

5-HT_{2B} RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

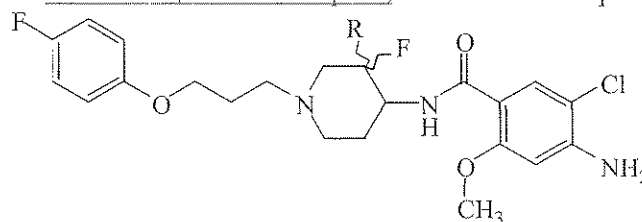
- 5 The present invention relates to novel fluorinated piperidine derivatives having antagonistic activity at the 5-HT_{2B} receptor, pharmaceutical compositions comprising these compounds and their use as a medicine.

BACKGROUND OF THE INVENTION

- 10 Cisapride is a serotonin 5-HT₄ receptor agonist useful as a gastroprokinetic drug. It interacts significantly with several other receptors such as 5-HT_{2A} and 5-HT_{2C}; D_{2L}; 5-HT_{3A/B}; Alpha_{1A}, Alpha_{2A}, Alpha_{2B} and Alpha_{2C}. It was withdrawn from some markets in 2000 due to reports of sudden cardiac arrhythmias. At the origin of this side effect is drug-induced QT prolongation by blockade of the hERG potassium channel
- 15 (human ether-a-go-go related gene). One of the known pharmacophores of a hERG channel blocker comprises a hydrophilic and a hydrophobic moiety linked by a middle part having a basic nitrogen atom. At physiological pH, the basic nitrogen is protonated and is involved in cation- π interaction with Tyr 652 residues within the hERG channel pore. In order to lower the pKa value of piperidine nitrogen atom, and thereby reduce
- 20 the likelihood of blockade of the hERG channel, derivatives of cisapride were prepared wherein 3-methoxy-piperidine was replaced by 3-fluoropiperidine and 3,3-difluoropiperidine.

~~SUMMARY OF THE INVENTION~~

- 25 The present ~~invention~~ disclosure, in a first aspect, concerns a compound of formula (I)



or a stereochemically isomeric form thereof, wherein

R is hydrogen or fluoro, or

an addition salt or a solvate thereof.

Illustrative of the ~~invention~~disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. In a second aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above and a pharmaceutically acceptable carrier. An illustration of the ~~invention~~disclosure is a pharmaceutical composition made by mixing any of the

compounds described above and a pharmaceutically acceptable carrier. Illustrating the inventiondisclosure is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier. In a third aspect, there is provided a process for preparing a pharmaceutical composition as defined above, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined above.

Exemplifying the inventiondisclosure are methods of treating a disorder mediated by the 5-HT_{2B} receptor, comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Further exemplifying the inventiondisclosure are methods of inhibiting the 5-HT_{2B} receptor, comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the inventiondisclosure is a method of treating a disorder selected from the group consisting of pulmonary arterial hypertension, pulmonary fibrosis, irritable bowel syndrome, cardiovascular disorders such as chronic heart disease, congestive heart failure and hypertension, comprising administering to a subject in need thereof, a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the inventiondisclosure is any of the compounds described above for use in treating pulmonary arterial hypertension, pulmonary fibrosis, irritable bowel syndrome, cardiovascular disorders such as chronic heart disease, congestive heart failure and hypertension, in a subject in need thereof. In a fourth aspect, there is provided a compound as defined above for use in the treatment or prevention of pulmonary arterial hypertension, pulmonary fibrosis or irritable bowel syndrome.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of formula (I) as defined hereinbefore, and pharmaceutically acceptable salts thereof. The compounds of formula (I) are selective antagonists at the 5-HT_{2B} receptor.

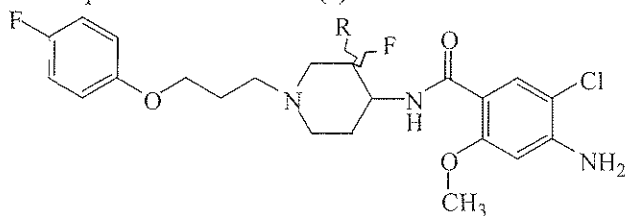
In an embodiment of the present invention, R is fluoro and the compound is a racemic mixture or an addition salt or a solvate thereof.

In another embodiment of the present invention, R is fluoro and the compound has an optical rotation $[\alpha] = +14.1^\circ$ ($c=0.3$, MeOH, $\lambda = 598$ nm; 20°C), or an addition salt or a solvate thereof.

5 In another embodiment of the present invention, R is fluoro and the compound has an optical rotation $[\alpha] = -14.4^\circ$ ($c=0.3$, MeOH, $\lambda = 598$ nm; 20°C), or an addition salt or a solvate thereof.

CLAIMS

1. A compound of Formula (I)



- 5 or a stereochemically isomeric form thereof, wherein
R is hydrogen or fluoro, or
an addition salt or a solvate thereof.
- 10 2. The compound according to claim 1 wherein R is fluoro and the compound is a racemic mixture, or an addition salt or a solvate thereof.
- 15 3. The compound according to claim 1 wherein R is fluoro and the compound has an optical rotation $[\alpha] = -14.4^\circ$ ($c=0.3$, MeOH, $\lambda = 598$ nm; 20°C), or an addition salt or a solvate thereof.
4. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of claims 1 to 3 and a pharmaceutically acceptable carrier.
- 20 5. A process for preparing a pharmaceutical composition as defined in claim 4, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a ~~therapeutically~~therapeutically effective amount of a compound as defined in any one of claims 1 to 3.
- 25 6. A compound as defined in any one of claims 1 to 3 for use in the treatment or prevention of pulmonary arterial hypertension, pulmonary fibrosis or irritable bowel syndrome.