SPIROPIPERIDINE COMPOUNDS AS ORL-1 RECEPTOR ANTAGONISTS

Orphanin FQ (OFQ)/Nociceptin is a 17 amino acid peptide that has high affinity for the ORL1 G-protein coupled receptor (GPCR). The ORL1 receptor is a Class A GPCR that is expressed primarily in the central nervous system and peripheral nervous system as well as in the gastrointestinal tract, smooth muscle, and immune system. While related structurally to opioid peptides/receptors the OFQ/Nociceptin system exhibits no significant cross reactivity to classical opioid peptides/receptors and exhibits anti-opioid activity in vivo (for example ORQ/Nociceptin has been reported to exhibit anti-nociceptive properties).

Nociceptin/orphanin FQ receptor (NOC/OFQ) antagonists, specifically antagonists of the ORL-1 receptor have demonstrated anti-depressant activity and anorectic activity in numerous studies with animal models for depression and feeding behavior. As such, ORL-1 antagonists are deemed to be useful in the treatment of depression and/or the treatment of overweight, obesity, and/or weight maintenance post treatment for overweight or obesity.

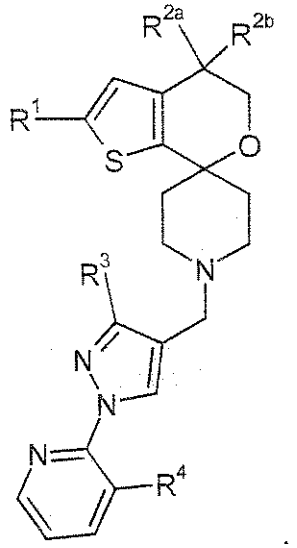
WO 2003/095427 describes certain spiropiperidinyl compounds as ORL-1 antagonists for use as analgesics.

Yoshizumi, Takashi et al. (2008), *Design, synthesis, and structure-activity relationship study of a novel class of ORL-1 receptor antagonists based on N-biarylmethyl spiropiperidine*, Bioorganic & Medicinal Chemistry Letters vol. 18, pg. 3778-3782, describes certain *N*-biarylmethyl-spiropiperidine compounds as selective ORL-1 antagonists.

The present disclosure~~invention~~ provides a family of 4',5'-dihydrospiro[piperidine-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 disclosure~~invention~~ have favorable biopharmaceutical and pharmacokinetic properties (e.g. solubility, oral exposure, and

CNS permeability). Certain of the compounds of the present disclosure~~invention~~ exhibit reduced oxidative metabolism resulting in favorable oral bioavailability. Certain compounds have also demonstrated through animal models that the compounds of the present disclosure~~invention~~ are useful for the treatment of migraine.

In a first aspect, there is~~The present invention~~ provided~~s~~ a compound~~s~~ of Formula I:



I

wherein

R^1 is fluoro or chloro;

R^{2a} and R^{2b} are each hydrogen or are each fluoro;

R^3 is hydrogen, methyl, hydroxymethyl, or $(C_1$-$C_3)$ alkoxymethyl;

R^4 is selected from the group consisting of fluoro, chloro, cyano, cyanomethyl, $(C_1$-$C_3)$ alkyl, cyclopropyl, hydroxymethyl, methoxy, cyclopropylmethoxy, aminocarbonylmethoxy, $(C_1$-$C_3)$ alkoxymethyl, cyclopropyloxymethyl, cyclopropylmethoxymethyl, 1-hydroxy-1-methylethyl, aminocarbonyloxymethyl, methylaminocarbonyloxymethyl, dimethylaminocarbonyloxymethyl, aminocarbonyl, aminocarbonylmethyl, $-CH_2-NR^5R^6$, hydroxyimine, methoxyimine, morpholin-4-yl, morpholin-4-ylmethyl, Ar^1, $-CH_2Ar^1$, tetrahydrofuran-2-yl, 3-oxomorpholin-4-ylmethyl, 2-oxopyrrolidin-1-ylmethyl, and 2-oxopiperidin-1-ylmethyl;

R^5 is hydrogen, C_1-C_3 alkyl, cyanomethyl, $-C(O)CH_3$, or aminocarbonylmethyl;

R^6 is hydrogen or methyl; and

Ar^1 is a moiety selected from the group consisting of imidizol-1-yl, imidizol-2-yl, 2-methylimidizol-1-yl, pyrazol-1-yl, 1,2,3-triazol-1-yl; 1,2,3-triazol-2-yl; 1,2,4-triazol-1-yl, isoxazol-3-yl, oxazol-5-yl, and 3-methyl-1,2,4-oxadiazol-5-yl; or a pharmaceutically acceptable salt thereof.

In another aspect of the disclosureinvention there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier, diluent, or excipient. OneIn an embodiment of this aspect of the invention, the pharmaceutical composition further comprises at least one additional therapeutic ingredient, as for example an SSRI antidepressant, as for example fluoxetine. In a further aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, a selective serotonin reuptake inhibitor (SSRI) antidepressant and a pharmaceutically acceptable carrier, diluent, or excipient. Furthermore, there is providedthis aspect of the invention provides a pharmaceutical composition adapted for the treatment of depression comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof. In another embodiment of this aspect of the invention there is provided a pharmaceutical composition adapted for the treatment of overweight, obesity and/or weight maintenance, comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof. A further embodiment provides a pharmaceutical composition adapted for the treatment of migraine comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable excipients, carriers, or diluents thereof.

In a further aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In a further aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity or overweight in a human.

In a further aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of migraine.

In a further aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression.

In a further aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of obesity or overweight in a human.

In a further aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of migraine.

In a further aspect, there is provided the use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of depression.

The present disclosure~~invention~~ also provides a method of treating depression in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof. A further embodiment provides a method of treating depression in a mammal comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, and an effective amount of an SSRI antidepressant, or a pharmaceutically acceptable salt thereof, as for example fluoxetine. Other embodiments of the disclosure~~invention~~ provide methods of treating overweight and/or obesity, and/or a method for weight maintenance comprising administering to a

mammal in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In one particular embodiment of these aspects of the invention, the mammal is a human.

This disclosure~~invention~~ also provides a compound of Formula I or a pharmaceutically acceptable salt thereof for use in therapy. There is~~Within this aspect, the invention~~ provides~~d~~ a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of depression in mammals, particularly humans. The disclosure~~invention~~ also provides a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an SSRI antidepressant, or a pharmaceutically acceptable salt thereof, as for example fluoxetine, for use in the treatment of depression in mammals, particularly humans. Further, the present disclosure~~this aspect of the invention~~ includes any one of the following: a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of overweight; a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of obesity; a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the maintenance of weight (for weight maintenance), particularly after treatment for overweight or obesity; a compound of Formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of migraine.

There is also~~Another aspect of this invention~~ provides~~d~~ the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of depression. Another embodiment of the disclosure~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of overweight, obesity, and/or the maintenance of weight. Yet another embodiment of the disclosure~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of migraine.

Compounds of this disclosure~~invention~~ are bases, and accordingly react with a number of organic and inorganic acids to form pharmaceutically acceptable salts. Pharmaceutically acceptable salts of each of the compounds of the present disclosure~~invention~~ are contemplated within the scope of the present application. The term "pharmaceutically acceptable salt" as used herein, refers to any salt of a compound of Formula I that is substantially non-