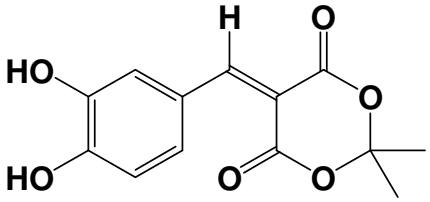
PHENOLIC COMPOUND AND COMBINATION THEREOF WITH A BENZODIAZEPIN FUSED TO 1,4-DIHIDROPYRIDINE FOR THE TREATMENT OF CENTRAL NERVOUS AND VASCULAR SYSTEMS AFFECTIONS.

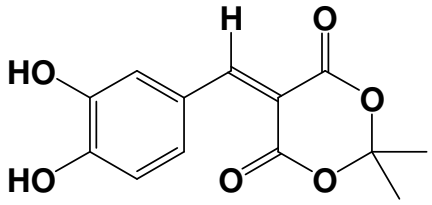
SUMMARY

In one example, there is provided a phenolic compound of formula I in free form or its salts, hydrates, crystalline forms, metabolites, prodrugs:



I

In one aspect, the present disclosure refers to pharmaceutical composition characterized in that it comprises as a pharmaceutically active ingredient a phenolic compound of formula I:



I

in free form, as a salt, hydrate or in crystalline form, together with one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure refers to pharmaceutical combination for the treatment of diseases of the central nervous and vascular system comprising the compound of formula I as defined herein in free form, as a salt, hydrate or in crystalline form, and further comprising 3-ethoxycarbonyl-2-methyl-4-(2-nitrophenyl)-4,11-dihydro-1H-pyrido[2,3-b][1,5]benzodiazepine, and further comprising one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound of formula I as defined herein in free form, as a salt, hydrate or in crystalline form, and further comprising 3-ethoxycarbonyl-2-methyl-4-(2-nitrophenyl)-4,11-dihydro-1H-pyrido[2,3-b][1,5]benzodiazepine, and further comprising one or more pharmaceutically acceptable excipients.

In another aspect, the present disclosure refers to use of the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.

In another example, there is provided pharmaceutical composition as described herein for the treatment of cerebral ischemia, Parkinson's disease and different types of dementia.

In another aspect, the present disclosure refers to use of the compound of formula I as defined herein in free form, as a salt, hydrate or in crystalline form in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.

In another aspect, the present disclosure refers to use of the pharmaceutical combination as defined herein in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.

DESCRIPTION

The present invention relates to Chemistry, Pharmaceutical and in particular to the preparation of formulations from phenolic or polyphenolic compound derivatives and from derivatives of phenolic or polyphenolic compounds combined with tricyclic systems of the benzodiazepine type fused to derivatives of 1,4 Dihydropyridines with action on the Central Nervous and Vascular System.

In the case of diseases of multifactorial origin such as cardiovascular, cerebrovascular, neurodegenerative, neuropsychiatric and neurological, a single medication is not enough to treat them effectively, so a multiple medication therapy should be used. There are two main reasons for the absence of drugs for the treatment of these diseases: 1) drugs targeting a single pathological mechanism and 2) use of high doses that increases the risk of adverse reactions.

Neurodegeneration is a common theme of many diseases of the nervous system and disorders such as dementia, Alzheimer's disease (AD), Parkinson's disease (PD). These diseases are devastating and expensive to manage, while current treatments are inadequate. The urgency of this problem is compounded by the fact that the incidence of these age-related diseases is increasing rapidly due to the demographic changes that are occurring.

The progressive aging of the world population brings with it the unwanted consequence of an increase in neurodegenerative diseases and senile dementias.

PD is a neurodegenerative disease, with symptoms of motor dysfunction: slow movements, rigidity, resting tremor and alterations in balance. As the disease progresses, many patients develop non-motor symptoms, including anxiety, depression, constipation, and dementia.

These characteristics are attributed to a large reduction in the striatal content of dopamine and to a loss of dopaminergic neurons in the substantia nigra pars compacta (Gauthier, 1982). Clinical signs of PD appear after dopaminergic neuronal death exceeds a threshold of 70-80% and a loss of striatal nerve endings exceeding 50-60% (Agid, 1991).

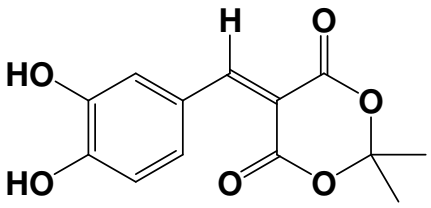
Investigations of the developmental mechanisms of PD have indicated that the loss of dopaminergic neurons in the nigra pars substance compact is related to the mitochondrial-I complex deficit (Jenner 1998).

Although there are drugs that relieve Parkinson's symptoms, the chronic use of these drugs is not effective in preventing the progression of PD and has been associated with debilitating side effects. It is therefore of great interest to develop neuroprotective therapies that delay or even stop the degenerative progression.

Worldwide, an estimated 46.8 million people live with dementia. This number is estimated to increase almost twice every 20 years; to 74.7 million in 2030 and 131.5 million by 2050. Dementia also has a huge economic impact. Today, the estimated total worldwide cost of dementia is $ 818

CLAIMS

1. Pharmaceutical composition characterized in that it comprises as a pharmaceutically active ingredient a phenolic compound of formula I:



I

in free form, as a salt, hydrate or in crystalline form,
together with one or more pharmaceutically acceptable excipients.

2. Pharmaceutical combination for the treatment of diseases of the central nervous and vascular system, comprising the compound of formula I as defined in claim 1 in free form, as a salt, hydrate or in crystalline form, and further comprising 3-ethoxycarbonyl-2-methyl-4-(2-nitrophenyl)-4,11-dihydro-1H-pyrido[2,3-b][1,5] benzodiazepine, and further comprising one or more pharmaceutically acceptable excipients.
3. Pharmaceutical combination according to claim 2, wherein the 3-ethoxycarbonyl-2-methyl-4-(2-nitrophenyl)-4,11-dihydro-1H-pyrido[2,3-b][1,5]benzodiazepine is in the form of a racemate or in the form of its dextrorotatory or levorotatory enantiomer.
4. A pharmaceutical composition comprising a compound of formula I as defined in claim 1 in free form, as a salt, hydrate or in crystalline form, and further comprising 3-ethoxycarbonyl-2-methyl-4-(2-nitrophenyl)-4,11-dihydro-1H-pyrido[2,3-b][1,5]benzodiazepine, and further comprising one or more pharmaceutically acceptable excipients.
5. Use of the pharmaceutical composition according to claim 1 or claim 4 in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.
6. The use according to claim 5, wherein the disease is selected from the group consisting of cerebral ischemia, Parkinson's disease and different types of dementia including Alzheimer's disease and vascular dementia.
7. Use of the compound of formula I as defined in claim 1 in free form, as a salt, hydrate or in crystalline form in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.
8. Use of the pharmaceutical combination as defined in claim 2 or claim 3 in the manufacture of a medicament for the treatment of diseases of the central nervous and vascular system.
9. The use according to claim 8, wherein the disease of the central nervous and vascular system is cerebral ischemia.

10. The use according to claim 8, wherein the disease of the central nervous and vascular system is Parkinson's disease.

11. The use according to claim 8, wherein the disease of the central nervous and vascular system is related to different types of dementias.

12. The use according to claim 11, wherein the dementia is Alzheimer's disease.

13. The use according to claim 11, wherein the dementia is vascular dementia.