**Description**

**A COMPOSITION CONTAINING PICRORETOSIDE DERIVATIVES THAT EXHIBIT PRO-DOPAMINERGIC CHARACTER FOR INCREASING THE SENSITIVITY OF DOPAMINE 5 RECEPTOR**

**Technical Field**

The invention relates to a composition formed for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action.

**State of the Art**

In biochemistry, receptor refers to two meanings that partially overlap. According to the first meaning, the receptor is a protein involved in the signal transduction and it carries a signal outside a cell into the cell. The protein, which enables the signal to be converted from one form into another, may be outside as well as inside the cell. According to the second meaning, the receptor is a molecule to which a protein or particle outside a cell binds on the cell membrane in order to enter the cell. The component binding to the cell may be a protein (e.g. cholera toxin), a virus (e.g. HIV) or a lipoprotein particle (e.g. LDL). According to this second meaning, the receptor is generally a protein, but it may also be a carbohydrate or lipid (for example, the cholera toxin binds to a ganglioside called GM1). The structural activity of the receptors may be blocked by the binding of an inverse agonist. The mutations leading to the increase in the structural activity are the causes for some hereditary diseases, such as precocious puberty (due to mutations in the luteinizing hormone receptor) and hyperthyroidism (due to mutations in thyroid stimulating hormone receptors). The stimulants act as inverse agonists on the dopamine receptors.

Dopamine (DA) is a chemical naturally produced in the body. In the brain, it activates the dopamine receptors, thus serving as a neurotransmitter. Dopamine is also secreted from hypothalamus and it mixed with blood to serve as a neurohormone. Its duty as a neurohormone is to suppress the secretion of prolactin from the frontal lobe of pituitary gland.

According to the state of the art, the invention no. EP1366044B1 with classification "C07D 413/12" entitled "8-{4-[3-(5-fluoro-1H-indol-3-yl)propyl]-1-piperazinyl}-2-methyl-2H-1,4-benzoxazin-3(4H)-one methanesulfonate with high affinity for the dopamine D2 receptor and the serotonin reuptake site”relates to the novel mesylate of a phenylpiperazine derivative of the formula (I). This salt has favorable properties as compared with the free base of this compound.

Further, the invention no. EP2501704B1 entitled "Spiropiperidine compounds as oral-1 receptor antagonists" provides a family of 4',5'-dihydrospirolpiperidine-4,7'-thieno[2,3-c]pyran] compounds with high antagonist potency for the ORL-1 receptor and high in vivo ORL-1 receptor occupancy in the CNS. Additionally, certain of the compounds have a favorable cardiotoxicology profile as determined by selectivity over the hERG channel activity, as well as high selectivity over other physiologically important receptors (e.g. mu, kappa and delta opioids, serotonin, and dopamine receptors). Further, certain of the compounds of the present invention have favorable biopharmaceutical and pharmacokinetic properties (e.g. solubility, oral exposure, and CNS permeability). Certain of the compounds of the present invention exhibit reduced oxidative metabolism resulting in favorable oral bioavailability. Certain compounds have also demonstrated through animal models that the compounds of the present invention are useful for the treatment of migraine

Further, the invention no. EP1969003B1 entitled "Uses of a novel neurotrophic factor protein" discloses a novel neurotrophic factor protein, MANF2 and a genetic sequence encoding the same. The molecule will be useful in the development of a range of therapeutics and diagnostics useful in the treatment, prophylaxis and/or diagnosis of MANF2 dependent conditions. The molecule of the present invention is also a useful effector of primary and central neurons, particularly the dopaminergic neurons in the central nervous system and the growth factor genes.

As a result, the presence of the need for a composition for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action and the inadequacy of the existing solutions have made it necessary to perform an improvement in the relevant art.

**Object of the Invention**

In order to eliminate the disadvantages of the state of the art, an object of the invention is to enable an increase in the sensitivity of dopamine 5 receptor.

Another object of the invention is to enable the suppression of monoamine oxidase B.

Another object of the invention is to enable the suppression of phenylethanolamine N-methyltransferase.

In order to achieve the aforesaid advantages, the invention is a composition for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action, said composition being obtained by the components selected from the group comprising 2,​2-​difluoro-​N-​[(2R,4R)-​4-di​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester, 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester that are used individually or in combinations.

The structural and characteristic features and all the advantages of the invention will become more clearly understood from the detailed description provided below and therefore, the evaluation must be made taking this detailed description into consideration.

**Detailed Description of the Invention**

The invention is a composition containing picroretoside derivatives formed for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action. Said composition enables an increase in the sensitivity of dopamine 5 receptor, enables the suppression of monoamine oxidase B and enables the suppression of phenylethanolamine N-methyltransferase.

The composition according to the invention contains 2,​2-​difluoro-​N-​[(2R,4R)-​4-dihydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester, 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester.

Said composition is obtained by a mixture of the aforesaid components according to the following ratios by weight:

1-99% 2,​2-​difluoro-​N-​[(2R,4R)-​4-di​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester,

99-1% 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester.

The composition is obtained from the aforesaid components selected from the aforesaid group and used according to the mentioned weight ratio ranges individually or in combinations.

Said invention also encompasses the use of said composition for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action and the manufacture thereof for this purpose.

**CLAIMS**

1. A composition for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action, said composition being obtained by the components selected from the group comprising 2,​2-​difluoro-​N-​[(2R,4R)-​4-di​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester, 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester that are used individually or in combinations.
2. A composition according to Claim 1 characterized in that it comprises 1-99% by weight 2,​2-​difluoro-​N-​[(2R,4R)-​4-di​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester.
3. A composition according to Claim 1 characterized in that it comprises 99-1% by weight 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester.
4. Use of the components according to Claims 1 to 3 obtained individually or in combinations selected from the group consisting of 2,​2-​difluoro-​N-​[(2R,4R)-​4-di​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)methyl]-​picroretoside-ethyl-ester, 2,​2-​difluoro-​N-​[(1R,​2R)-​2-​hydroxy-​1-​(hydroxyethyl)-​2-​(4-​aminophenyl)ethyl]-​picroretoside-phenyl-ester for the manufacture of a composition for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action.

**ABSTRACT**

**A COMPOSITION CONTAINING PICRORETOSIDE DERIVATIVES THAT EXHIBIT PRO-DOPAMINERGIC CHARACTER FOR INCREASING THE SENSITIVITY OF DOPAMINE 5 RECEPTOR**

The invention relates to a composition formed for increasing the sensitivity of dopamine 5 receptor and for exhibiting pro-dopaminergic action.

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