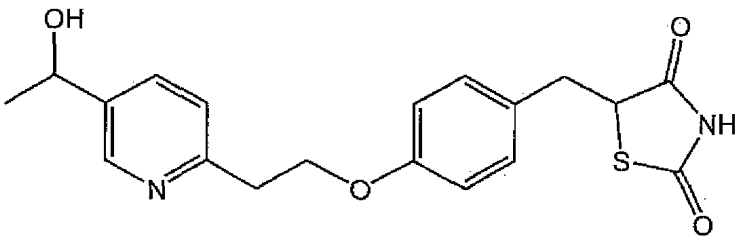
Summary of the invention

Surprisingly it has been found that central NS disorders can be treated by 5-[4-[2-(5-(1-hydroxyethyl)-2-pyridinyl)ethoxy]benzyl]-2,4-thiazolidinedione of formula (**1**), the M-IV metabolite of Pioglitazone.



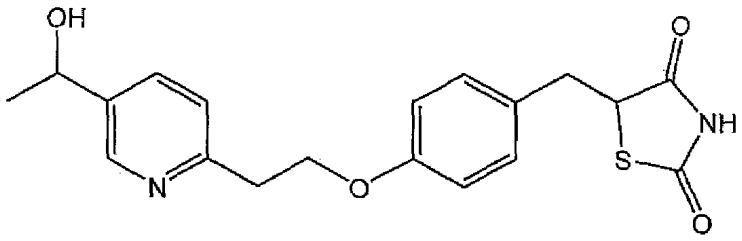
(**1**)

or a salt thereof.

The NS disorders include, but are not limited to, disorders in which the nervous system is affected during the entire progression of the diseases such as neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis (ALS), degenerative ataxias, multiple system atrophy and leukodystrophies), cerebrovascular diseases (e.g., global or local ischemia, intracerebral hemorrhage, stroke), seizures and epilepsy, viral diseases (e.g., meningitis, encephalitis), multiple sclerosis, brain tumors, and injury. NS disorders also include disorders in which the nervous system is only affected in the latest stages of the development of the condition and include rare metabolic diseases such as organic acidemias or fatty acid disorders and genetic mitochondrial disorders.

The invention is based at least in part on data showing the unexpected ability of the compound of formula (**1**) to cross the blood brain barrier. In addition, the compound of the invention has one or more desirable drug properties such as good oral bioavailability, low systemic plasma clearance, and a good volume of distribution. Furthermore, the compound of the invention is a reasonably "clean" drug, since in vivo it only converts to 5-(4-(2-(5-acetyl-2-pyridyl)ethoxy)benzyl)-2,4-thiazolidinedione (M-III metabolite of Pioglitazone) and both are excreted. Side effects due to unwanted metabolites are therefore minimised.

Thus, according to an aspect of the invention, there is provided use of a compound of formula (1) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a central nervous system disorder



(**1**),

wherein the disorder is selected from the group consisting of a neurodegenerative disease, a cerebrovascular disease, seizure, epilepsy, a viral disease, a neuroinflammatory disease, a brain tumour, an organic acidemias, a fatty acid disorder, and a genetic mitochondrial disorder. Also disclosed is a compound of formula (**1**) or pharmaceutically acceptable salts thereof or mixture of compounds of formula (**1**) for use as a medicament in particular for the treatment or prevention of central NS disorders. Also disclosed is the use of a compound

of formula (**1**) or pharmaceutically acceptable salts thereof or mixture of compounds of formula (**1**) for the manufacture of a medicament in particular for the treatment or prevention of central NS disorders. Also disclosed is a method for the treatment or prevention of a disease of central NS comprising administering to a subject in need thereof an effective amount of a compound of formula (**1**) or pharmaceutically acceptable salts thereof or mixture of compounds of formula (**1**). Also disclosed are pharmaceutical compositions comprising a compound of formula **(1)** or pharmaceutically acceptable salts thereof or mixtures of compounds of formula (**1**).

Also disclosed are novel compounds (**2**) to (**5**):

(**2**) (R)-5-(4-(2-(5-((R)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione

(**3**) (R)-5-(4-(2-(5-((S)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione

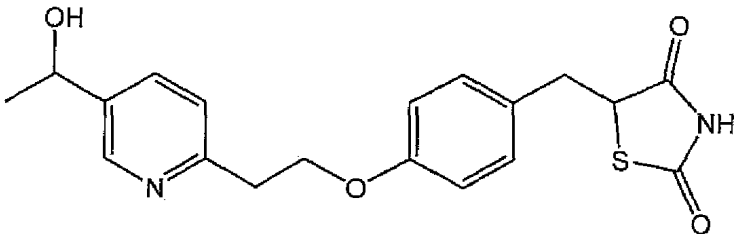
(**4**) (S)-5-(4-(2-(5-((R)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione

(**5**) (S)-5-(4-(2-(5-((S)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione

or a pharmaceutically acceptable salt thereof

Also disclosed are mixtures of one or more of the compounds (**2**) to (**5**) or pharmaceutically acceptable salts thereof for use in the treatment or prevention of central nervous system disorders. Also disclosed is the use of one or more of the compounds (**2**) to (**5**) or pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment or prevention of central NS disorders. Also disclosed is a method for the treatment or prevention of a disease of central NS comprising administering to a subject in need thereof an effective amount of one or more of the compounds (**2**) to (**5**) or pharmaceutically acceptable salts thereof.

Also disclosed are pharmaceutical compositions comprising a one or more compounds of formulae (**2**) to (**5**) or pharmaceutically acceptable salts thereof, including mixtures of compounds of formula (**2**) to (**5**) for use in the treatment or prevention of central NS disorders.



(**1**)

Also disclosed is a method for treating or preventing central nervous system disorders, including neurodegenerative diseases (such as Alzheimer's disease, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis (ALS), degenerative ataxias, multiple system atrophy, multiple sclerosis and leukodystrophies such as ALD), cerebrovascular diseases, seizures, epilepsy, viral diseases, brain tumours, neuroinflammatory diseases NS disorders that affect the nervous system in the latest stages of the development of the condition including rare metabolic diseases such as organic acidemias or fatty acid disorders and genetic mitochondrial disorders through the administration of a compound of formula (**1**) or a pharmaceutically acceptable salt thereof, or of one or more compounds of formulae (**2**) to (**5**) or pharmaceutically acceptable salts thereof.

Description of the figures

FIG 1 represents the concentration of compound of formula (**1**) in plasma of a C57BL/6 mouse after a single intravenous administration of 1 mg/Kg of said compound.

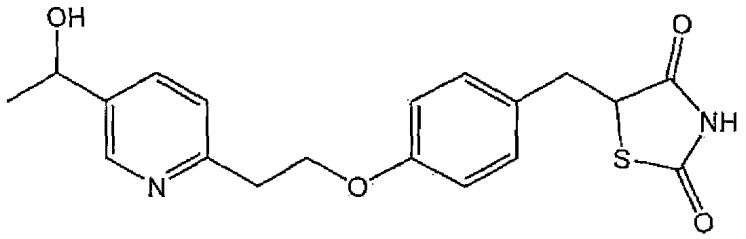
FIG 2 represents the concentrations of compound of formula (**1**) in plasma of a C57BL/6 mouse after a single oral administration of 4.5 mg/Kg of said compound.

FIG 3 represents the concentration of compound of formula (**1**) in brain tissue of a C57BL/6 mouse after a single oral administration of 4.5 mg/Kg of said compound (line with circle markers) and after a single intravenous administration of 1 mg/Kg of said compound (line with square markers).

FIG4 represents the brain plasma ration calculated based on levels of Pioglitazone, MIV, MIII and MII in plasma and brain quantified at Cmax (maximal concentration) following oral dosing of a single administration of Pioglitazone at 4.5 mg/kg in male C57BL/6 mice.

CLAIMS

1. Use of a compound of formula (**1**) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or prevention of a central nervous system disorder



(**1**),

wherein the disorder is selected from the group consisting of a neurodegenerative disease, a cerebrovascular disease, seizure, epilepsy, a viral disease, a neuroinflammatory disease, a brain tumour, an organic acidemias, a fatty acid disorder, and a genetic mitochondrial disorder.

2. Use of a compound of formula (**1**) according to claim 1, wherein the compound of formula (**1**) is:
   (**2**) (R)-5-(4-(2-(5-((R)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione;
   (**3**) (R)-5-(4-(2-(5-((S)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione;
   (**4**) (S)-5-(4-(2-(5-((R)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione; or
   (**5**) (S)-5-(4-(2-(5-((S)-1-hydroxyethyl)pyridine-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione; or a pharmaceutically acceptable salt thereof.

3. Use of a mixture of two or more of the compounds defined in claim 2, wherein the mixture is optically active, for the manufacture of a medicament for the treatment or prevention of the central nervous system disorder selected from the group consisting of a neurodegenerative disease, a cerebrovascular disease, seizure, epilepsy, a viral disease, a neuroinflammatory disease, a brain tumour, an organic acidemia, a fatty acid disorder, and a genetic mitochondrial disorder.

4. Use of a mixture according to claim 3, wherein said mixture comprises
   (a) said compound (**2**) and said compound(**3**), or a pharmaceutically acceptable salt thereof;

(b) said compound (**4**) and said compound (**5**), or a pharmaceutically acceptable salt thereof;

(c) said compound (**2**) and said compound (**4**), or a pharmaceutically acceptable salt thereof; or

(d) said compound (**3**) and said compound (**5**), or a pharmaceutically acceptable salt thereof.

5. Use of a compound or mixture of compounds according to any one of claims 1 to 4, wherein the disorder is a neurodegenerative disease.

6. Use of a compound or mixture of compounds according to claim 5 wherein the neurodegenerative disease is Alzheimer's disease, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis (ALS), degenerative ataxias, multiple sclerosis, multiple system atrophy, leukodystrophy, spinal muscular atrophy (SMA), primary lateral sclerosis (PLS), progressive bulbar palsy, or pseudobulbar palsy.

7. Use of a compound or mixture of compounds according to claim 6, wherein the neurodegenerative disease is leukodystrophy.

8. Use of a compound or mixture of compounds according to claim 6, wherein the leukodystrophy is adrenoleukodystrophy (ALD or X-ALD).

9. Use of a compound or mixture of compounds according to claim 6, wherein the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, ALS, or multiple sclerosis.

10. Use of a compound or mixture of compounds according to claim 6, wherein the neurodegenerative disease is Huntington's chorea or Friedreich's ataxia.

11. Use of a compound or mixture of compounds according to any one of claims 1 to 4, wherein the central nervous system disorder is a cerebrovascular disease.

12. Use of a compound or mixture of compounds according to any one of claims 1 to 4, wherein the central nervous system disorder is a neuroinflammatory disease.

13. Use of a compound or mixture of compounds according to anyone of claims 1 to 12 wherein the medicament is to be administered with another therapeutic agent.

14. Use of a compound or mixture of compounds according to claim 13, wherein the compound or mixture of compounds and said other therapeutic agent are provided in combination.

15. Use of the compound or mixture of compounds according to any one of claims 1 to 14, wherein the compound or mixture of compounds is provided in a dosage form.

16. Use of the compound or mixture of compounds according to claim 15, wherein the dosage form is an oral dosage form.

17. Use of the compound or mixture of compounds according to claim 16, wherein the oral dosage form is an oral solution or an oral suspension.

18. Use of the compound or mixture of compounds according to claim 15 or 16, wherein the oral dosage form is selected from the group consisting of tablets, capsules, pills, and granules.

19. Use of the compound or mixture of compounds according to any one of claims 15 to 18, wherein the compound or mixture of compounds in the dosage form is at a dosage of from 0.1 mg to 200 mg.

20. Use of the compound or mixture of compounds according to claim 19, wherein the dosage is from 10 mg to 100 mg.

21. Use of the compound or mixture of compounds according to claim 15, wherein the dosage form is suitable for topical, epicutaneous, subcutaneous, transdermal, intramuscular, parenteral, ocular, rectal, vaginal, inhalation, buccal, sublingual, or intranasal delivery,

22. Use of the compound or mixture of compounds according to claim 21, wherein the dosage form is sublingual.