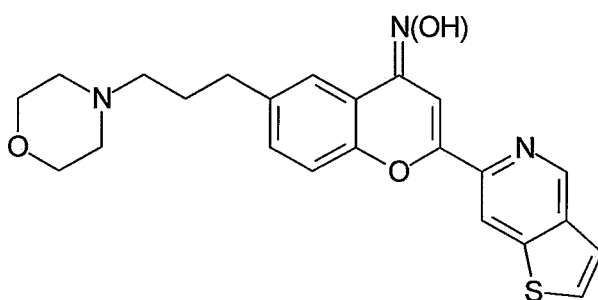


BRAIN-PENETRANT CHROMONE OXIME DERIVATIVE FOR THE THERAPY OF LEVODOPA-INDUCED DYSKINESIA

SUMMARY

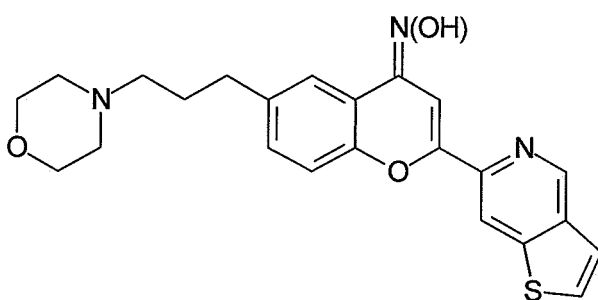
In one aspect, the present invention refers to use of a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof, for the preparation of a medicament for the treatment or prevention of levodopa-induced dyskinesia.

In another aspect, the present invention refers to use of a compound of the following formula (I)



(I)

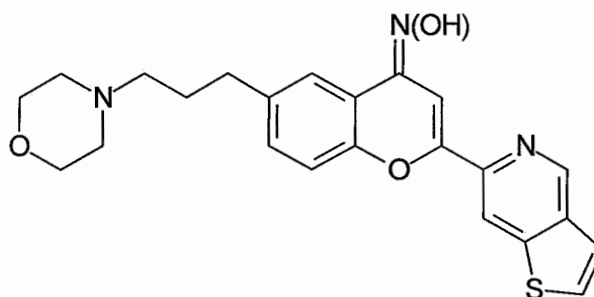
or a pharmaceutically acceptable salt, solvate or prodrug thereof, for the preparation of a medicament for the treatment or prevention of Parkinson's disease, wherein said medicament is to be administered in combination with levodopa or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In yet another aspect, the present invention refers to use of levodopa or a pharmaceutically

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acceptable salt, solvate or prodrug thereof for the preparation of a medicament for the treatment or prevention of Parkinson's disease, wherein said medicament is to be

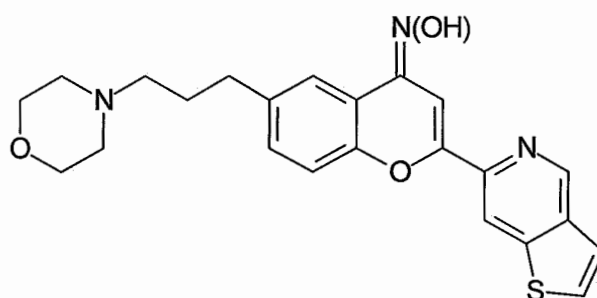
administered in combination with a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

In still another aspect, the present invention refers to use of a first compound and a second compound for the preparation of a medicament for the treatment or prevention of Parkinson's disease, wherein said first compound is a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof, and wherein said second compound is levodopa or a pharmaceutically acceptable salt, solvate or prodrug thereof.

DETAILED DESCRIPTION

The present invention provides a chromone oxime derivative of formula (I), as described and defined further below, which is a modulator of nervous system receptors sensitive to the neuroexcitatory amino acid glutamate and presents an advantageously high brain exposure upon oral administration, for the treatment or prevention of levodopa-induced dyskinesia. The present invention also provides an improved therapy of Parkinson's disease, using the chromone oxime derivative of formula (I) in combination with levodopa.

It is known that glutamate is involved in numerous nervous functions. Important roles are

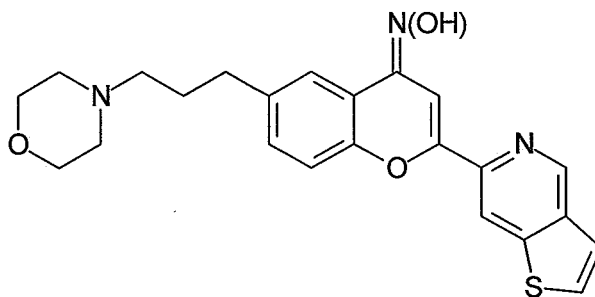
therefore attributed to glutamatergic receptors, in particular as regards the conduction of nerve impulse, synaptic plasticity, the development of the nervous system, learning and memory.

Glutamate is also the main endogenous neurotoxin, being responsible for the neuronal death observed after ischemia, hypoxia, epileptic fits or traumatisms of the brain. Therefore glutamate receptors are clearly considered to be involved in various disorders of the nervous system and neurodegenerative diseases.

The glutamatergic system includes glutamate receptors and transporters as well as enzymes of glutamate metabolism. Two main types of glutamatergic receptors have been characterized: ionotropic (iGluRs) and metabotropic (mGluRs) receptors. Ionotropic glutamate receptors have been identified based on their pharmacology and subsequently through molecular biology. The iGluR family includes the NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and the kainate receptor subfamilies, so named for the chemical agonist that selectively binds to the subfamily members. iGluRs are voltage-gated ion channels that allow cation influx upon glutamate binding. They are directly responsible for the generation of action potentials, they initiate neuroplastic changes in the CNS and are responsible for many diseases, including chronic pain. Metabotropic glutamate receptors are a family of seven transmembrane domain G-protein-coupled receptors (GPCR). So far, eight mGluR subtypes have been identified (mGluR1–mGluR8) and classified into three groups (I-III) based upon sequence homology, transduction mechanism and pharmacological profile. mGluRs belong to family 3 of the GPCR superfamily, and as such, they are characterized by a

CLAIMS

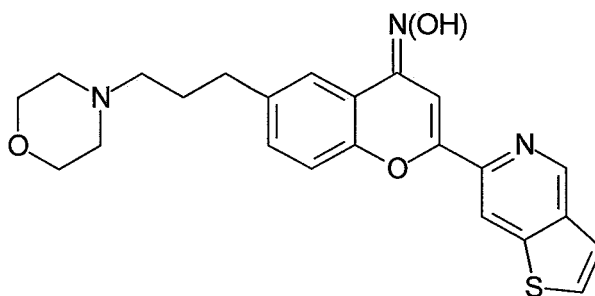
1. Use of a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof, for the preparation of a medicament for the treatment or prevention of levodopa-induced dyskinesia.

2. The use of claim 1, wherein said compound has the (E)-configuration at the oxime group comprised in formula (I).
3. The use of claim 1 or 2, wherein said compound is in the form of a hydrochloride salt.
4. The use of any one of claims 1 to 3, wherein said medicament is for oral administration.
5. Use of a compound of the following formula (I)

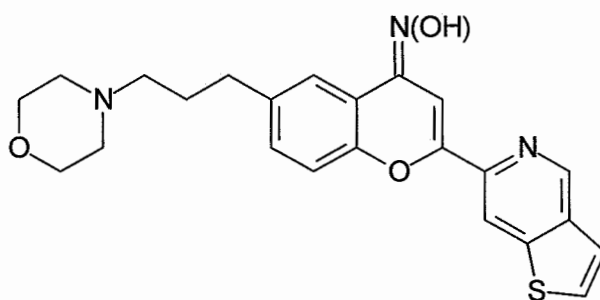


(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof, for the preparation

of a medicament for the treatment or prevention of Parkinson's disease, wherein said medicament is to be administered in combination with levodopa or a pharmaceutically acceptable salt, solvate or prodrug thereof.

6. Use of levodopa or a pharmaceutically acceptable salt, solvate or prodrug thereof for the preparation of a medicament for the treatment or prevention of Parkinson's disease, wherein said medicament is to be administered in combination with a compound of the following formula (I)



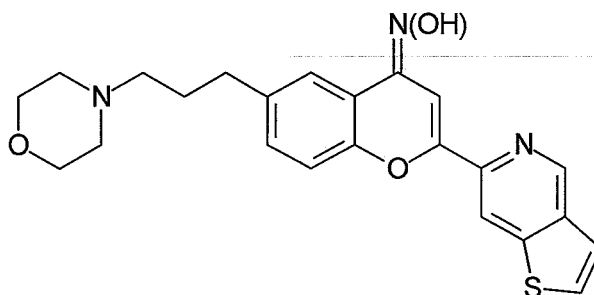
(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

7. The use of claim 5 or 6, wherein the compound of formula (I) has the (E)-configuration at the oxime group comprised in formula (I).
8. The use of any one of claims 5 to 7, wherein the compound of formula (I) is in the form of a hydrochloride salt.
9. The use of any one of claims 5 to 8, wherein said compound of formula (I) or the pharmaceutically acceptable salt, solvate or prodrug thereof and said levodopa or the pharmaceutically acceptable salt, solvate or prodrug thereof are to be administered simultaneously.
10. The use of claim 9, wherein said compound of formula (I) or the pharmaceutically acceptable salt, solvate or prodrug thereof and said levodopa or the pharmaceutically acceptable salt, solvate or prodrug thereof are provided in a single medicament.
11. The use of claim 9, wherein said compound of formula (I) or the pharmaceutically acceptable salt, solvate or prodrug thereof and said levodopa or the pharmaceutically acceptable salt, solvate or prodrug thereof are provided in separate medicaments.

12. The use of any one of claims 5 to 8, wherein said compound of formula (I) or the pharmaceutically acceptable salt, solvate or prodrug thereof and said levodopa or the pharmaceutically acceptable salt, solvate or prodrug thereof are to be administered sequentially.
13. The use of any one of claims 5 to 12, wherein the medicament(s) comprising said compound of formula (I) or the pharmaceutically acceptable salt, solvate or prodrug thereof and said levodopa or the pharmaceutically acceptable salt, solvate or prodrug thereof is/are for oral administration.
14. Use of a first compound and a second compound for the preparation of a medicament for the treatment or prevention of Parkinson's disease,

wherein said first compound is a compound of the following formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or prodrug thereof,

and wherein said second compound is levodopa or a pharmaceutically acceptable salt, solvate or prodrug thereof.

15. The use of claim 14, wherein the compound of formula (I) has the (E)-configuration at the oxime group comprised in formula (I).
16. The use of claim 14 or 15, wherein the compound of formula (I) is in the form of a hydrochloride salt.
17. The use of any one of claims 14 to 16, wherein said medicament is for oral administration.

18. The use of any one of claims 5 to 17, wherein said medicament(s) is/are to be administered in combination with a levodopa decarboxylase inhibitor and/or a catechol-O-methyl transferase (COMT) inhibitor.
19. The use of claim 18, wherein said medicament(s) is/are to be administered in combination with a levodopa decarboxylase inhibitor and with a COMT inhibitor.
20. The use of claim 18 or 19, wherein the levodopa decarboxylase inhibitor is carbidopa, benserazide, α -methyldopa, α -difluoromethyldopa, or a pharmaceutically acceptable salt or solvate of any one of these agents.
21. The use of any one of claims 18 to 20, wherein the COMT inhibitor is entacapone, tolcapone, nitecapone, opicapone, or a pharmaceutically acceptable salt or solvate of any one of these agents.
22. The use of any one of claims 1 to 21, wherein said medicament(s) is/are for administration to a human.