

5-Fluoro-3-iodo-2-methyl-8-propoxy-1H-quinolin-4-one

¹H-NMR (CDCl₃) δppm:

0.97 (3H, t, J=7.4 Hz), 1.78-1.88 (2H, m), 2.70 (3H, s), 6.92-7.00 (1H, m), 7.17-7.22 (1H, m)

Reference Example 67

8-Cyclopropylmethoxy-5-fluoro-3-iodo-1H-quinolin-4-one

¹H-NMR (DMSO-d₆) δppm:

0.36-0.40 (2H, m), 0.56-0.63 (2H, m), 1.28-1.31 (1H, m), 3.99 (2H, d, J=7.0 Hz), 6.97 (1H, dd, J=8.8 Hz, J=11.9 Hz), 7.19 (1H, dd, J=4.0 Hz, J=8.8 Hz), 8.19 (1H, s), 11.48 (1H, brs)

Reference Example 68

8-Cyclopropylmethoxy-1-ethyl-5-fluoro-3-iodo-1H-quinolin-4-one

Potassium carbonate (450 mg, 3.26 mmol) was added to a DMF solution (5 ml) of 8-cyclopropylmethoxy-5-fluoro-3-iodo-1H-quinolin-4-one (910 mg, 2.53 mmol). The mixture was stirred for 15 minutes at room temperature. Ethyl iodide (0.31 ml, 3.87 mmol) was added thereto, and the resulting mixture was stirred at 60°C for 2 hours. After the reaction mixture was cooled to room temperature, water was added, and the resulting mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure and the residue was then purified by silica gel column chromatography (dichloromethane : ethyl acetate = 40 : 1 → 15 : 1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 750 mg of powdery pale dark brown 8-cyclopropylmethoxy-1-ethyl-5-fluoro-3-iodo-1H-quinolin-4-one (yield: 77%).

¹H-NMR (DMSO-d₆) δppm:
0.34-0.38 (2H, m), 0.57-0.64 (2H, m), 1.26-1.36 (4H, m), 3.93 (2H, d, J=7.3 Hz), 4.56 (2H, q, J=7.0 Hz), 7.05 (1H, dd, J=8.9 Hz, J=11.4 Hz), 7.24 (1H, dd, J=4.6 Hz, J=9.0 Hz), 8.45 (1H, s)

Reference Example 69

2,2,2-Trifluoro-N-(5-fluoro-2-propoxyphenyl)acetamide

A dichloromethane solution (60 ml) of 5-fluoro-2-propoxyaniline (10.0g, 59.1 mmol) was cooled with ice, and triethylamine (16.5 ml) was added thereto. Then, trifluoroacetic anhydride (14.8 g, 70.5 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane. The organic layer was washed with water, and dried over anhydrous sodium sulfate. The resulting dry product was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (n-hexane : ethyl acetate = 10 : 1). The purified product was concentrated to dryness under reduced pressure to thereby obtain 15.83 g of powdery white 2,2,2-trifluoro-N-(5-fluoro-2-propoxyphenyl)acetamide (yield: 99%).

¹H-NMR (CDCl₃) δppm:

1.03 (3H, t, J=7.5 Hz), 1.79-1.93 (2H, m), 3.98 (2H, t, J=6.5 Hz),
6.80-6.86 (2H, m), 8.10-8.12 (1H, m), 8.64 (1H, brs)

5 Reference Example 70

Ethyl ester of 4,4,4-trifluoro-3-(5-fluoro-2-propoxyphenylamino)
buta-2-enoic acid

Carboethoxymethylene triphenylphosphorane (41.52 g,
119.2 mmol) was added to a toluene solution (100 ml) of 2,2,2-
10 trifluoro-N-(5-fluoro-2-propoxyphenyl)acetamide (15.83 g, 59.1
mmol). The mixture was stirred under a nitrogen atmosphere while
heating under reflux for 4 hours. The reaction mixture was cooled
to room temperature, concentrated under reduced pressure, and the
residue was then purified by silica gel column chromatography (n-
15 hexane : ethyl acetate = 10 : 1). The purified product was
concentrated under reduced pressure to thereby obtain 19.7 g of
oily yellow ethyl ester of 4,4,4-trifluoro-3-(5-fluoro-2-
propoxyphenylamino)buta-2-enoic acid (yield: 99%).

¹H-NMR (CDCl₃) δppm:

20 1.02 (3H, t, J=7.5 Hz), 1.28 (3H, t, 7.0 Hz), 1.74-1.88 (2H, m),
3.85 (2H, t, J=6.5 Hz), 4.17 (2H, q, J=7.0 Hz), 5.41 (1H, s),
6.77-6.97 (3H, m), 9.77 (1H, brs)

Reference Example 71

25 5-Fluoro-8-propoxy-2-trifluoromethyl-1H-quinolin-4-one

Diphenyl ether (15 ml) was added to ethyl ester of
4,4,4-trifluoro-3-(5-fluoro-2-propoxyphenylamino)buta-2-enoic
acid (19.7 g, 59.0 mmol), and the mixture was stirred for 1.5
hours while heating under reflux. The reaction mixture was cooled
30 to room temperature, n-hexane was added, and the precipitate was
collected by filtration. The substance remaining on the filter
was washed with n-hexane, and dried to thereby obtain 16.2 g of
powdery white 5-fluoro-8-propoxy-2-trifluoromethyl-1H-quinolin-4-
one (yield: 94%).

35 ¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.5 Hz), 1.76-1.90 (2H, m), 4.07 (2H, t, J=6.5 Hz),
7.18-7.32 (3H, m), 12.26 (1H, brs)

Reference Example 72

5 5-Fluoro-3-iodo-8-propoxy-2-trifluoromethyl-1H-quinolin-4-one

Potassium carbonate (3.73 g, 27 mmol) and iodide (6.85 g, 27 mmol) were added to a DMF solution (20 ml) of 5-fluoro-8-propoxy-2-trifluoromethyl-1H-quinolin-4-one (6.0 g, 20.7 mmol) in that order, and the resulting mixture was stirred at room
10 temperature for 1.5 hours. A saturated sodium sulfite aqueous solution (20 ml) and ethyl acetate were added to the reaction mixture, and the precipitated solid was collected by filtration. The filtrate was washed with water, and then dried over anhydrous sodium sulfate. The dried filtrate was concentrated under reduced
15 pressure. The residue and the substance collected by the advance filtration were combined, and dissolved in ethanol, and then concentrated. The residue was recrystallized from an ethyl acetate-n-hexane mixed solvent to thereby obtain 4.7 g of powdery white 5-fluoro-3-iodo-8-propoxy-2-trifluoromethyl-1H-quinolin-4-
20 one (yield: 55%).

¹H-NMR (DMSO-d₆) δppm:

0.96 (3H, t, J=7.5 Hz), 1.70-1.80 (2H, m), 3.95 (2H, t, J=6.5 Hz),
6.64-6.85 (2H, m), 12.02 (1H, brs)

25 Reference Example 73

1-(5-Bromo-2-cyclopentyloxyphenyl)ethanone

Potassium carbonate (6.55 g, 47.4 mmol), cyclopentyl bromide (8.25 g, 55.3 mmol) and DMF (5 ml) were added to a DMF solution (10 ml) of 5'-bromo-2'-hydroxyacetophenone (8.5 g, 39.5
30 mmol), and the resulting mixture was stirred at 60°C for 4.5 hours. Potassium carbonate (3.0 g, 21.7 mmol) and cyclopentyl bromide (2.0 g, 13.4 mmol) were added to the resultant mixture, and stirred at 60°C for 9 hours. After the reaction mixture was cooled to room temperature, water was added, and the resulting mixture
35 was extracted with ethyl acetate. The organic layer was washed

with a saturated sodium chloride aqueous solution, and then concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (n-hexane: ethyl acetate=9:1). The purified product was concentrated under reduced pressure to thereby obtain 11.3 g of oily pale yellow 1-(5-bromo-2-cyclopentyloxyphenyl)ethanone (yield: 100%).

¹H-NMR (CDCl₃) δppm:

1.68-1.95 (8H, m), 2.58 (3H, s), 4.83-4.87 (1H, m), 6.83 (1H, d, J=8.9 Hz), 7.49 (1H, dd, J=2.6 Hz, 8.9 Hz), 7.82 (1H, d, J=2.6 Hz)

Reference Example 74

1-(5-Bromo-2-cyclopentyloxyphenyl)ethanone oxime

1-(5-Bromo-2-cyclopentyloxyphenyl)ethanone (5.0 g, 17.65 mmol) was dissolved in a mixed solvent of chloroform (18 ml) and methanol (70 ml). Hydroxylamine hydrochloride (1.88 g, 27.0 mmol) and pyridine (4.36 ml, 54.1 mmol) were added to the resulting solution, and the mixture was stirred for 6 hours while heating under reflux. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure. 2N Hydrochloric acid (13.9 ml) was added to the residue, and the resulting mixture was extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution, dried over magnesium sulfate, and concentrated to dryness under reduced pressure. The residue was washed with n-hexane and dried to thereby obtain 4.6 g of powdery white 1-(5-bromo-2-cyclopentyloxyphenyl)ethanone oxime (yield: 87%).

¹H-NMR (CDCl₃) δppm:

1.65-1.90 (8H, m), 2.17 (3H, s), 4.72-4.76 (1H, m), 6.76 (1H, d, J=8.4 Hz), 7.35-7.41 (2H, m), 7.99 (1H, brs)

Reference Example 75

N-(5-Bromo-2-cyclopentyloxyphenyl)acetamide

1-(5-Bromo-2-cyclopentyloxyphenyl)ethanone oxime (4.56 g, 15.3 mmol) was suspended in acetonitrile (100 ml). Indium

(III) chloride (507 mg, 2.29 mmol) was added thereto, and the resultant was heated under reflux for 2 hours under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, and then concentrated under reduced pressure. The residue was
5 extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution, and then concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (n-hexane: ethyl acetate=8:1→4:1). The purified product was concentrated under
10 reduced pressure to thereby obtain 3.41 g of oily pale yellow N-(5-bromo-2-cyclopentyloxyphenyl)acetamide (yield: 75%).

¹H-NMR (CDCl₃) δppm:

1.67-1.94 (8H, m), 2.18 (3H, s), 4.75-4.81 (1H, m), 6.72 (1H, d, J=8.7 Hz), 7.10 (1H, dd, J=2.3 Hz, 8.7 Hz), 7.67 (1H, brs), 8.55
15 (1H, d, J=2.3 Hz)

Reference Example 76

5-Bromo-2-cyclopentyloxyaniline

Concentrated hydrochloric acid (5.8 ml) was added to an
20 ethanol solution (100 ml) of N-(5-bromo-2-cyclopentyloxyphenyl)acetamide (3.4 g, 11.4 mmol), and the resulting mixture was stirred for 3 hours while heating under reflux. After the reaction mixture was cooled to room temperature, a 5N sodium hydroxide solution (14.2 ml) was added to obtain a pH
25 of 11. The resulting mixture was then extracted with dichloromethane. The organic layer was washed with a saturated sodium chloride aqueous solution, and then concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (n-hexane: ethyl acetate=4:1). The purified
30 product was concentrated under reduced pressure to thereby obtain 2.97 g of oily pale yellow 5-bromo-2-cyclopentyloxyaniline (yield: 100%).

¹H-NMR (CDCl₃) δppm:

1.62-1.89 (8H, m), 3.80 (2H, brs), 4.71-4.75 (1H, m), 6.61 (1H, d, J=8.4 Hz), 6.75-6.81 (2H, m)
35

Example 1

5-Fluoro-3-furan-3-yl-8-propoxy-1H-quinolin-4-one

- 5-Fluoro-3-iodo-8-propoxy-1H-quinolin-4-one (780 mg,
5 2.24 mmol) was suspended in a mixed solvent of toluene (10 ml)
and methanol (1.6 ml), and furan-3-boronic acid (752 mg),
tetrakis triphenylphosphine palladium (130 mg, 0.11 mmol), and a
2N sodium carbonate aqueous solution (2.25 ml) were added thereto
in that order. The mixture was stirred under a nitrogen
10 atmosphere at 110°C for 20 hours. After the reaction mixture was
cooled to room temperature, water was added, and the resulting
mixture was extracted with dichloromethane. The organic layer was
concentrated under reduced pressure, the residue was then
purified by silica gel column chromatography (dichloromethane :
15 methanol = 60 : 1 → 50 : 1). The purified product was
concentrated under reduced pressure and was recrystallized from
ethanol to thereby obtain 180 mg of powdery pale yellow 5-fluoro-
3-furan-3-yl-8-propoxy-1H-quinolin-4-one (yield: 58%).

Melting point 214-215°C

- 20 ¹H-NMR (DMSO-d₆) δppm:
1.02 (3H, J=7.3 Hz), 1.78-1.87 (2H, m), 4.09 (2H, t, J=6.4 Hz),
6.87-6.95 (2H, m), 7.13 (1H, dd, J=3.8 Hz, J= 8.8 Hz), 7.67 (1H,
s), 8.11 (1H, s), 8.51 (1H, s), 11.50 (1H, brs)

- 25 The compounds of the following Examples 2 to 5 were
prepared in the same manner as the above Example 1, using
corresponding starting materials.

Example 2

- 30 5-Fluoro-3-(3-fluoro-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one
Gray powder (ethanol)

Melting point 194-195°C

- ¹H-NMR (DMSO-d₆) δppm:
1.03 (3H, t, J=7.3 Hz), 1.79-1.87 (2H, m), 3.84 (3H, s), 4.09 (2H,
35 t, J=6.4 Hz), 6.90 (1H, dd, J=8.7 Hz, J= 12.1 Hz), 7.12-7.19 (2H,

m), 7.35-7.39 (1H, m), 7.56 (1H, dd, J=2.0 Hz, J=13.5 Hz), 7.87 (1H, s), 11.40 (1H, brs)

Example 3

5 5-Fluoro-8-propoxy-3-thiophen-3-yl-1H-quinolin-4-one

Pale brown powder (ethanol)

Melting point 208-210°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.75-1.89 (2H, m), 4.08 (2H, t, J=6.4 Hz),
10 6.90 (1H, dd, J=8.7 Hz, J=12.1 Hz), 7.13 (1H, dd, J=3.9 Hz, J=8.8 Hz), 7.50-7.57 (2H, m), 8.14 (1H, s), 8.19-8.21 (1H, m),
11.42 (1H, brs)

Example 4

15 3-(3-Chloro-4-methoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale yellow powder (ethanol)

Melting point 217-218°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.78-1.86 (2H, m), 3.85 (3H, s), 4.08 (2H,
20 t, J=6.4 Hz), 6.90 (1H, dd, J=8.8 Hz, J= 12.0 Hz), 7.10-7.15 (2H, m), 7.51 (1H, dd, J=2.1 Hz, J= 8.5 Hz), 7.74 (1H, d, J=2.1 Hz),
7.87 (1H, s), 11.45 (1H, brs)

Example 5

25 5-Fluoro-8-propoxy-3-(4-trifluoromethoxyphenyl)-1H-quinolin-4-one

Pale gray powder (ethanol)

Melting point 212-214°C

¹H-NMR (DMSO-d₆) δppm:

1.03 (3H, t, J=7.3 Hz), 1.79-1.87 (2H, m), 4.09 (2H, t, J=6.4 Hz),
30 6.92 (1H, dd, J=8.8 Hz, J= 12.0 Hz), 7.16 (1H, dd, J=3.9 Hz, J=8.8 Hz), 7.35 (2H, d, J=8.5 Hz), 7.73 (2H, d, J=8.7 Hz), 7.91 (1H, s), 11.45 (1H, brs)

Example 6

35 5-Fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

Amberlyst 15 (1.0 g, a product of Sigma Aldrich Corp.) was added to a benzene solution (150 ml) of 5-fluoro-2-propoxyaniline (16.25 g, 96.0 mmol) and ethyl α -(hydroxymethylene)-4-methoxyphenyl acetate (21.34 g, 96.0 mmol).

- 5 The mixture was heated under reflux for 14 hours while using a Dean-Stark trap and being stirred. The reaction mixture was cooled to room temperature, the resin was removed by filtration, and the filtrate was concentrated under reduced pressure. Diphenyl ether (40 ml) was added to the residue, and the mixture
10 was heated using a mantle heater and stirred under reflux for 2 hours. The reaction mixture was cooled to room temperature and purified directly by silica gel column chromatography (dichloromethane : methanol = 100 : 0 $\rightarrow$ 30 : 1 $\rightarrow$ 20 : 1). The purified product was concentrated under reduced pressure, and the
15 residue was recrystallized from ethanol to thereby obtain 5.28 g of powdery pale yellow 5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one (yield: 17%).

Melting point 196-197°C

¹H-NMR (DMSO-d₆) δ ppm:

- 20 1.02 (3H, t, J=7.3 Hz), 1.78-1.86 (2H, m), 3.75 (3H, s), 4.07 (2H, t, J=6.4 Hz), 6.83-6.96 (3H, m), 7.11 (1H, dd, J=3.9 Hz, J=8.8 Hz), 7.53 (2H, d, J=8.8 Hz), 7.81 (1H, s), 11.50 (1H, brs)

- The compounds of the following Examples 7 to 46 were
25 prepared in the same manner as the above Example 6, using corresponding starting materials.

Example 7

5-Fluoro-3-(2-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

- 30 White powder (ethyl acetate)

Melting point 193-195°C

¹H-NMR (CDCl₃) δ ppm:

- 1.05 (3H, t, J=7.5 Hz), 1.82-1.97 (2H, m), 3.77 (3H, s), 4.05 (2H, t, J=6.3 Hz), 6.77-7.02 (4H, m), 7.26-7.29 (1H, m), 7.42-7.45 (1H, m), 7.72-7.74 (1H, m), 8.83 (1H, brs)
35

Example 8

3-(2,4-Dimethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

5 Melting point 116-118°C

¹H-NMR (CDCl₃) δppm:

1.07 (3H, t, J=7.5 Hz), 1.84-1.98 (2H, m), 3.76 (3H, s), 3.84 (3H, s), 4.06 (2H, t, J=7.5 Hz), 6.54-6.58 (2H, m), 6.77-6.92 (2H, m), 7.38-7.42 (1H, m), 7.72-7.75 (1H, m), 8.79 (1H, brs)

10

Example 9

5-Fluoro-8-isopropoxy-3-(4-methoxyphenyl)-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 193-194°C

15 ¹H-NMR (CDCl₃) δppm:

1.39 (6H, d, J=5.0 Hz), 3.79 (3H, s), 4.58 (1H, q, J=5.0 Hz), 6.79-6.92 (4H, m), 7.54-7.57 (2H, m), 7.68-7.71 (1H, m), 8.80 (1H, brs)

20 Example 10

3-(2,4-Dichlorophenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 256-259°C

¹H-NMR (DMSO-d₆) δppm:

25 1.01 (3H, t, J=7.5 Hz), 1.79-1.87 (2H, m), 4.08 (2H, t, J=6.3 Hz), 6.88-6.98 (1H, m), 6.96-7.72 (1H, m), 7.37-7.47 (2H, m), 7.65-7.67 (1H, m), 7.75-7.77 (1H, m), 11.42 (1H, brs)

Example 11

30 8-Ethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 155-156°C

¹H-NMR (CDCl₃) δppm: 1.46 (3H, t, J=7.5 Hz), 3.81 (3H, s), 4.14 (2H, q, J=7.5 Hz), 6.77-6.94 (4H, m), 7.54-7.60 (2H, m), 7.71-

35 7.73 (1H, m), 9.02 (1H, brs)

Example 12

3-(2,4-Dimethoxyphenyl)-8-ethoxy-5-fluoro-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

5 Melting point 154-155°C

¹H-NMR (CDCl₃) δppm:

1.44 (3H, t, J=7.5 Hz), 3.73 (3H, s), 3.81 (3H, s), 4.12 (2H, q, J= 7.5 Hz), 6.50-6.53 (2H, m), 6.54-6.89 (2H, m), 7.35-7.39 (1H, m), 7.69-7.72 (1H, m), 8.97 (1H, brs)

10

Example 13

3-(2,4-Dichlorophenyl)-8-ethoxy-5-fluoro-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 236-237°C

15 ¹H-NMR (DMSO-d₆) δppm:

1.40 (3H, t, J=7.5 Hz), 4.17 (2H, q, J=7.5 Hz), 6.88-7.00 (1H, m), 7.22-7.32 (1H, m), 7.38-7.45 (2H, m), 7.64-7.65 (1H, m), 7.74-7.75 (1H, m), 11.40 (1H, brs)

20 Example 14

5-Fluoro-3-(4-methoxyphenyl)-8-morpholin-4-yl-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 249-251°C

¹H-NMR (CDCl₃) δppm:

25 2.75-3.22 (4H, m), 3.65-4.15 (4H, m), 6.85-6.93 (3H, m), 7.34-7.40 (1H, m), 7.54-7.58 (2H, m), 7.74-7.77 (1H, m), 10.02 (1H, brs)

Example 15

30 5-Fluoro-3-(2-isopropoxy-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 204-206°C

¹H-NMR (CDCl₃) δppm:

35 1.09 (3H, t, J=6.3 Hz), 1.23 (3H, s), 1.26 (3H, s), 1.87-2.01 (2H,

m), 3.83 (3H, s), 4.08 (2H, t, J=6.3 Hz), 4.34-4.50 (1H, m),
6.55-6.60 (2H, m), 6.78-6.93 (2H, m), 7.50 (1H, d, J=7.5 Hz),
7.80 (1H, d, J=7.5 Hz), 8.73 (1H, brs)

5 Example 16

5-Fluoro-3-(4-methoxy-2-methylphenyl)-8-propoxy-1H-quinolin-4-one
White powder (ethyl acetate)

Melting point 197-199°C

¹H-NMR (CDCl₃) δppm:

10 1.06 (3H, t, J=6.3 Hz), 1.80-2.00 (2H, m), 2.24 (3H, s), 3.80 (3H,
s), 4.07 (2H, t, J=6.3 Hz), 6.70-6.94 (4H, m), 7.07 (1H, d, J=7.5
Hz), 7.54 (1H, d, J=7.5 Hz), 8.80 (1H, brs)

Example 17

15 5-Fluoro-3-(2-fluoro-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one
White powder (ethyl acetate-ethanol)

Melting point 230-232°C

¹H-NMR (CDCl₃) δppm:

1.05 (3H, t, J=7.5 Hz), 1.80-2.00 (2H, m), 3.80 (3H, s), 4.06 (2H,
20 t, J=7.5 Hz), 6.64-6.93 (4H, m), 7.53-7.60 (1H, m), 7.74-7.78 (1H,
m), 8.86 (1H, brs)

Example 18

5-Fluoro-3-(4-methoxyphenyl)-8-pyrrolidin-1-yl-1H-quinolin-4-one

25 Pale brown powder (ethyl acetate-n-hexane)

Melting point 100-105°C

¹H-NMR (CDCl₃) δppm:

1.90-2.08 (4H, m), 3.01-3.20 (4H, m), 3.81 (3H, s), 6.81-6.94 (3H,
m), 7.29-7.34 (1H, m), 7.55-7.60 (2H, m), 7.74-7.76 (1H, m), 9.41
30 (1H, brs)

Example 19

3-(4-Ethoxy-2-methoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one
Pale brown powder (ethyl acetate)

35 Melting point 118-120°C

¹H-NMR (CDCl₃) δppm:

1.06 (3H, t, J=7.5 Hz), 1.39 (3H, t, J=7.5 Hz), 1.83-1.98 (2H, m),
3.75 (3H, s), 4.00-4.14 (4H, m), 6.51-6.55 (2H, m), 6.76-6.91 (2H,
5 m), 7.38 (1H, d, J=6.2 Hz), 7.72 (1H, d, J=6.2 Hz), 8.65 (1H,
brs)

Example 20

5-Fluoro-3-(4-isopropoxy-2-methoxyphenyl)-8-propoxy-1H-quinolin-
4-one

10 White powder (ethyl acetate-n-hexane)

Melting point 113-115°C

¹H-NMR (CDCl₃) δppm:

1.04 (3H, t, J=7.5 Hz), 1.33 (3H, s), 1.36 (3H, s), 1.80-1.95 (2H,
m), 3.72 (3H, s), 4.03 (2H, t, J=7.5 Hz), 4.50-4.71 (1H, m),
15 6.49-6.53 (2H, m), 6.78-6.86 (2H, m), 7.34-7.38 (1H, m), 7.42-
7.74 (1H, m), 8.82 (1H, brs)

Example 21

5,6-Difluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

20 Pale brown powder (ethyl acetate-n-hexane)

Melting point 198-200°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.78-1.86 (2H, m), 3.75 (3H, s), 4.11 (2H,
t, J=6.4 Hz), 6.93 (2H, d, J=8.8 Hz), 7.38 (1H, dd, J=6.5 Hz, J=
25 12.3 Hz), 7.54 (2H, d, J=8.8 Hz), 7.81 (1H, s), 11.50 (1H, brs)

Example 22

8-Bromo-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

30 Melting point 134-135°C

¹H-NMR (DMSO-d₆) δppm:

3.78 (3H, s), 6.94-7.02 (3H, m), 7.52 (2H, d, J=6.3 Hz), 7.84 (1H,
s), 7.89-8.00 (1H, m), 11.20 (1H, brs)

35 Example 23

5-Fluoro-3-(4-methoxyphenyl)-8-(pyrrolidin-1-carbonyl)-1H-quinolin-4-one

Orange powder (ethyl acetate)

Melting point 236-237°C

5 ¹H-NMR (DMSO-d₆) δppm:

1.77-1.91 (4H, m), 3.29-3.34 (2H, m), 3.54-3.59 (2H, m), 3.76 (3H, s), 6.94 (2H, d, J=8.7 Hz), 7.02 (1H, dd, J=8.3 Hz, J=11.8 Hz), 7.53 (2H, d, J=8.7 Hz), 7.71 (1H, dd, J=5.1 Hz, J=8.3 Hz), 7.88 (1H, s), 11.26 (1H, s)

10

Example 24

8-Cyclopropylmethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate-ethanol)

15 Melting point 190-191°C

¹H-NMR (DMSO-d₆) δppm:

0.33-0.39 (2H, m), 0.55-0.62 (2H, m), 1.26-1.34 (1H, m), 3.75 (3H, s), 3.99 (2H, d, J=7.0 Hz), 6.83-6.95 (3H, m), 7.12 (1H, dd, J=3.8 Hz, J= 8.8 Hz), 7.53 (2H, d, J=8.6 Hz), 7.82 (1H, s), 11.34

20 (1H, brs)

Example 25

8-(N-Cyclohexyl-N-methylamino)-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

25 Pale yellow powder (ethyl acetate)

Melting point 224-225°C

¹H-NMR (DMSO-d₆) δppm:

1.00-1.24 (5H, m), 1.53-1.99 (5H, m), 2.65 (3H, s), 3.78 (3H, s), 6.92-6.99 (3H, m), 7.50-7.57 (3H, s), 7.87 (1H, s), 10.93 (1H,

30 brs)

Example 26

N-{3-[5-Fluoro-3-(4-methoxyphenyl)-4-oxo-1,4-dihydroquinolin-8-yloxy]propyl}acetamide

35 Pale brown powder (ethanol)

Melting point 229-231°C

¹H-NMR (DMSO-d₆) δppm:

- 1.80 (3H, s), 1.91-1.96 (2H, m), 3.24-3.31 (2H, m), 3.74 (3H, s),
4.12 (2H, t, J=5.6 Hz), 6.84-7.13 (4H, m), 7.53 (2H, d, J=8.6 Hz),
5 7.83 (1H, s), 8.01 (1H, brs), 11.40 (1H, brs)

Example 27

N-{3-[5-Fluoro-3-(4-methoxyphenyl)-4-oxo-1,4-dihydroquinolin-8-yloxy]propyl}methanesulfonamide

- 10 Pale brown powder (ethanol)

Melting point 120-121°C

¹H-NMR (DMSO-d₆) δppm:

- 1.96-2.06 (2H, m), 2.88 (3H, s), 3.10-3.30 (2H, m), 3.75 (3H, s),
4.18 (2H, t, J=5.9 Hz), 6.85-6.95 (3H, m), 7.00-7.16 (2H, m),
15 7.54 (2H, d, J=8.7 Hz), 7.82 (1H, s), 11.34 (1H, brs)

Example 28

5-Fluoro-8-(N-isobutyl-N-methylamino)-3-(4-methoxyphenyl)-1H-quinolin-4-one

- 20 White powder (ethyl acetate)

Melting point 144-145°C

¹H-NMR (DMSO-d₆) δppm:

- 0.86 (3H, s), 0.91 (3H, s), 1.61-1.67 (1H, m), 2.61 (3H, s), 2.80
(2H, d, J=6.75 Hz), 3.79 (3H, s), 6.91-6.99 (3H, m), 7.46-7.57
25 (3H, m), 7.88 (1H, s), 11.02 (1H, brs)

Example 29

5-Fluoro-8-(N-isopropyl-N-methylamino)-3-(4-methoxyphenyl)-1H-quinolin-4-one

- 30 White powder (ethyl acetate)

Melting point 267-269°C

¹H-NMR (DMSO-d₆) δppm:

- 1.04 (3H, s), 1.06 (3H, s), 2.62 (3H, s), 3.10-3.18 (1H, m), 3.76
(3H, s), 6.90-6.98 (3H, m), 7.47-7.55 (3H, m), 7.85 (1H, s),
35 10.94 (1H, brs)

Example 30

5-Fluoro-3-(4-methoxyphenyl)-8-(N-methyl-N-propylamino)-1H-quinolin-4-one

5 Pale yellow powder (ethyl acetate)

Melting point 145-146°C

¹H-NMR (DMSO-d₆) δppm:

0.79 (3H, t, J=7.5 Hz), 1.31-1.45 (2H, m), 2.63 (3H, s), 2.85 (2H, t, J=7.5 Hz), 3.76 (3H, s), 6.89-6.97 (3H, m), 7.43-7.54 (3H, m),
10 7.82 (1H, s), 11.07 (1H, brs)

Example 31

5-Fluoro-3-(4-methoxyphenyl)-8-(4,4,4-trifluorobutoxy)-1H-quinolin-4-one

15 White powder (ethyl acetate)

Melting point 171-172°C

¹H-NMR(DMSO-d₆) δppm:

1.99-2.08 (2H, m), 2.48-2.61 (2H, m), 3.74 (3H, s), 4.17 (2H, t, J=5.9 Hz), 6.84-6.94 (3H, m), 7.11 (1H, dd, J=3.8 Hz, J=8.8 Hz),
20 7.53 (2H, d, J=8.7 Hz), 7.82 (1H, s), 11.40 (1H, brs)

Example 32

1-{3-[5-fluoro-3-(4-methoxyphenyl)-4-oxo-1,4-dihydroquinolin-8-yloxy]propyl}-1,3,3-trimethyl urea

25 Brown amorphous solid (diethyl ether)

¹H-NMR (DMSO-d₆) δppm:

2.00-2.05 (2H, m), 2.63 (6H, s), 2.74 (3H, s), 3.20-3.40 (2H, m), 3.76 (3H, s), 4.12 (2H, t, J=6.0 Hz), 6.85-6.96 (3H, m), 7.14 (1H, dd, J=3.9 Hz, J=8.8 Hz), 7.55 (2H, d, J=8.7 Hz), 7.81 (1H, s),
30 11.40 (1H, brs)

Example 33

3-(4-Ethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

35 Melting point 203-205°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.13 (3H, t, J=7.0 Hz), 1.76-1.91 (2H, m),
3.99-4.13 (4H, m), 6.84-6.94 (3H, m), 7.12-7.17 (1H, m), 7.50 (2H,
d, J=7.5 Hz), 7.79 (1H, s), 11.25 (1H, brs)

5

Example 34

5-Fluoro-8-[N-(2-methoxyethyl)-N-methylamino]-3-(4-methoxyphenyl)-1H-quinolin-4-one hydrochloride

Pale yellow powder (ethyl acetate)

10 Melting point 100-101°C

¹H-NMR (DMSO-d₆) δppm:

2.78(3H, s), 3.08 (2H, t, J=5.3 Hz), 3.33 (3H, s), 3.49(2H, t,
J=5.3 Hz), 3.81 (3H, s), 6.94-7.02 (3H, m), 7.50-7.62 (3H, m),
8.00 (1H, s), 11.16 (1H, brs)

15

Example 35

3-(4-Cyclopropylmethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

20 Melting point 162-163°C

¹H-NMR (DMSO-d₆) δppm:

0.30-0.35 (2H, m), 0.54-0.58 (2H, m), 1.01 (3H, t, J=7.5 Hz),
1.10-1.30 (1H, m), 1.72-1.91 (2H, m), 3.80 (2H, d, J=7.0 Hz),
4.07 (2H, t, J=6.4 Hz), 6.84-6.93 (3H, m), 7.11-7.16 (1H, m),

25 7.50 (2H, d, J= 8.8 Hz), 7.79 (1H, s), 11.25 (1H, brs)

Example 36

5-Fluoro-8-(2-methoxyethoxy)-3-(4-methoxyphenyl)-1H-quinolin-4-one

30 Pale yellow powder (ethyl acetate)

Melting point 142-144°C

¹H-NMR (DMSO-d₆) δppm:

3.31 (3H, s), 3.70-3.80 (2H, m), 3.75 (3H, s), 4.20-4.30 (2H, m),
6.84-6.94 (3H, m), 7.16 (1H, dd, J=3.6 Hz, J=8.7 Hz), 7.53 (2H, d,
35 J=8.4 Hz), 7.82 (1H, s), 11.10 (1H, brs)

Example 37

8-Cyclopentyloxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

5 Melting point 213-215°C

¹H-NMR (DMSO-d₆) δppm:

1.50-1.70 (2H, m), 1.71-2.00 (6H, m), 3.75 (3H, s), 4.92-4.95 (1H, m), 6.83-6.95 (3H, m), 7.09 (1H, dd, J=3.9 Hz, J= 8.8 Hz), 7.53 (2H, d, J=8.6 Hz), 7.80 (1H, s), 11.20 (1H, brs)

10

Example 38

5-Fluoro-3-(4-methylsulfanylphenyl)-8-propoxy-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 198-199°C

15 ¹H-NMR (CDCl₃) δppm:

1.07 (3H, t, J=7.4 Hz), 1.85-2.04 (2H, m), 2.50 (3H, s), 4.07 (2H, t, J=6.6 Hz), 6.80-6.94 (2H, m), 7.27-7.31 (2H, m), 7.56 (2H, d, J=8.4 Hz), 7.74 (1H, d, J=8.2 Hz), 8.81 (1H, brs)

20 Example 39

5-Fluoro-3-(4-methoxyphenyl)-8-(tetrahydrofuran-2-ylmethoxy)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 108-110°C

25 ¹H-NMR (DMSO-d₆) δppm:

1.67-1.75 (1H, m), 1.81-1.90 (2H, m), 2.02-2.09 (1H, m), 3.65-3.83 (2H, m), 3.75 (3H, s), 4.10 (2H, d, J=4.6 Hz), 4.25-4.29 (1H, m), 6.84-6.95 (3H, m), 7.17 (1H, dd, J=3.8 Hz, J=8.8 Hz), 7.53 (2H, d, J=8.7 Hz), 7.82 (1H, s), 11.20 (1H, brs)

30

Example 40

5-Fluoro-3-(4-methoxyphenyl)-8-propylsulfanyl-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 173-174°C

35 ¹H-NMR (DMSO-d₆) δppm:

0.90 (3H, t, J=7.3 Hz), 1.40-1.52 (2H, m), 2.79 (2H, t, J=7.2 Hz), 3.77 (3H, s), 6.93-7.04 (3H, m), 7.51-7.55 (2H, m), 7.79-7.87 (2H, m), 11.24 (1H, brs)

5 Example 41

8-Cyclobutylmethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 193-194°C

10 ¹H-NMR (DMSO-d₆) δppm:

1.79-1.93 (4H, m), 2.04-2.09 (2H, m), 2.76-2.81 (1H, m), 3.74 (3H, s), 4.08 (2H, d, J=6.8 Hz), 6.83-6.93 (3H, m), 7.11 (1H, dd, J=3.8 Hz, J=8.8 Hz), 7.52 (2H, d, J=8.6 Hz), 7.82 (1H, s), 11.20 (1H, brs)

15

Example 42

8-tert-Butoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale brown powder (ethyl acetate-diethyl ether)

Melting point 206-208°C

20 ¹H-NMR (DMSO-d₆) δppm:

1.40 (9H, s), 3.76 (3H, s), 6.84-6.96 (3H, m), 7.31 (1H, dd, J=4.3 Hz, J=8.8 Hz), 7.54 (2H, d, J=8.8 Hz), 7.82 (1H, s), 10.95 (1H, brs)

25 Example 43

5-Fluoro-8-methoxy-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale dark brown powder (ethyl acetate)

¹H-NMR (DMSO-d₆) δppm:

3.76 (3H, s), 3.95 (3H, s), 6.87-6.95 (3H, m), 7.15 (1H, dd, J=3.8 Hz, J=8.8 Hz), 7.54 (2H, d, J=8.7 Hz), 7.76 (1H, s), 11.50 (1H, brs)

Example 44

5-Fluoro-8-methoxymethoxy-3-(4-methoxyphenyl)-1H-quinolin-4-one

35 Pale dark brown powder (dichloromethane-methanol)

¹H-NMR (CDCl₃) δppm:

3.44 (3H, s), 3.76 (3H, s), 5.20 (2H, s), 6.76-6.87 (3H, m),
7.18-7.23 (1H, m), 7.52 (2H, d, J=7.8 Hz), 7.69 (1H, s), 9.68 (1H,
brs)

5

Example 45

8-(3-Benzyloxypropoxy)-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-
4-one

Dark brown amorphous solid

10 ¹H-NMR (DMSO-d₆) δppm:

2.08-2.13 (2H, m), 3.68 (2H, t, J=6.2Hz), 3.77 (3H, s), 4.22 (2H,
t, J=6.0 Hz), 4.48 (2H, s), 6.84-6.97 (3H, m), 7.13-7.18 (1H, m),
7.21-7.29 (5H, m), 7.55 (2H, d, J=8.7 Hz), 7.76 (1H, s), 11.25
(1H, brs)

15

Example 46

8-(2-Benzyloxypropoxy)-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-
4-one

Dark brown amorphous solid

20 ¹H-NMR (DMSO-d₆) δppm:

1.32 (3H, d, J=6.2Hz), 3.76 (3H, s), 3.98-4.24 (3H, m), 4.54-4.69
(2H, m), 6.84-6.96 (3H, m), 7.16-7.30 (6H, m), 7.54 (2H, d, J=8.7
Hz), 7.78 (1H, s), 11.19 (1H, brs)

25 Example 47

8-Cyclopropylmethoxy-5-fluoro-3-(4-methoxyphenyl)-2-methyl-1H-
quinolin-4-one

Amberlyst 15 (350 mg, a product of Sigma Aldrich Corp.)
was added to a benzene solution (40 ml) of 2-cyclopropylmethoxy-
30 5-fluoroaniline (760 mg, 4.2 mmol) and ethyl α-acetyl-4-
methoxyphenyl acetate (1.0 g, 4.2 mmol), and the mixture was
heated under reflux for 19 hours while using a Dean-Stark trap
and being stirred. The reaction mixture was cooled to room
temperature, the resin was removed by filtration, and the
35 filtrate was concentrated under reduced pressure. Diphenyl ether

(2.2 ml) was added to the residue, and the mixture was heated using a mantle heater and then stirred for 1 hour under reflux. The reaction mixture was cooled to room temperature and purified directly by silica gel column chromatography (dichloromethane :

5 methanol = 80 : 1 $\rightarrow$ 60 : 1). The purified product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to thereby obtain 120 mg of powdery pale yellow 8-cyclopropylmethoxy-5-fluoro-3-(4-methoxyphenyl)-2-methyl-1H-quinolin-4-one (yield: 8%).

10 Melting point 167-169°C

¹H-NMR (DMSO-d₆) δppm:

0.35-0.39 (2H, m), 0.54-0.61 (2H, m), 1.31-1.37 (1H, m), 2.23 (3H, s), 3.76 (3H, s), 4.02 (2H, d, J=7.0 Hz), 6.80-6.94 (3H, m), 7.08-7.18 (3H, m), 10.62 (1H, brs)

15

The compound of the following Example 48 was prepared in the same manner as the above Example 47, using corresponding starting materials.

20 Example 48

2-Ethyl-5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one
Pale brown powder (ethyl acetate-n-hexane)

Melting point 169-171°C

¹H-NMR (DMSO-d₆) δppm:

25 0.98-1.05 (6H, m), 1.80-1.89 (2H, m), 2.56 (2H, t, J=7.5 Hz), 3.77 (3H, s), 4.13 (2H, t, J=6.6 Hz), 6.81-6.95 (3H, m), 7.05-7.17 (3H, m), 10.40 (1H, brs)

Example 49

30 5-Fluoro-8-propoxy-3-pyridin-3-yl-1H-quinolin-4-one

5-Fluoro-3-iodo-8-propoxy-1H-quinolin-4-one (600 mg, 1.73 mmol) was suspended in 1,2-dimethoxyethane (12 ml). 3-pyridine boronic acid (752 mg), 1,1'-

bis(diphenylphosphino)ferrocene dichloro palladium(II)-

35 dichloromethane complex (PdCl₂(DPPF)) (76 mg, 0.093 mmol), and 2N

sodium carbonate aqueous solution (2.54 ml) were added to the resulting suspension in that order. The mixture was stirred at 90°C for 2 hours under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, water was added, and the
5 resulting mixture was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (dichloromethane : methanol = 15 : 1). The purified product was concentrated under reduced pressure, and then recrystallized from
10 ethanol to thereby obtain 185 mg of powdery pale brown 5-fluoro-8-propoxy-3-pyridin-3-yl-1H-quinolin-4-one (yield: 36%).

Melting point 234-236°C

¹H-NMR (DMSO-d₆) δppm:

1.01 (3H, t, J=7.3 Hz), 1.77-1.86 (2H, m), 4.08 (2H, t, J=6.4 Hz),
15 6.93 (1H, dd, J=8.8 Hz, J=12.0 Hz), 7.13-7.18 (1H, m), 7.37-7.42 (1H, m), 7.97 (1H, s), 8.01-8.05 (1H, m), 8.44-8.46 (1H, m), 8.77 (1H, d, J=2.1 Hz), 11.55 (1H, brs)

The compounds of the following Examples 50 to 66 were
20 prepared in the same manner as the above Example 49, using corresponding starting materials.

Example 50

3-(4-Ethoxy-3-fluorophenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one
25 Pale yellow powder (ethanol)

Melting point 176-177°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.33 (3H, t, J=6.9 Hz), 1.75-1.89 (2H, m),
4.05-4.14 (4H, m), 6.90 (1H, dd, J=8.7 Hz, J=12.1 Hz), 7.09-7.16
30 (2H, m), 7.32-7.36 (1H, m), 7.52-7.58 (1H, m), 7.87 (1H, s), 11.45 (1H, s)

Example 51

5-Fluoro-8-propoxy-3-pyridin-4-yl-1H-quinolin-4-one
35 Pale brown powder (ethanol)

Melting point 259-261°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.78-1.86 (2H, m), 4.09 (2H, t, J=6.4 Hz),
6.96 (1H, dd, J=8.8 Hz, J=12.0 Hz), 7.19 (1H, dd, J=3.8 Hz, J=8.8
5 Hz), 7.71 (2H, d, J=6.1 Hz), 8.06 (1H, s), 8.52 (2H, d, J=6.1 Hz),
11.50 (1H, brs)

Example 52

5-Fluoro-3-(4-phenoxyphenyl)-8-propoxy-1H-quinolin-4-one

10 Pale brown powder (ethanol)

Melting point 228-230°C

¹H-NMR (DMSO-d₆) δppm:

1.01 (3H, t, J=7.3 Hz), 1.77-1.85 (2H, m), 4.07 (2H, t, J=6.2Hz),
6.90 (1H, dd, J=8.8 Hz, J=12.1Hz), 6.97-7.02 (4H, m), 7.10-7.15
15 (2H, m), 7.34-7.63 (4H, m), 7.88 (1H, s), 11.40 (1H, brs)

Example 53

3-(4-Ethylphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

20 Melting point 153-154°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.17 (3H, t, J=7.5 Hz), 1.78-1.86 (2H, m),
2.59 (2H, q, J=7.5 Hz), 4.08 (2H, t, J=6.4 Hz), 6.89 (1H, dd,
J=8.8 Hz, J= 12.1Hz), 7.10-7.21 (3H, m), 7.50 (2H, d, J=8.0 Hz),
25 7.83 (1H, s), 11.40 (1H, brs)

Example 54

3-(4-Acetylphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale red powder (ethyl acetate)

30 Melting point 180-181°C

¹H-NMR (DMSO-d₆) δppm:

0.95 (3H, t, J=7.5 Hz), 1.71-1.83 (2H, m), 2.51 (3H, m), 4.02 (2H,
t, J=6.6 Hz), 6.84-6.91 (1H, m), 7.10-7.14 (1H, m), 7.72 (2H, d,
J=8.4 Hz), 7.87-7.90 (3H, m), 11.40 (1H, brs)

Example 55

Methyl 4-(5-fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)
benzoate

White powder (ethyl acetate)

5 Melting point 201-202°C

¹H-NMR (DMSO-d₆) δppm:

1.01 (3H, t, J=7.3 Hz), 1.77-1.91 (2H, m), 3.86 (3H, s), 4.09 (2H,
t, J=6.5 Hz), 6.90-6.99 (1H, m), 7.17-7.22 (1H, m), 7.80 (2H, d,
J=8.5 Hz), 7.94-7.98 (3H, m), 11.48 (1H, brs)

10

Example 56

5-Fluoro-8-propoxy-3-[4-(pyrrolidine-1-carbonyl)phenyl]-1H-
quinolin-4-one

Pale red powder (ethyl acetate)

15 Melting point 236-237°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.79-1.89 (6H, m), 3.43-3.49 (4H, m),
4.08 (2H, t, J=6.5 Hz), 6.89-6.97 (1H, m), 7.15-7.20 (1H, m),
7.51 (2H, d, J=8.6 Hz), 7.67 (2H, d, J=8.6 Hz), 7.90 (1H, s),

20 11.40 (1H, brs)

Example 57

4-(5-Fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)-N,N-
dimethylbenzamide

25 Pale brown powder (ethyl acetate)

Melting point 235-237°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.80-1.89 (2H, m), 2.97 (6H, s), 4.08 (2H,
t, J=6.4 Hz), 6.89-6.93 (1H, m), 7.15-7.20 (1H, m), 7.39 (2H, d,
J=8.0 Hz), 7.67 (2H, d, J=8.0 Hz), 7.90 (1H, s), 11.41 (1H, brs)

30

Example 58

5-Fluoro-3-furan-2-yl-8-propoxy-1H-quinolin-4-one

Pale brown powder (ethyl acetate)

35 Melting point 210-212°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.78-1.90 (2H, m), 4.10 (2H, t, J=6.6 Hz),
6.54-6.56 (1H, m), 6.90-6.99 (1H, m), 7.15-7.21 (2H, m), 7.64-
7.65 (1H, m), 8.20 (1H, s), 11.47 (1H, brs)

5

Example 59

5-Fluoro-8-propoxy-3-thiophen-2-yl-1H-quinolin-4-one

Pale red powder (ethyl acetate)

Melting point 211-213°C

10 ¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.5 Hz), 1.78-1.90 (2H, m), 4.10 (2H, t, J=6.5 Hz),
6.92-7.20 (3H, m), 7.41-7.59 (2H, m), 8.34 (1H, s), 11.63 (1H,
brs)

15 Example 60

3-(5-Fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)thiophene-2-
carbaldehyde

White powder (ethyl acetate)

Melting point 190-191°C

20 ¹H-NMR (DMSO-d₆) δppm:

1.01 (3H, t, J=7.4 Hz), 1.79-1.88 (2H, m), 4.08 (3H, t, J=6.5 Hz),
6.92-7.00 (1H, m), 7.18-7.23 (1H, m), 7.32 (1H, d, J=5.0 Hz),
7.98 (1H, s), 8.04-8.06 (1H, m), 9.73 (1H, s), 11.40 (1H, brs)

25 Example 61

3-(4-Dimethylaminophenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 206-207°C

¹H-NMR (DMSO-d₆) δppm:

30 1.01 (3H, t, J=7.4 Hz), 1.79-1.88 (2H, m), 2.90 (6H, s), 4.07 (2H,
t, J=6.4 Hz), 6.71 (2H, d, J=9.0 Hz), 6.82-6.90 (1H, m), 7.09-
7.14 (1H, m), 7.45 (2H, d, J=9.0 Hz), 7.76 (1H, s), 11.18 (1H,
brs)

35 Example 62

3-(3,4-Dimethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale red powder (ethyl acetate)

Melting point 217-218°C

¹H-NMR (DMSO-d₆) δppm:

- 5 1.02 (3H, t, J=7.5 Hz), 1.78-1.88 (2H, m), 3.76 (6H, s), 4.07 (2H, t, J=6.4 Hz), 6.85-6.97 (2H, m), 7.08-7.16 (2H, m), 7.30 (1H, s), 7.82 (1H, s), 11.28 (1H, brs)

Example 63

- 10 5-Fluoro-3-(6-methoxypyridin-3-yl)-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 215-216°C

¹H-NMR (DMSO-d₆) δppm:

- 1.02 (3H, t, J=7.5 Hz), 1.77-1.91 (2H, m), 3.86 (3H, s), 4.08 (2H, 15 t, J=6.3 Hz), 6.81-6.96 (2H, m), 7.14-7.19 (1H, m), 7.77-7.99 (2H, m), 8.35 (1H, s), 11.39 (1H, brs)

Example 64

- 20 3-(2,6-Dimethoxypyridin-3-yl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale red powder (ethyl acetate)

Melting point 198-199°C

¹H-NMR (DMSO-d₆) δppm:

- 1.01 (3H, t, J=7.3 Hz), 1.76-1.90 (2H, s), 3.83 (3H, s), 3.89 (3H, 25 s), 4.07 (2H, t, J=6.3 Hz), 6.39 (1H, d, J=7.1 Hz), 6.86-6.94 (1H, m), 7.13-7.17 (1H, m), 7.68 (1H, d, J=7.1 Hz), 7.81 (1H, s), 11.23 (1H, brs)

Example 65

- 30 3-(2,5-Dimethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one

Pale red powder (ethyl acetate)

Melting point 156-157°C

¹H-NMR (DMSO-d₆) δppm:

- 1.03 (3H, t, J=7.3 Hz), 1.80-1.90 (2H, m), 3.65 (3H, s), 3.71 (3H, 35 s), 4.09 (2H, t, J=6.3 Hz), 6.87-6.91 (4H, m), 6.94-6.95 (1H, m),

7.73 (1H, s), 11.18 (1H, brs)

Example 66

8-Cyclopropylmethoxy-1-ethyl-5-fluoro-3-(4-methoxyphenyl)-1H-
5 quinolin-4-one

Brown powder (ethyl acetate-n-hexane)

Melting point 150-152°C

¹H-NMR (DMSO-d₆) δppm:

0.34-0.38 (2H, m), 0.57-0.64 (2H, m), 1.27-1.39 (4H, m), 3.75 (3H,
10 s), 3.92 (2H, d, J=7.2Hz), 4.60 (2H, q, J=6.8 Hz), 6.91-6.99 (3H,
m), 7.17 (1H, dd, J=4.5 Hz, J=8.9 Hz), 7.60 (2H, d, J=8.7 Hz),
7.98 (1H, s)

Example 67

15 5-Fluoro-3-(4-methoxyphenyl)-2-methyl-8-propoxy-1H-quinolin-4-one

5-Fluoro-3-iodo-2-methyl-8-propoxy-1H-quinolin-4-one

(400 mg, 1.11 mmol), 4-methoxyphenyl boronic acid (504 mg, 3.3
mmol), 1,1'-bis(diphenylphosphino)ferrocene dichloro palladium
(II)-dichloro methane complex (PdCl₂(DPPF)) (100 mg, 0.12 mmol)
20 and a 2N sodium carbonate aqueous solution (1 ml) were added to
1,2-dimethoxyethane (3 ml), and the mixture was heated at 170°C
for 10 minutes (microwave reactor). The reaction mixture was
cooled to room temperature, and filtration with Celite was
carried out. The filtrate was extracted with dichloromethane, and
25 washed with water. The organic layer was dried over anhydrous
magnesium sulfate, and then concentrated under reduced pressure.
The residue was then purified by silica gel column chromatography
(dichloromethane : methanol = 100 : 0 → 40 : 1). The purified
product was concentrated under reduced pressure, and the residue
30 was recrystallized from ethyl acetate to thereby obtain 230 mg of
powdery white 5-fluoro-3-(4-methoxyphenyl)-2-methyl-8-propoxy-1H-
quinolin-4-one (yield: 61%).

Melting point 211-212°C

¹H-NMR (DMSO-d₆) δppm:

35 0.98 (3H, t, J=7.3 Hz), 1.79-1.90 (2H, m), 2.23 (3H, s), 3.76 (3H,

s), 4.10 (2H, t, J=6.5 Hz), 6.93-6.95 (2H, m), 7.07-7.09 (2H, m),
7.72-7.73 (1H, m), 7.83 (1H, s), 10.50 (1H, brs)

The compounds of the following Examples 68 to 85 were
5 prepared in the same manner as the above Example 67, using
corresponding starting materials.

Example 68

5-Fluoro-2-methyl-8-propoxy-3-pyridin-3-yl-1H-quinolin-4-one

10 White powder (ethyl acetate)

Melting point 190-192°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.5 Hz), 1.77-1.89 (2H, m), 2.27 (3H, s), 4.12 (2H,
t, J=6.7 Hz), 6.85-6.93 (1H, m), 7.16-7.21 (1H, m), 7.38-7.43 (1H,
15 m), 7.63-7.67 (1H, m). 8.40-8.50 (2H, m), 10.70 (1H, brs)

Example 69

5-Fluoro-2-methyl-8-propoxy-3-pyridin-4-yl-1H-quinolin-4-one

White powder (ethyl acetate)

20 Melting point 265-266°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.5 Hz), 1.78-1.92 (2H, m), 2.28 (3H, s), 4.12 (2H,
t, J=6.8 Hz), 6.86-6.94 (1H, m), 7.17-7.21 (1H, m), 7.25 (2H, d,
J=6.0 Hz), 8.55 (2H, d, J=6.0 Hz), 10.72 (1H, brs)

25

Example 70

5-Fluoro-2-methyl-8-propoxy-3-(4-trifluoromethoxyphenyl)-1H-
quinolin-4-one

Pale yellow powder (ethyl acetate)

30 Melting point 167-168°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.3 Hz), 1.78-1.92 (2H, m), 2.25 (3H, s), 4.10 (2H,
t, J=6.6 Hz), 6.83-6.92 (1H, m), 7.15-7.20 (1H, m), 7.31-7.38 (4H,
m), 10.64 (1H, brs)

35

Example 71

3-(4-Ethylphenyl)-5-fluoro-2-methyl-8-propoxy-1H-quinolin-4-one

Pale red powder (ethyl acetate)

Melting point 221-222°C

5 ¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.3 Hz), 1.18 (3H, t, J=7.5 Hz), 1.80-1.89 (2H, m),
2.23 (3H, s), 2.58 (2H, q, J=7.5 Hz), 4.10 (2H, t, J=6.6 Hz),
6.82-6.89 (1H, m), 7.08-7.22 (5H, m), 10.53 (1H, brs)

10 Example 72

5-Fluoro-2-methyl-8-propoxy-3-thiophen-2-yl-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 233-234°C

¹H-NMR (DMSO-d₆) δppm:

15 0.98 (3H, t, J=7.3 Hz), 1.77-1.89 (2H, m), 2.46 (3H, s), 4.11 (2H,
t, J=6.8 Hz), 6.86-7.20 (4H, m), 7.52-7.55 (1H, m), 10.70 (1H,
brs)

Example 73

20 3-(4-Dimethylaminophenyl)-5-fluoro-2-methyl-8-propoxy-1H-
quinolin-4-one

White powder (ethyl acetate)

Melting point 255-257°C

¹H-NMR (DMSO-d₆) δppm:

25 1.00 (3H, t, J=7.5 Hz), 1.80-1.90 (2H, m), 2.26 (3H, s), 2.91 (6H,
s), 4.11 (2H, t, J=6.6 Hz), 6.72 (2H, d, J=8.7 Hz), 6.80-6.89 (1H,
m), 7.00 (2H, d, J=8.7 Hz), 7.11-7.17 (1H, m), 10.45 (1H, brs)

Example 74

30 5-Fluoro-3-(4-fluorophenyl)-2-methyl-8-propoxy-1H-quinolin-4-one
Pale brown powder (ethyl acetate)

Melting point 196-197°C

¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.80-1.91 (2H, m), 2.25 (3H, s), 4.12 (2H,
35 t, 6.8 Hz), 6.84-6.92 (1H, m), 7.15-7.29 (5H, m), 10.06 (1H, brs)

Example 75

3-(2,4-Dimethoxyphenyl)-5-fluoro-2-methyl-8-propoxy-1H-quinolin-4-one

5 Pale brown powder (ethyl acetate)

Melting point 100-101°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.5 Hz), 1.80-1.86 (2H, m), 2.11 (3H, s), 3.65 (3H, s), 3.78 (3H, s), 4.10 (2H, t, J=6.8 Hz), 6.51-6.59 (2H, m),
10 6.80-6.94 (2H, m), 7.11-7.17 (1H, m), 10.47 (1H, brs)

Example 76

5-Fluoro-3-furan-2-yl-2-methyl-8-propoxy-1H-quinolin-4-one

Pale brown powder (ethyl acetate)

15 Melting point 203-204°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.5 Hz), 1.78-1.89 (2H, m), 2.47 (3H, s), 4.10 (2H, t, J=6.8 Hz), 6.52-6.54 (1H, m), 6.67-6.69 (1H, m), 6.86-6.95 (1H, m), 7.15-7.20 (1H, m), 7.67-7.68 (1H, m), 10.66 (1H, m)

20

Example 77

5-Fluoro-3-(4-methoxyphenyl)-8-propoxy-2-trifluoromethyl-1H-quinolin-4-one

White powder (n-hexane-ethyl acetate)

25 Melting point 170-171°C

¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.76-1.90 (2H, m), 3.80 (3H, s), 4.11 (2H, t, J=6.5 Hz), 6.98 (2H, d, J=8.7 Hz), 7.15-7.25 (4H, m), 10.11 (1H, brs)

30

Example 78

5-Fluoro-3-furan-2-yl-8-propoxy-2-trifluoromethyl-1H-quinolin-4-one

Pale yellow powder (n-hexane-ethyl acetate)

35 Melting point 134-136°C

¹H-NMR (DMSO-d₆) δppm:

0.99 (3H, t, J=7.5 Hz), 1.76-1.90 (2H, m), 4.11 (2H, t, J=6.6 Hz),
6.59-6.65 (2H, m), 7.21-7.33 (2H, m), 7.81 (1H, m), 10.08 (1H,
brs)

5

Example 79

3-(4-Dimethylaminophenyl)-5-fluoro-8-propoxy-2-trifluoromethyl-
1H-quinolin-4-one

Pale yellow powder (n-hexane-ethyl acetate)

10 Melting point 176-177°C

¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.4 Hz), 1.76-1.91 (2H, m), 2.94 (6H, s), 4.11 (2H,
t, J=6.6 Hz), 6.75 (2H, d, J=8.8 Hz), 7.03 (2H, d, J=8.8 Hz),
7.21-7.24 (2H, m), 10.00 (1H, brs)

15

Example 80

3-(4-Ethylphenyl)-5-fluoro-8-propoxy-2-trifluoromethyl-1H-
quinolin-4-one

White powder (n-hexane-ethyl acetate)

20 Melting point 187-188°C

¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.20 (3H, t, J=7.5 Hz), 1.77-1.91 (2H, m),
2.62-2.71 (2H, q, J=7.5 Hz), 4.12 (2H, t, J=6.6 Hz), 7.13-7.29
(6H, m), 10.23 (1H, brs)

25

Example 81

5-Fluoro-3-(4-fluorophenyl)-8-propoxy-2-trifluoromethyl-1H-
quinolin-4-one

Brown powder (n-hexane-ethyl acetate)

30 Melting point 154-155°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.3 Hz), 1.81-1.89 (2H, m), 4.13 (2H, t, J=6.5 Hz),
7.10-7.31 (4H, m), 7.80-7.86 (1H, m), 8.08 (1H, s), 10.24 (1H,
brs)

35

Example 82

5-Fluoro-8-propoxy-3-(4-trifluoromethoxyphenyl)-2-trifluoromethyl-1H-quinolin-4-one

Pale red powder (n-hexane-ethyl acetate)

5 Melting point 143-144°C

¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.77-1.91 (2H, m), 4.12 (2H, t, J=6.6 Hz), 7.19-7.54 (6H, m), 10.44 (1H, brs)

10 Example 83

5-Fluoro-2-isopropyl-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate-n-hexane)

Melting point 195-197°C

15 ¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.16 (6H, d, J=7.0 Hz), 1.78-1.92 (2H, m), 2.86-2.97 (1H, m), 3.77 (3H, s), 4.13 (2H, t, J=6.4 Hz), 6.84-7.22 (6H, m), 8.98 (1H, brs)

20 Example 84

5-Fluoro-3-furan-2-yl-2-isopropyl-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate-n-hexane)

Melting point 113-114°C

¹H-NMR (DMSO-d₆) δppm:

25 0.99 (3H, t, J=7.5 Hz), 1.21(6H, d, J=7.0 Hz), 1.80-1.89 (2H, m), 3.11-3.16 (1H, m), 4.12 (2H, t, J=6.4 Hz), 6.48-6.54 (2H, m), 6.90-6.98 (1H, m), 7.20-7.25 (1H, m), 7.69-7.70 (1H, m), 9.29 (1H, brs)

30 Example 85

5-Fluoro-8-propoxy-3-thiophen-2-yl-2-trifluoromethyl-1H-quinolin-4-one

Pale yellow powder (ethyl acetate-n-hexane)

Melting point 149-150°C

35 ¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.4 Hz), 1.76-1.90 (2H, m), 4.11 (2H, t, 6.4 Hz),
7.10-7.30 (4H, m), 7.72-7.75 (1H, m), 10.52 (1H, brs)

Example 86

5 5-Fluoro-8-furan-2-yl-3-(4-methoxyphenyl)-1H-quinolin-4-one
8-bromo-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one
(150 mg, 0.43 mmol), 2-furan boronic acid (145 mg, 1.3 mmol),
1,1'-bis(diphenylphosphino)ferrocene dichloro palladium (II)-
dichloromethane complex (PdCl₂(DPPF)) (35 mg, 0.04 mmol) and a 2N
10 sodium carbonate aqueous solution (1 ml) were added to 1,2-
dimethoxyethane (3 ml), and the mixture was heated at 180°C for 10
minutes (microwave reactor). After the reaction mixture was
cooled to room temperature, dichloromethane was added, and then
filtration with Celite was carried out. The filtrate was
15 extracted with dichloromethane and washed with water. The organic
layer was dried over anhydrous magnesium sulfate, and then
concentrated under reduced pressure. The residue was then
purified by silica gel column chromatography (dichloromethane).
The purified product was concentrated under reduced pressure, and
20 the residue was recrystallized from n-hexane-ethyl acetate to
thereby obtain 100 mg of powdery slightly orange 5-fluoro-8-
furan-2-yl-3-(4-methoxyphenyl)-1H-quinolin-4-one (yield: 70%).

Melting point 209-211°C

¹H-NMR (DMSO-d₆) δppm:

25 3.79 (3H, s), 6.74-6.77 (1H, m), 6.96-7.00 (3H, m), 7.07-7.15 (1H,
m), 7.55-7.59 (2H, m), 7.81-7.93 (3H, m), 11.00 (1H, brs)

The compounds of the following Examples 87 and 88 were
prepared in the same manner as the above Example 86, using
30 corresponding starting materials.

Example 87

5-Fluoro-3-(4-methoxyphenyl)-8-thiophen-3-yl-1H-quinolin-4-one
Pale yellow powder (ethyl acetate)

35 Melting point 183-184°C

¹H-NMR (DMSO-d₆) δppm:

3.76 (3H, s), 6.93-7.09 (3H, m), 7.30-7.32 (1H, m), 7.49-7.54 (3H, m), 7.76-7.80 (3H, m), 10.64 (1H, brs)

5 Example 88

8-Benzo[b]thiophen-2-yl-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale yellow powder (ethyl acetate)

Melting point 276-277°C

10 ¹H-NMR (DMSO-d₆) δppm:

3.76 (3H, s), 6.84-6.92 (3H, m), 7.30-7.40 (2H, m), 7.62-7.66 (2H, m), 7.84-7.99 (5H, m), 11.03 (1H, brs)

Example 89

15 4-(5-Fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)benzoic acid

Methyl 4-(5-fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)benzoate (330 mg, 0.93 mmol) was suspended in a mixed solvent of ethanol (3 ml) and THF (3 ml). A 1.24N lithium hydroxide aqueous solution (2 ml) was added, and the mixture was stirred at room temperature for 3 hours. Water was added to the reaction mixture, and then the resulting mixture was extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and concentrated to dryness under reduced pressure to thereby obtain 300 mg of powdery white 4-(5-fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl)benzoic acid (yield: 95%).

¹H-NMR (DMSO-d₆) δppm:

1.01-1.07(3H, t, J=7.3 Hz), 1.80-1.91(2H, m), 4.09-4.14(2H, t, J=6.4 Hz), 6.85-7.24(3H, m), 7.75-7.78(2H, m), 7.92-7.95(2H, m), 11.51(1H, brs), 12.84(1H, brs)

Example 90

5-Fluoro-3-[4-(morpholine-4-carbonyl)phenyl]-8-propoxy-1H-quinolin-4-one

35 4-(5-Fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-

yl)benzoic acid (260 mg, 0.76 mmol), morpholine (99.5 mg, 1.14 mmol), WSC (189 mg, 0.99 mmol) and HOBT (151 mg, 0.99 mmol) were added to DMF (10 ml), and the mixture was stirred at room temperature for 15 hours. The reaction mixture was concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (dichloromethane : methanol = 30 : 1). The purified product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to thereby obtain 80 mg of powdery white 5-fluoro-3-[4-(morpholine-4-carbonyl)phenyl]-8-propoxy-1H-quinolin-4-one (yield: 26%).

Melting point 234-236°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.4 Hz), 1.80-1.89 (2H, m), 3.40-3.60 (8H, m), 4.09 (2H, t, J=6.5 Hz), 6.89-6.98 (1H, m), 7.16-7.21 (1H, m), 7.41 (2H, d, J=8.3 Hz), 7.69 (2H, d, J=8.3 Hz), 7.91 (1H, s), 11.41 (1H, brs)

Example 91

5-Fluoro-3-(4-methoxyphenyl)-1-methyl-8-propoxy-1H-quinolin-4-one
Sodium hydride (60% in oil, 76 mg, 1.9 mmol) was added to a DMF solution (10 ml) of 5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one (400 mg, 1.22 mmol). The mixture was stirred at room temperature for 15 minutes. Methyl iodide (225 mg, 1.6 mmol) was added thereto, and then the resulting mixture was stirred at room temperature for 19 hours. Water and ethyl acetate were added to the reaction mixture to separate the mixture into two layers. The organic layer was washed with water, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (n-hexane : ethyl acetate = 1 : 1). The purified product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to thereby obtain 365 mg of powdery pale yellow 5-fluoro-3-(4-methoxyphenyl)-1-methyl-8-propoxy-1H-quinolin-4-one (yield: 72%).

Melting point 147-148°C

¹H-NMR (DMSO-d₆) δppm:

0.98 (3H, t, J=7.5 Hz), 1.77 (2H, m), 3.76 (3H, s), 3.98 (2H, t, J=6.4 Hz), 4.08 (3H, s), 6.91-7.01 (3H, m), 7.19-7.24 (1H, m),
5 7.57-7.61 (2H, m), 7.96 (1H, s)

The compounds of the following Examples 92 to 94 were prepared in the same manner as the above Example 91, using corresponding starting materials.

10

Example 92

1-Ethyl-5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 123-125°C

15 ¹H-NMR (DMSO-d₆) δppm:

1.00 (3H, t, J=7.3 Hz), 1.29 (3H, t, J=6.8 Hz), 1.79-1.88 (2H, m),
3.76 (3H, s), 4.03 (2H, t, J=6.5 Hz), 4.52 (2H, q, J=6.8 Hz),
6.91-7.02 (3H, m), 7.22-7.27 (1H, m), 7.60 (2H, d, J=8.7 Hz),
8.00 (1H, s)

20

Example 93

1-(2-Ethoxyethyl)-5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

White powder (ethyl acetate)

25 Melting point 108-109°C

¹H-NMR (DMSO-d₆) δppm:

0.96-1.09 (6H, m), 1.77-1.89 (2H, m), 3.65 (2H, t, J=5.0 Hz),
3.78 (3H, s), 4.02 (2H, t, J=6.8 Hz), 4.72 (2H, t, J=5.0 Hz),
6.94-7.04 (3H, m), 7.23-7.29 (1H, m), 7.57 (2H, d, J=8.7 Hz),
30 7.93 (1H, s)

Example 94

1-Cyclopropylmethyl-5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

35 Pale yellow powder (n-hexane)

Melting point 60-62°C

¹H-NMR (DMSO-d₆) δppm:

0.36-0.51 (4H, m), 1.07(3H, t, J=7.4 Hz), 1.26-1.30 (1H, m),
1.86-1.94 (2H, m), 4.09 (2H, t, J=6.5 Hz), 6.96-7.08 (3H, m),
5 7.28-7.33 (1H, m), 7.61-7.66 (2H, m), 8.05 (1H, s)

Example 95

5-Fluoro-3-(4-hydroxyphenyl)-8-propoxy-1H-quinolin-4-one

A dichloromethane solution (5 ml) of 5-fluoro-3-(4-
10 methoxyphenyl)-8-propoxy-1H-quinolin-4-one (249 mg, 0.76 mmol)
was cooled to -10°C in a methanol-ice bath. A 1N boron tribromide
(4.08 ml) was added thereto, and the mixture was stirred at room
temperature for 6 hours. Ice water and dichloromethane were added
to the reaction mixture, and the resultant insoluble matter was
15 collected by filtration. The filtrate was separated and the
organic layer was concentrated under reduced pressure. The
residue and the substance remaining on the filter were mixed, and
the mixture was purified by silica gel column chromatography
(dichloromethane : methanol = 60 : 1 → 25 : 1). The purified
20 product was concentrated under reduced pressure. Ethyl acetate
was added to crystallize the residue. The crystals were collected
by filtration, washed with ethyl acetate, and then dried to
thereby obtain 220 mg of powdery pale yellow 5-fluoro-3-(4-
hydroxyphenyl)-8-propoxy-1H-quinolin-4-one (yield: 92%).

25 Melting point 271-272°C

¹H-NMR (DMSO-d₆) δppm:

1.03 (3H, t, J=7.3 Hz), 1.78-1.87 (2H, m), 4.08 (2H, t, J=6.4 Hz),
6.77 (2H, d, J=8.6 Hz), 6.87 (1H, dd, J=8.8 Hz, J=12.1Hz), 7.12
(1H, dd, J=3.9 Hz, J=8.8 Hz), 7.41 (2H, d, J=8.6 Hz), 7.77 (1H,
30 s), 9.43 (1H, brs), 11.20 (1H, brs)

Example 96

5-Fluoro-8-hydroxy-3-(4-hydroxyphenyl)-1H-quinolin-4-one

5-Fluoro-8-methoxy-3-(4-methoxyphenyl)-1H-quinolin-4-
35 one (1.0 g, 3.34 mmol) was suspended in dichloromethane (40 ml),

and the suspension was cooled to -10°C in a methanol-ice bath. A 1N boron tribromide (17 ml) was added thereto, and the resulting mixture was stirred at room temperature for 15 hours. Ice water and dichloromethane were added to the reaction mixture, and the
5 resultant insoluble matter was collected by filtration. The substance remaining on the filter was washed with water, dried and purified by silica gel column chromatography (dichloromethane : methanol = 20 : 1 $\rightarrow$ 8 : 1 $\rightarrow$ ethyl acetate : methanol = 4 : 1). The purified product was concentrated under
10 reduced pressure and ethyl acetate was then added to crystallize the residue. The crystals were collected by filtration, washed with ethyl acetate, and dried to thereby obtain 360 mg of powdery pale gray 5-fluoro-8-hydroxy-3-(4-hydroxyphenyl)-1H-quinolin-4-one (yield: 40%).
15 Melting point $303-305^{\circ}\text{C}$ (decomposition)
 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ ppm:
6.74-6.82 (3H, m), 6.94 (1H, dd, $J=4.1\text{ Hz}$, $J=8.5\text{ Hz}$), 7.41 (2H, d, $J=8.3\text{ Hz}$), 7.74 (1H, s), 9.46 (1H, brs), 10.70 (1H, brs),
11.32 (1H, brs)

20

Example 97

5-Fluoro-3-(4-hydroxy-2-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

Aluminum chloride (108 mg, 0.81 mmol) was added to a
25 dichloromethane solution (5 ml) of 5-fluoro-3-(4-isopropoxy-2-methoxyphenyl)-8-propoxy-1H-quinolin-4-one (120 mg, 0.31 mmol). The mixture was stirred at room temperature for 1 hour. Water and dichloromethane were added to the reaction mixture, and separated. The organic layer was then washed with water. The washed organic
30 layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (dichloromethane : methanol = 10 : 1). The purified product was concentrated under reduced pressure, and the residue was recrystallized from ethyl
35 acetate to thereby obtain 100 mg of powdery white 5-fluoro-3-(4-

hydroxy-2-methoxyphenyl)-8-propoxy-1H-quinolin-4-one (yield: 90%).

Melting point 251-253°C

¹H-NMR (DMSO-d₆) δppm:

1.01-1.07(3H, t, J=7.4 Hz), 1.77-1.88(2H, m), 3.63(3H, s), 4.07-
5 4.12(2H, t, J=6.6 Hz), 6.33-6.43(2H, m), 6.84-6.90(1H, m), 7.02-
7.11(2H, m), 7.61-7.64(1H, m), 9.39(1H, s), 11.07(1H, brs)

The compound of the following Example 98 was prepared
in the same manner as the above Example 97, using corresponding
10 starting materials.

Example 98

5-Fluoro-3-(2-hydroxy-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-
one

15 White powder (ethyl acetate)

Melting point 208-209°C

¹H-NMR (DMSO-d₆) δppm:

1.02 (3H, t, J=7.5 Hz), 1.81-1.90 (2H, m), 3.73 (3H, s), 4.11 (2H,
t, J=6.5 Hz), 6.43-6.51 (2H, m), 6.98-7.06 (1H, m), 7.16-7.25 (2H,
20 m), 7.95 (1H, s), 10.23 (1H, s), 11.93 (1H, brs)

Example 99

5-Fluoro-8-hydroxy-3-(4-methoxyphenyl)-1H-quinolin-4-one

2N Hydrochloric acid (6.0 ml) was added to an ethanol
25 solution (18 ml) of 5-fluoro-8-methoxymethoxy-3-(4-
methoxyphenyl)-1H-quinolin-4-one (350 mg, 1.06 mmol). The mixture
was stirred at 55°C for 1 hour. The stirred mixture was cooled to
room temperature, and 1N sodium hydrate (11.6 ml) was added
thereto to obtain a pH of 3 to 4. The mixture in which pH was
30 adjusted was concentrated under reduced pressure, and the residue
was then purified by silica gel column chromatography
(dichloromethane : methanol = 50 : 1 → 20 : 1). The purified
product was concentrated under reduced pressure, and the residue
was crystallized from ethanol, collected by filtration, washed
35 with ethanol, and dried to thereby obtain 165 mg of powdery pale

dark brown 5-fluoro-8-hydroxy-3-(4-methoxyphenyl)-1H-quinolin-4-one (yield: 54%).

Melting point 270-272°C

¹H-NMR (DMSO-d₆) δppm:

- 5 3.75 (3H, s), 6.79 (1H, dd, J=8.5 Hz, J= 12.1Hz), 6.90-6.97 (3H, m), 7.53 (2H, d, J=8.6 Hz), 7.77 (1H, s), 10.60 (1H, brs), 11.40 (1H, brs)

Example 100

- 10 5-Fluoro-3-(2-hydroxymethylthiophen-3-yl)-8-propoxy-1H-quinolin-4-one

- 3-(5-Fluoro-4-oxo-8-propoxy-1,4-dihydroquinolin-3-yl) thiophene-2-carbaldehyde (120 mg, 0.39 mmol) was suspended in ethanol (5 ml), and sodium borohydride (19.24 mg) was added to
15 the suspension. The resulting mixture was stirred at room temperature for 1 hour. Dichloromethane was added to the reaction mixture, which was washed with water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was then purified by silica gel column
20 chromatography (dichloromethane : methanol = 30 : 1). The purified product was concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate to thereby obtain 110 mg of powdery white 5-fluoro-3-(2-hydroxymethylthiophen-3-yl)-8-propoxy-1H-quinolin-4-one (yield: 82%).

- 25 Melting point 181-184°C

¹H-NMR (DMSO-d₆) δppm:

- 1.01 (3H, t, J=7.3 Hz), 1.79-1.88 (2H, m), 4.07 (2H, t, J=6.4 Hz), 4.47 (2H, d, J=5.4 Hz), 5.48 (1H, t, J=5.4 Hz), 6.87-6.96 (1H, m), 7.11-7.19 (2H, m), 7.39-7.40 (1H, m), 7.88 (1H, s), 11.36 (1H,
30 brs)

Example 101

5-Fluoro-8-(3-hydroxypropoxy)-3-(4-methoxyphenyl)-1H-quinolin-4-one

- 35 8-(3-Benzoyloxypropoxy)-5-fluoro-3-(4-methoxyphenyl)-1H-

quinolin-4-one (1.95 g, 4.49 mmol) and a 10% palladium carbon (720 mg) were added to ethanol (50 ml). The mixture was stirred at 50°C for 7.5 hours under a hydrogen atmosphere (1 atmosphere) and subjected to a catalytic reduction. The reaction mixture was cooled to room temperature, and filtration with Celite was conducted to remove the solvent. The filtrate was concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (dichloromethane : methanol = 80 : 1 → 20 : 1). The purified product was concentrated under reduced pressure, and the residue was concentrated to dryness to thereby obtain 820 mg of pale dark brown amorphous solid 5-fluoro-8-(3-hydroxypropoxy)-3-(4-methoxyphenyl)-1H-quinolin-4-one (yield: 53%).

¹H-NMR (DMSO-d₆) δppm:

1.92-2.02 (2H, m), 3.65 (2H, t, J=5.9 Hz), 4.20 (2H, t, J=6.2Hz), 4.59 (1H, brs), 6.84-6.95 (3H, m), 7.14 (1H, dd, J=3.9 Hz, J= 8.8 Hz), 7.55 (2H, d, J=8.7 Hz), 7.80 (1H, s), 11.27 (1H, brs)

The compound of the following Example 102 was prepared in the same manner as the above Example 101, using corresponding starting materials.

Example 102

5-Fluoro-8-(2-hydroxypropoxy)-3-(4-methoxyphenyl)-1H-quinolin-4-one

White powder (ethyl acetate)

Melting point 216-218°C

¹H-NMR (DMSO-d₆) δppm:

1.19 (3H, d, J=6.2Hz), 3.76 (3H, s), 3.82-4.12 (3H, m), 5.25 (1H, brs), 6.84-6.96 (3H, m), 7.12 (1H, dd, J=3.9 Hz, J= 8.8 Hz), 7.56 (2H, d, J=8.8 Hz), 7.86 (1H, s), 11.20 (1H, brs)

The compounds of the following Examples 103 and 104 were prepared in the same manner as the above Example 1, using corresponding starting materials.

Example 103

5-Chloro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one

Pale brown powder (ethyl acetate)

5 Melting point 194-196°C

¹H-NMR (DMSO-d₆) δppm:

1.03 (3H, t, J=7.3 Hz), 1.80-1.87 (2H, m), 3.76 (3H, s), 4.11 (2H, t, J=6.4 Hz), 6.93 (2H, d, J=8.6 Hz), 7.12 (1H, d, J=8.5 Hz), 7.17 (1H, d, J=8.5 Hz), 7.54 (2H, d, J=8.6 Hz), 7.80 (1H, s),
10 11.23 (1H, brs)

Example 104

5-Bromo-8-cyclopentyloxy-3-(4-methoxyphenyl)-1H-quinolin-4-one

Pale brown powder (ethanol)

15 Melting point 213-215°C

¹H-NMR (DMSO-d₆) δppm:

1.59-1.70 (2H, m), 1.71-2.00 (6H, m), 3.75 (3H, s), 4.97-5.00 (1H, m), 6.94 (2H, d, J=8.7Hz), 7.04 (1H, d, J=8.5 Hz), 7.40 (1H, d, J=8.4 Hz), 7.53 (2H, d, J=8.7 Hz), 7.81 (1H, s), 11.20 (1H, brs)
20

Pharmacological Test 1

Evaluation of improvement of mitochondrial dysfunction using human neuroblastoma cell lines SH-SY5Y treated with 1-methyl-4-phenylpyridinium (MPP⁺)

25 In human neuroblastoma cell lines SH-SY5Y in which mitochondrial activity was injured by MPP⁺ treatment (Bollimuntha S. et al., J Biol Chem, 280, 2132-2140 (2005) and Shang T. et al., J Biol Chem, 280, 34644-34653 (2005)), improvement of the mitochondrial dysfunction was evaluated on the basis of the
30 measurement value of the mitochondrial oxidation reduction activity using Alamar Blue fluorescent dye after the compound addition (Nakai M. et al, Exp Neurol, 179, 103-110 (2003)).

The human neuroblastoma cell lines SH-SY5Y were cultured in Dulbecco's Modified Eagle's Medium containing 10%
35 fetal bovine serum (DMEM containing 50 units/ml penicillin and 50

µg/ml streptomycin as antibiotics) at 37°C in the presence of 5% carbon dioxide. Cells were scattered on a poly-D-lysine-coated 96-well black plate at a concentration of $3-6 \times 10^4$ cells/cm² (medium amount: 100 µl/well), and cultured in the above medium
5 for two days. Further, the medium was changed to a DMEM containing a 1% N2 supplement (N2-DMEM) or to a medium (100 µl/well) in which 1.5 mM MPP⁺ was dissolved. The cells were cultured therein for 39 to 48 hours, and then subjected to a
10 mitochondrial oxidation reduction activity measurement system. A sample compound that had been previously dissolved in dimethyl sulfoxide (DMSO) was diluted with N2-DMEM, and added in a volume of 10 µl/well 24 hours before the activity measurement (final compound concentration: 0.01 to 1 µg/ml).

After removal of the medium by suction, a balanced salt
15 solution containing 10% Alamar Blue (154 mM sodium chloride, 5.6 mM potassium chloride, 2.3 mM calcium chloride, 1.0 mM magnesium chloride, 3.6 mM sodium bicarbonate, 5 mM glucose, 5 mM HEPES, pH 7.2) was added in a volume of 100 µl/well, and reacted in an incubator at 37°C for 1 hour. The fluorescent intensity was
20 detected using a fluorescence detector (a product of Hamamatsu Photonics K.K., excitation wavelength 530 nm, measurement wavelength 580 nm) to thereby measure the mitochondrial oxidation reduction activity.

The fluorescent intensity of the well of the cells
25 cultured in a medium containing MPP⁺ and in each of the sample compounds was relatively evaluated based on a 100% fluorescent intensity of the well of the cells cultured in a medium containing DMSO alone (final concentration: 0.1%). When the MPP⁺-induced cell groups exhibited higher fluorescent intensity than
30 the cell groups cultured in DMSO alone, the test compound was judged to have the improved activity of the mitochondrial dysfunction.

Table 1

Evaluation of improvement of mitochondrial dysfunction using human neuroblastoma cell lines SH-SY5Y treated with 1-methyl-4-phenylpyridinium (MPP⁺)

5

Test Compound Concentration ($\mu\text{g/ml}$)	Fluorescence Intensity (%)					
	0	0.01	0.03	0.1	0.3	1
Compound of Example 1	50	51	62	70	66	64
Compound of Example 3	51	54	63	70	78	74
Compound of Example 4	47	56	61	70	72	59
Compound of Example 6	53	59	71	85	88	83
Compound of Example 21	46	52	59	63	74	57
Compound of Example 24	54	60	70	82	78	84
Compound of Example 25	41	46	56	66	50	24
Compound of Example 30	46	50	54	69	64	56
Compound of Example 31	38	45	45	57	59	48
Compound of Example 34	60	69	74	77	78	87
Compound of Example 35	63	75	88	99	95	65
Compound of Example 36	59	63	65	74	71	91
Compound of Example 37	57	64	73	78	70	61
Compound of Example 38	54	66	67	86	81	78
Compound of Example 40	53	60	64	76	70	72
Compound of Example 47	49	51	58	71	73	82
Compound of Example 53	48	53	56	67	60	67
Compound of Example 59	50	53	56	67	66	54
Compound of Example 61	61	70	65	85	80	86

Table 1 (continued)

Test Compound Concentration ($\mu\text{g/ml}$)	Fluorescence Intensity (%)					
	0	0.01	0.03	0.1	0.3	1
Compound of Example 62	55	66	62	79	84	80
Compound of Example 63	56	58	65	74	75	85
Compound of Example 64	56	55	65	74	72	77
Compound of Example 66	57	66	72	83	77	60
Compound of Example 70	53	56	57	67	71	63
Compound of Example 71	50	56	61	73	78	72
Compound of Example 86	46	52	59	68	61	39
Compound of Example 87	58	63	66	79	63	51
Compound of Example 91	55	65	69	81	82	83
Compound of Example 92	55	63	75	77	69	55
Compound of Example 93	58	66	79	86	80	69
Compound of Example 94	51	56	67	69	59	41
Compound of Example 100	53	56	56	71	73	84

Pharmacological Test 2

- 5 Evaluation of dopaminergic neuronal protective activity using C57BL/6 mouse treated with 1-methyl-4-phenyl 1,2,3,6-tetrahydro pyridine (MPTP)

Using a mouse having MPTP-injured dopaminergic neurons (Chan P. et al., J Neurochem, 57,348-351 (1991)), the dopamine
10 neuroprotective activity was evaluated based on dopamine contents and protein levels of tyrosine hydroxylase (TH) and dopamine transporter (DAT) (i.e., dopaminergic neuronal marker proteins) in the brain corpus striatum region after the compound administration (Mori A. et al., Neurosci Res, 51, 265-274(2005)).

15 A male C57BL/6 mouse (provided by Japan Charles River

Inc., 10 to 12 weeks) was used as a test animal. MPTP was dissolved in a physiological salt solution so that the concentration became 4 mg/ml, and then administered to the mouse subcutaneously in a volume of 10 ml/kg. The test compound was
5 suspended in a 5% gum arabic/physiological salt solution (w/v) so that a compound having a concentration of 1 mg/ml could be obtained. Each of the test compounds or solvents thereof was orally administered to the mouse after 30 minutes, 24 hours, and 48 hours of the MPTP administration. The mouse was decapitated
10 after 72 hours of the MPTP administration, the brain was removed, and each side of the striatum was dissected.

The left striatum was used as a sample to detect the protein level by Western blot analysis. Each tissue was homogenized in a HEPES buffer sucrose solution (0.32 M sucrose, 4
15 μ g/ml pepstatin, 5 μ g/ml aprotinin, 20 μ g/ml trypsin inhibitor, 4 μ g/ml leupeptin, 0.2 mM phenylmethanesulfonyl fluoride, 2 mM ethylenediaminetetraacetic acid (EDTA), 2 mM ethylene glycol bis (β aminoethyl ether) tetraacetic acid, 20 mM HEPES, pH 7.2), and assayed for protein using a bicinchoninic acid kit for protein
20 assay (provided by Pierce Corporation). Each homogenized sample, having an equal amount of protein which had been dissolved in a Laemmli sample buffer solution, was subjected to electrophoresis through sodium dodecyl sulfurate polyacrylamide gels. The protein separated by electrophoresis was electrically transferred to
25 polyvinylidene fluoride membranes. The membranes were reacted with specific primary antibody for TH, DAT, and housekeeping proteins, i.e., the α 1 subunit of Na^+/K^+ -ATPase and actin (Na^+/K^+ -ATPase, a product of UpState Biotechnology Inc.; others are products of Chemi-Con Corporation). Subsequently, a horseradish
30 peroxidase-labeled secondary antibody (a product of Amersham K.K.) for each primary antibody was fixed, and the chemiluminescence associated with enzyme activity of peroxidase was detected using X-ray film. The density of the protein band on the film was analyzed using a densitometer (a product of Bio-rad
35 Laboratories Inc.) to obtain the TH value relative to Na^+/K^+ -

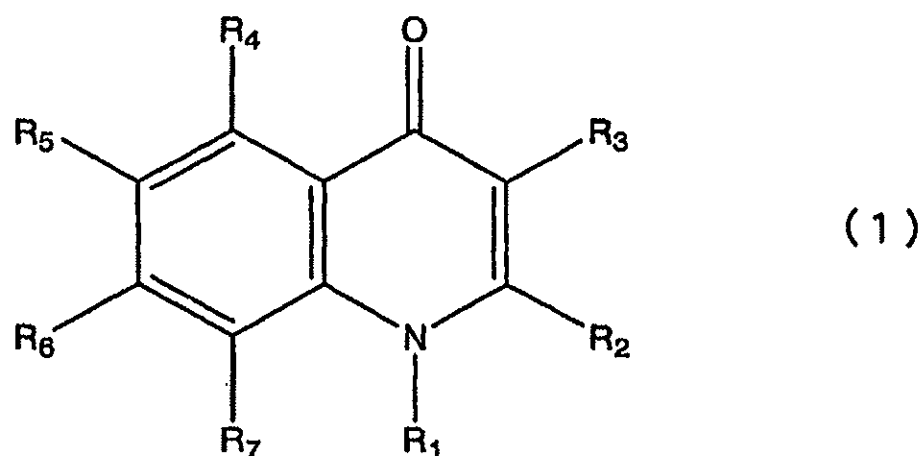
ATPase and the DAT value relative to actin.

The right striatum, the tissue weight of which was measured immediately after dissection, was used as an analysis sample for determining the dopamine content. Each tissue was
5 homogenized in a 0.1 N perchloric acid solution containing isoproterenol as an internal standard substance of the measurement, using an ultrasonic homogenizer while being cooled with ice. The supernatant obtained from 20,000 g of homogenate that had been centrifuged at 4°C for 15 minutes was subjected to a
10 high performance liquid chromatography with a reversed phase column (a product of Eicom Corporation). A mobile phase 15% methanol 0.1 M citric acid/0.1 M sodium acetate buffer solution (containing 190 mg/l 1-sodium octane sulfonate, 5 mg/l EDTA, pH 3.5) was flowed at a rate of 0.5 ml/min, and the dopamine peak of
15 each sample was detected using an electrochemical detector (applied voltage +750 mV vs. Ag/AgCl, a product of Eicom Corporation). With reference to the identified dopamine peak, the dopamine content per tissue weight was calculated in each sample using analysis software (a product of Gilson Inc.).

20 In both analyses, the value of the sample derived from the MPTP-induced mice in which only the test compound or the solvent was administered was expressed relative to the value of the sample derived from the mice without MPTP treatment (100%). Values were analyzed statistically using a nonclinical
25 statistical analysis system. Values of significance probability < 0.05 were defined as statistically significant. In the MPTP-induced mice, when the test drug group showed an increase in protein level compared to the solvent group, and a significant difference was observed between these groups at t-assay, the test
30 drug was judged to have dopamine neuroprotective activity.

Claims

1. A quinolone compound represented by General Formula (1)



or a salt thereof,

wherein R_1 represents a hydrogen atom, a C_1 - C_6 alkyl group, a cyclo C_{3-8} alkyl C_1 - C_6 alkyl group, or a C_1 - C_6 alkoxy C_1 - C_6 alkyl group;

R_2 represents a hydrogen atom, a C_1 - C_6 alkyl group, or a halogen-substituted C_1 - C_6 alkyl group;

R_3 represents a phenyl group, a furyl group, a thienyl group, or a pyridyl group, each of the groups optionally being substituted with one or more groups selected from the group consisting of the following (1) to (16) on the aromatic or heterocyclic ring represented by the above R_3 :

- (1) C_1 - C_6 alkyl groups,
- (2) C_1 - C_6 alkoxy groups,
- (3) halogen-substituted C_1 - C_6 alkoxy groups,
- (4) a phenoxy group,
- (5) C_1 - C_6 alkylthio groups,
- (6) a hydroxy group,
- (7) hydroxy C_1 - C_6 alkyl groups,
- (8) halogen atoms,
- (9) C_1 - C_6 alkanoyl groups,
- (10) C_1 - C_6 alkoxy carbonyl groups,
- (11) amino groups optionally substituted with one or more C_1 - C_6 alkyl groups,
- (12) carbamoyl groups optionally substituted with one or more C_1 - C_6 alkyl groups,
- (13) cyclo C_{3-8} alkyl C_1 - C_6 alkoxy groups,

- (14) pyrrolidinyl carbonyl groups,
- (15) morpholinyl carbonyl groups, and
- (16) a carboxyl group;

R₄ represents a halogen atom;

R₅ represents a hydrogen atom or a halogen atom;

R₆ represents a hydrogen atom; and

R₇ represents any one of groups (1) to (15) below;

- (1) a hydroxy group,
- (2) a halogen atom,
- (3) a C₁-C₆ alkoxy group,
- (4) a halogen-substituted C₁-C₆ alkoxy group,
- (5) a hydroxy C₁-C₆ alkoxy group,
- (6) a C₁-C₆ alkoxy C₁-C₆ alkoxy group,
- (7) an amino group optionally substituted with one or more members selected from the group consisting of C₁-C₆ alkyl groups, C₁-C₆ alkoxy C₁-C₆ alkyl groups, and cyclo C₃₋₈ alkyl groups,
- (8) an amino C₁-C₆ alkoxy group optionally substituted on the amino group with one or more members selected from the group consisting of C₁-C₆ alkyl groups, C₁-C₆ alkanoyl groups, C₁-C₆ alkyl sulfonyl groups, and carbamoyl groups optionally substituted with one or more C₁-C₆ alkyl groups,
- (9) a cyclo C₃₋₈ alkyloxy group,
- (10) a cyclo C₃₋₈ alkyl C₁-C₆ alkoxy group,
- (11) a tetrahydrofuryl C₁-C₆ alkoxy group,
- (12) a C₁-C₆ alkylthio group,
- (13) a heterocyclic group selected from the group consisting of morpholinyl groups, pyrrolidinyl groups, furyl groups, thienyl groups, and benzothienyl groups,
- (14) a phenyl C₁-C₆ alkoxy C₁-C₆ alkoxy group, and
- (15) a pyrrolidinyl carbonyl group.

2. A quinolone compound of General Formula (1) or a salt thereof according to claim 1, wherein R₁ represents a hydrogen atom or a C₁-C₆ alkyl group;

R₂ represents a hydrogen atom or a C₁-C₆ alkyl group;

R₃ represents a phenyl group or a pyridyl group, each of the groups optionally being substituted with one or two groups selected from the group consisting of the following (1), (2), (6), and (8) on the aromatic or heterocyclic ring represented by the above R₃:

- (1) C₁-C₆ alkyl groups,
- (2) C₁-C₆ alkoxy groups,
- (6) a hydroxy group, and
- (8) halogen atoms;

R₄ represents a halogen atom;

R₅ represents a hydrogen atom;

R₆ represents a hydrogen atom; and

R₇ represents any one of groups (3), (4), and (7) below:

- (3) a C₁-C₆ alkoxy group,
- (4) a halogen-substituted C₁-C₆ alkoxy group, and
- (7) an amino group optionally substituted with one or two C₁-C₆ alkyl groups

3. A quinolone compound of General Formula (1) or a salt thereof according to claim 2 selected from the group consisting of:

- 5-fluoro-3-(4-methoxyphenyl)-2-methyl-8-propoxy-1H-quinolin-4-one,
- 5-fluoro-3-(4-methoxyphenyl)-1-methyl-8-propoxy-1H-quinolin-4-one,
- 3-(2,4-dimethoxyphenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one,
- 5-fluoro-8-isopropoxy-3-(4-methoxyphenyl)-1H-quinolin-4-one,
- 3-(2,4-dichlorophenyl)-5-fluoro-8-propoxy-1H-quinolin-4-one,
- 8-ethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one,
- 5-fluoro-3-(4-methoxy-2-methylphenyl)-8-propoxy-1H-quinolin-4-one,
- 5-fluoro-3-(4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one,
- 5-fluoro-3-(2-fluoro-4-methoxyphenyl)-8-propoxy-1H-quinolin-4-one,
- 5-fluoro-3-(4-hydroxyphenyl)-8-propoxy-1H-quinolin-4-one,
- 8-cyclopropylmethoxy-5-fluoro-3-(4-methoxyphenyl)-1H-quinolin-4-one,
- 5-fluoro-8-propoxy-3-pyridin-4-yl-1H-quinolin-4-one,
- 5-fluoro-3-(4-methoxyphenyl)-8-(N-methyl-N-propylamino)-1H-quinolin-4-one, and
- 5-fluoro-3-(4-methoxyphenyl)-8-(4,4,4-trifluorobutoxy)-1H-quinolin-4-one.

4. A pharmaceutical composition comprising a quinolone compound of General Formula (1) or a salt thereof according to claim 1 as an active ingredient and a pharmaceutically acceptable carrier.

5. A prophylactic and/or therapeutic agent comprising as an active ingredient a quinolone compound of General Formula (1) or a salt thereof according to claim 1 for use in the prophylaxis and/or treatment of neurodegenerative diseases, diseases induced by neurological dysfunction, or diseases induced by deterioration of mitochondrion function.

6. A prophylactic and/or therapeutic agent according to claim 5, wherein the neurodegenerative disease is selected from the group consisting of Parkinson's disease, Parkinson's syndrome, juvenile parkinsonism, striatonigral degeneration, progressive supranuclear palsy, pure akinesia, Alzheimer's disease, Pick's disease, prion disease, corticobasal degeneration, diffuse Lewy body disease, Huntington's disease, chorea-acanthocytosis, benign hereditary chorea, paroxysmal choreoathetosis, essential tremor, essential myoclonus, Gilles de la Tourette's syndrome, Rett's syndrome, degenerative ballism, dystonia musculorum deformance, athetosis, spasmodic torticollis, Meige syndrome, cerebral palsy, Wilson's diseases, Segawa's disease, Hallervorden-Spatz syndrome, neuroaxonal dystrophy, pallidal atrophy; spino-cerebellar degeneration, cerebral cortical atrophy, Holmes-type cerebellar atrophy, olivopontocerebellar atrophy, hereditary olivopontocerebellar atrophy, Joseph disease, dentatorubropallidoluysian atrophy, Gerstmann-Straussler-Scheinker disease, Friedreich's Ataxia, Roussy-Levy syndrome, May-White syndrome, congenital cerebellar ataxia, hereditary episodic ataxia, ataxia telangiectasia, amyotrophic lateral sclerosis, progressive bulbar palsy, spinal progressive muscular atrophy, spinobulbar muscular atrophy, Werdnig-Hoffmann disease, Kugelberg-Welander disease, hereditary spastic paraparesis, syringomyelia, syringobulbia, Arnold-Chiari malformation, Stiffman syndrome, Klippel-Feil syndrome, Fazio-Londe syndrome, lower myelopathy, Dandy-Walker syndrome, spina bifida, Sjogren-Larsson syndrome, radiation myelopathy, age-related macular degeneration, and cerebral apoplexy selected from the group consisting of cerebral infarction and cerebral hemorrhage.

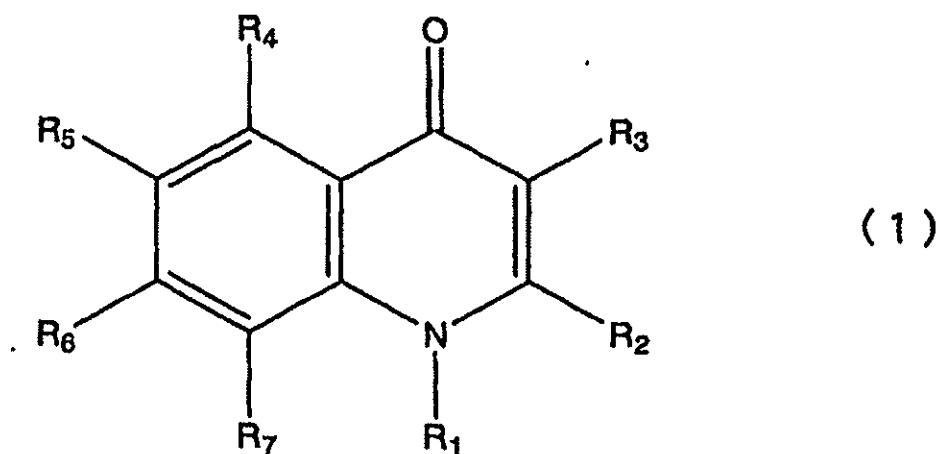
7. A prophylactic and/or therapeutic agent according to claim 5, wherein the disease induced by neurological dysfunction is selected from the group consisting of spinal cord injury, chemotherapy-induced neuropathy, diabetic neuropathy, radiation damage, and demyelinating diseases selected from the group consisting of multiple sclerosis, acute disseminated encephalomyelitis, transverse myelitis, progressive multifocal leucoencephalopathy, subacute sclerosing panencephalitis, chronic inflammatory demyelinating polyneuropathy and Guillain-Barre syndrome.

8. A prophylactic and/or therapeutic agent according to claim 5, wherein the disease induced by deterioration of mitochondrion function is selected from the group consisting of Pearson's

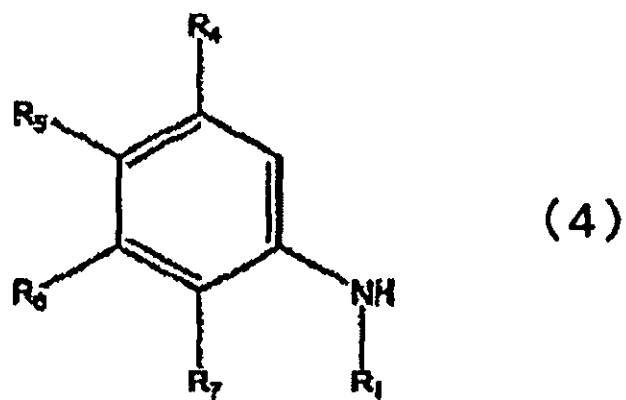
syndrome, diabetes, deafness, malignant migraine, Leber's disease, MELAS, MERRF, MERRF/MELAS overlap syndrome, NARP, pure myopathy, mitochondrial cardiomyopathy, myopathy, dementia, gastrointestinal ataxia, acquired sideroblastic anemia, aminoglycoside-induced hearing loss, complex III deficiency due to inherited variants of cytochrome, b, multiple symmetrical lipomatosis, ataxia, myoclonus, retinopathy, MNGIE, ANT1 disease, Twinkle disease, POLG disease, recurrent myoglobinuria, SANDO, ARCO, complex I deficiency, complex II deficiency, optic nerve atrophy, fatal infantile complex IV deficiency, mitochondrial DNA deficiency, mitochondrial DNA deficiency syndrome, Leigh's encephalomyelopathy, chronic-progressive-external-ophthalmoplegia syndrome (CPEO), Kearns-Sayre syndrome, encephalopathy, lactic acidemia, myoglobinuria, drug-induced mitochondrial diseases, schizophrenia, major depression disorder, bipolar I disorder, bipolar II disorder, mixed episode, dysthymic disorders, atypical depression, seasonal affective disorders, postpartum depression, minor depression, recurrent brief depressive disorder, intractable depression/chronic depression, double depression and acute renal failure.

9. A quinolone compound of General Formula (1) or a salt thereof according to claim 1 for use as a drug.

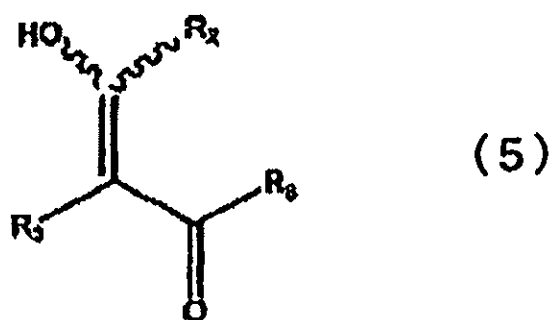
10. A process for producing a quinolone compound of General Formula (1)



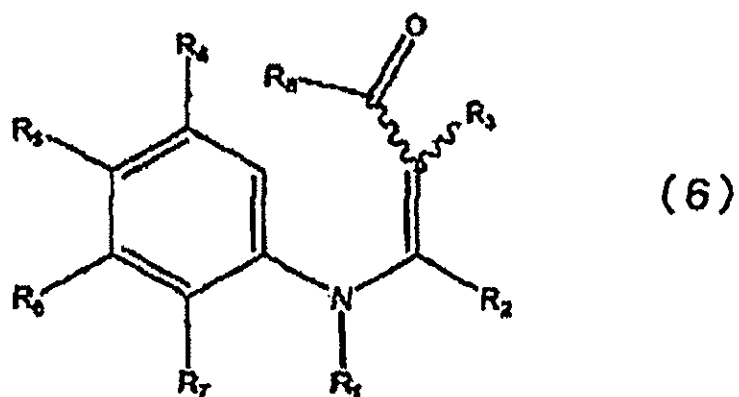
or a salt thereof, wherein R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are each defined above in claim 1, comprising reacting a compound represented by General Formula (4)



wherein R₁, R₄, R₅, R₆ and R₇ are each defined above in claim 1, with a compound represented by General Formula (5)



wherein R₂ and R₃ are each defined above in claim 1, and R₈ represents a C₁-C₆ alkoxy group, thereby giving an intermediate compound represented by General Formula (6)



wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 and R_8 are each defined above; and subjecting the resulting compound to a cyclization reaction.