DESCRIPTION

BENZOFURAN DERIVATIVES FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISORDERS

TECHNICAL FIELD

The present invention relates to the benzofuran derivatives and a pharmaceutical agent containing the same. More specifically, the present invention relates to the compound having excellent pharmacological activities such as a neurotrophic factor activity-enhancing activity, a glucose metabolism improving activity, a neuronal cell death inhibiting activity, a neurogenesis stimulating activity, a neuronal regeneration stimulating activity, a glucose metabolism improving activity, beta (β)-amyloid inhibiting activity, tau and phosphorylated tau inhibiting activity, a cognitive function improving activity and the like, which is effective as prophylactic and therapeutic agents for central nervous system disorders and the like.

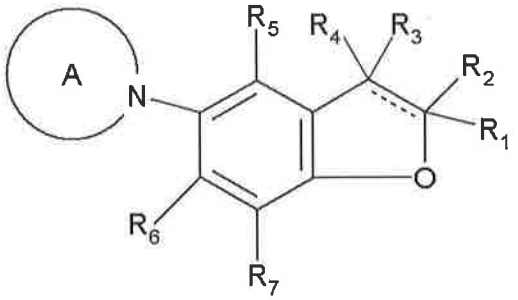
BACKGROUND ART

Neurodegenerative disorders are progressive disorders to cause destructive damages such as the nerve cell death. As principal neurodegenerative disorders, there have been known central nervous system disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease and the like, and peripheral neuropathies represented by diabetic neuropathy. Many of them relate to aging and, in fact, the onset increases with aging, whereas there are also some cases in which the onset begins even at a middle age and further at a younger age.

As a result of studies on the structure and function of brains, the roles of neurotransmitters and neurotrophic factors and so on have been gradually elucidated, but many parts of the causes of neurodegenerative disease are still unknown. For Parkinson's disease, its relationship with a specific neurotransmitter, namely dopamine, has been clarified, whereby L-DOPA that is the precursor of dopamine has been used as a drug for reducing the nerve symptoms and for recovering the function. However, L-DOPA does not suppress the progress of neurodegeneration, and the effect of L-DOPA is gradually lost with a progress of the disease condition, namely the degeneration and loss of dopaminergic neurons. Also, Alzheimer's disease is a disorder that is caused by the degeneration and loss of a variety of nerve cells such as acetylcholinergic neuronal cells, monoamine type neuronal cells, and the like, and causes deposit of senile plaque or change in neurofibrils. As for the drugs therefor,

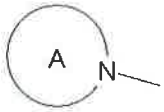
CLAIMS

1. A compound represented by the following Formula (I):

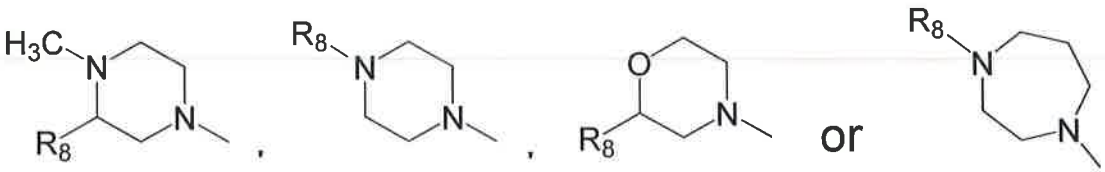


(I)

wherein the partial structural formula:



of Formula (I) is any one of the following formulae:



wherein:

R_8 is:

(1) C_{6-14} aryl which may be substituted with 1 to 3 substituents selected from (i) a halogen atom; (ii) C_{1-6} alkoxy which may be substituted with a halogen atom; (iii) C_{1-6} alkyl which may be substituted with a substituent selected from a halogen atom, a hydroxy, amino, and diC_{1-6} alkylamino; (iv) C_{1-6} alkylthio; (v) C_{1-6} alkylsulfonyl; (vi) cyano; (vii) carbamoyl; (viii) C_{1-6} alkylsulfinyl; and (ix) C_{1-6} alkylcarbonyl; or

(2) a 5- to 10- membered aromatic heterocyclic ring containing 1 to 4 hetero atoms selected from a nitrogen atom, a sulfur atom, and an oxygen atom, other than a carbon atom, and which may be substituted with 1 to 3 substituents selected from a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, and phenyl which may be substituted with C_{1-6} alkoxy;



is a single bond;

R_1 is a hydrogen atom or C_{1-6} alkyl which may be substituted with a hydroxy;

R_2 is:

(1) a hydrogen atom; or

(2) C_{1-6} alkyl which may be substituted with a substituent selected from a

hydroxy, amino, di-C_{1-6} alkylamino, (C_{1-6} alkyl)(benzyl)amino, mono-C_{1-6} alkylamino, di-benzylamino, C_{1-6} alkyl-carbonylamino, formyloxy, C_{1-6} alkylsulfonyloxy, cyano, carboxy, mono-C_{1-6} alkyl-carbamoyl, C_{1-6} alkoxy which may be substituted with a substituent selected from C_{1-6} alkoxy and phenyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, morpholino, 1,1-dioxidothiomorpholine, pyrazolyl, imidazolyl substituted with C_{1-6} alkyl, pyrrolidinyl, piperidinyl substituted with oxo or hydroxy, and 1,4-dioxa-8-azaspiro[4,5]deca-8-yl; or

R_1 and R_2 form a cyclopentane ring or a tetrahydropyran ring together with an adjacent carbon atom;

R_3 is a hydrogen atom;

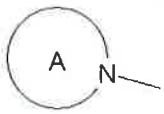
R_4 is a hydrogen atom;

R_5 is a hydrogen atom, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, phenyl substituted with diC_{1-6} alkylamino, or furyl;

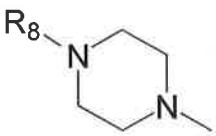
R_6 is a hydrogen atom, C_{1-6} alkyl, phenyl substituted with C_{1-6} alkyl, pyridyl, or a halogen atom, and

R_7 is a hydrogen atom, hydroxy, C_{1-6} alkyl which may be substituted with a hydroxy, C_{1-6} alkoxy which may be substituted with C_{1-6} alkoxy, or C_{1-6} alkylcarbonyl, or a salt thereof.

2. The compound according to claim 1, wherein the partial structural formula:



of Formula (I) is the following formula:



wherein:

R_8 is a phenyl which may be substituted with 1 to3 substituents selected from:

(1) a halogen atom;

(2) C_{1-6} alkoxy which may be substituted with a halogen atom;

(3) C_{1-6} alkyl which may be substituted with a substituent selected from a halogen atom, a hydroxy, amino, and diC_{1-6} alkylamino;

(4) C_{1-6} alkylthio;

(5) C_{1-6} alkylsulfonyl;

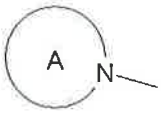
(6) cyano;

(7) carbamoyl;

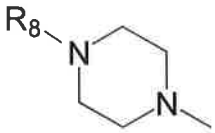
(8) C_{1-6} alkylsulfinyl; and

(9) C_{1-6} alkylcarbonyl.

3. The compound according to claim1, wherein the partial structural formula:



of Formula (I) is the following formula:



wherein:

R_8 is a phenyl which is substituted with 1 to 3 C_{1-6} alkoxy;

is a single bond;

R_1 is C_{1-6} alkyl;

R_2 is a hydrogen atom, or C_{1-6} alkyl which may be substituted with a hydroxy;

R_3 and R_4 are a hydrogen atom;

R_5 is C_{1-6} alkyl;

R_6 is C_{1-6} alkyl; and

R_7 is C_{1-6} alkyl or C_{1-6} alkoxy.

4. A compound according to claim 1 selected from

1-(4-methoxyphenyl)-4-(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)piperazine or a salt thereof;

1-(4-methoxyphenyl)-4-[(2R)-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl]piperazine or a salt thereof;

1-(4-methoxyphenyl)-4-[(2S)-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl]piperazine or a salt thereof;

1-(4-methoxyphenyl)-4-(7-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)piperazine or a salt thereof;

1-(4-ethoxyphenyl)-4-(7-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)piperazine or a salt thereof;

(-)-{5-[4-(4-methoxyphenyl)piperazin-1-yl]-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-2-yl}methanol or a salt

thereof; and
(+)-{5-[4-(4-methoxyphenyl)
piperazin-1-yl]-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-2-yl}methanol or a salt thereof.

5. The compound according to claim 1 of
1-(4-Methoxyphenyl)-4-(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)piperazine or a salt thereof.

6. The compound according to claim 1 of
1-(4-Methoxyphenyl)-4-[(2R)-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl]piperazine or a salt thereof.

7. The compound according to claim 1 of
1-(4-Methoxyphenyl)-4-[(2S)-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl]piperazine or a salt thereof.

8. The compound according to claim 1 of
1-(4-Methoxyphenyl)-4-(7-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)piperazine or a salt thereof.

9. The compound according to claim 1 of
1-(4-Ethoxyphenyl)-4-(7-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran-5-yl)
piperazine or a salt thereof.

10. The compound according to claim 1 of (-)-{5-[4-(4-methoxyphenyl)
piperazin-1-yl]-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-2-yl}methanol or a salt thereof.

11. The compound according to claim 1 of (+)-{5-[4-(4-methoxyphenyl)
piperazin-1-yl]-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-2-yl}methanol or a salt thereof.

12. A pharmaceutical composition comprising the compound according to any one of claims 1 to 11.

13. The pharmaceutical composition according to claim 12 for use in the prophylaxis or treatment of central nervous system diseases.

14. The pharmaceutical composition according to claim 12 for use in the prophylaxis or treatment of Alzheimer's disease.

15. Use of the compound according to any one of claims 1 to 11 for producing a prophylactic or therapeutic agent for central nervous system diseases.

16. Use of the compound according to any one of claims 1 to 11 for producing a prophylactic or therapeutic agent for Alzheimer's disease.

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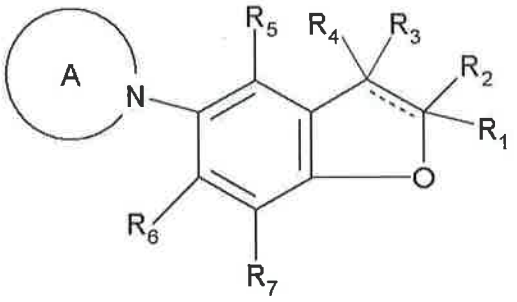
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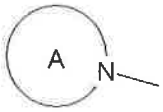
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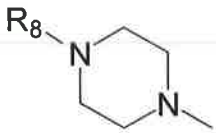


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wherein the partial structural formula:



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wherein:

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R_6 is C_{1-6} alkyl; and

R_7 is C_{1-6} alkyl or C_{1-6} alkoxy.

2. 1-(4-Methoxyphenyl)-4-(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl) piperazine or a salt thereof.

3. 1-(4-Methoxyphenyl)-4-[(2S)-2,4,6,7-tetramethyl-2,3-dihydro-1-benzofuran-5-yl] piperazine or a salt thereof.

4. 1-(4-Methoxyphenyl)-4-(7-methoxy-2,2,4,6-tetramethyl-2,3-dihydro-1-benzofuran -5-yl)piperazine or a salt thereof.

5. A pharmaceutical composition comprising the compound according to any one of claims 1 to 4.

6. The pharmaceutical composition according to claim 5, which is an IGF-1 signal modulator or protein kinase B activator.

7. The pharmaceutical composition according to claim 5, which is a prophylactic or therapeutic agent for central nervous system diseases.

8. The pharmaceutical composition according to claim 5, which is a prophylactic or therapeutic agent for Alzheimer's disease.

9. Use of the compound according to any one of claims 1 to 4 for producing a prophylactic or therapeutic agent for Alzheimer's disease.