

NOVEL AZETIDINE DERIVATIVES USEFUL AS MODULATORS OF CORTICAL CATECHOLAMINERGIC NEUROTRANSMISSION

5 TECHNICAL FIELD

The present disclosure relates to novel 3-benzyl-azetidine derivatives, useful for modulating levels of monoamines, such as dopamine, norepinephrine and serotonin, in cerebral cortical areas of the mammalian brain, and more specifically for the treatment of central nervous system disorders. The present disclosure also relates to the use of these compounds in a method for
10 therapy and to pharmaceutical compositions comprising the compounds of the present disclosure.

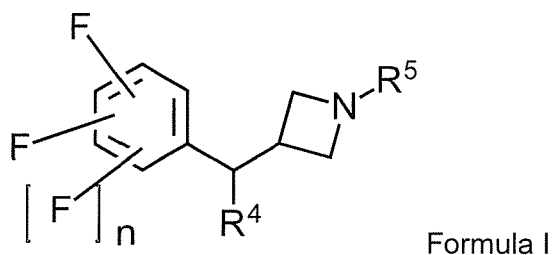
BACKGROUND

The cerebral cortex encompasses several major regions that are involved in higher functions
15 such as thought, feelings, memory and planning. Monoamines, such as dopamine, norepinephrine and serotonin, are important as neurotransmitters for mammalian cortical function. The ascending serotonergic and noradrenergic pathways innervate virtually all regions of the brain including the cerebral cortex. The dopaminergic neurons of the CNS have more distinct projections, including the meso-cortical pathway primarily innervating the frontal cortex,
20 in addition to a number of specific subcortical pathways. Primary or secondary dysfunctions in the activity of the monoamine pathways innervating the cerebral cortex lead to aberrations of the activity at cortical dopamine, norepinephrine and serotonin receptors and subsequently to manifestations of psychiatric and neurological symptoms.

25 The monoamines of the cortex modulate several aspects of cortical functions controlling affect, anxiety, motivation, cognition, attention, arousal and wakefulness. Thus, the catecholamines dopamine and norepinephrine exert strong influence on the frontal cortical areas, the integrity of which is essential for the so-called executive cognitive functions, related to e.g. attention, planning of actions and impulse control. Norepinephrine is a major part in the circuitry regulating
30 anxiety and fear and is thus believed to be dysregulated in anxiety disorders such as panic disorders, generalized anxiety disorder (GAD) and specific phobias. Concerning mood and affective functions, the usefulness of compounds facilitating particularly norepinephrine and serotonin neurotransmission in the treatment of depression and anxiety has strongly contributed to the widely-accepted concept that these neuro-transmitters are both involved in the regulation
35 of affective functions.

CLAIMS

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof,

wherein

R^4 is F or CH_3 ,

R^5 is H or C_1 - C_4 alkyl substituted with 0, 1, 2 or 3 F, and

n is 0, 1, 2 or 3.

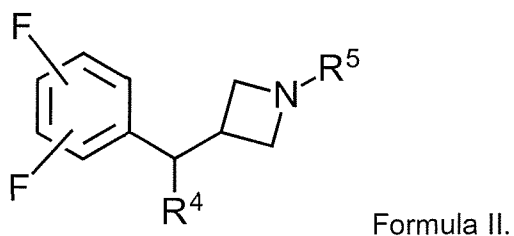
2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein

n is 0 or 1.

3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof,

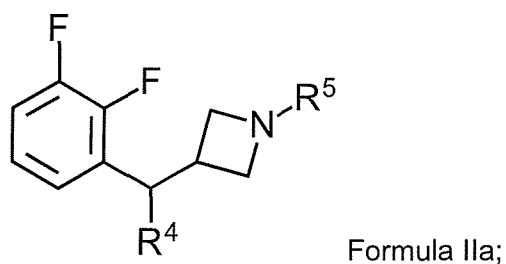
which is a compound of Formula II:

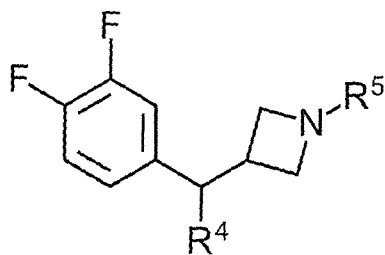


4. A compound according to claim 3, or a pharmaceutically acceptable salt thereof, which is

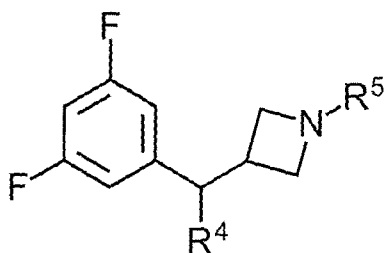
selected from the group consisting of compounds of Formula IIa, Formula IIb, Formula IIc,

Formula IId, Formula IIe and Formula IIf:

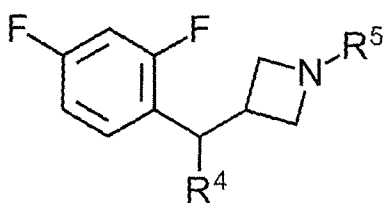




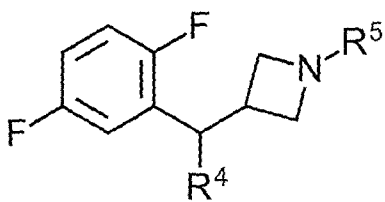
Formula IIb,



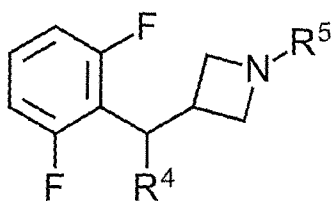
Formula IIc,



Formula II d,

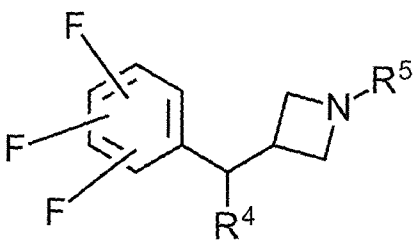


Formula IIe, and



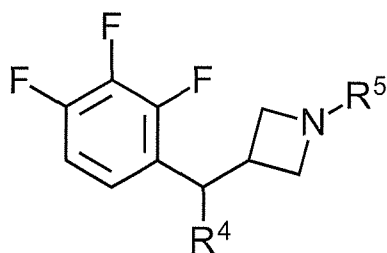
Formula II f.

5. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, which is a compound of Formula III:

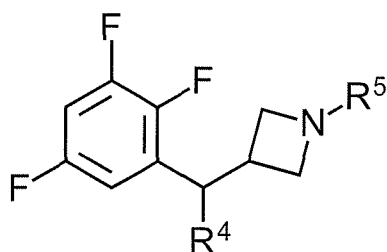


Formula III.

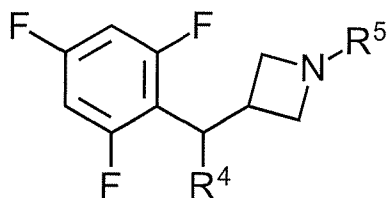
6. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, which is selected from the group consisting of compounds of Formula IIIa, Formula IIIb, Formula IIIc, Formula IIId and Formula IIIe:



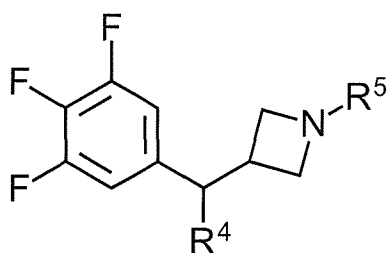
Formula IIIa,



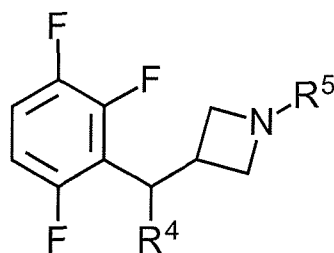
Formula IIIb,



Formula IIIc,



Formula IIId, and



Formula IIIe.

7. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^4 is F.

8. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R⁵ is H.

9. A compound according to claim 1, which is:

(-)-3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 (+)-3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 (-)-3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 (+)-3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(3,4-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(2,5-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(2,6-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(2,4-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[FLUORO(2,3,5-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(2,4,6-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(2,3,4-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(3,4,5-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,
 3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]-1-METHYL AZETIDINE,
 3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]-1-ETHYL AZETIDINE,
 3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]-1-PROPYL AZETIDINE,
 3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]-1-METHYL AZETIDINE,
 3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]-1-ETHYL AZETIDINE,
 3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]-1-PROPYL AZETIDINE,
 3-[FLUORO(2,3,5-TRIFLUOROPHENYL)METHYL]-1-METHYL AZETIDINE,
 1-ETHYL-3-[FLUORO(2,3,5-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(2,3,5-TRIFLUOROPHENYL)METHYL]-1-PROPYL AZETIDINE,
 1-ETHYL-3-[FLUORO(2,3,4-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(2,3,4-TRIFLUOROPHENYL)METHYL]-1-PROPYL AZETIDINE,
 1-ETHYL-3-[FLUORO(3,4,5-TRIFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(3,4,5-TRIFLUOROPHENYL)METHYL]-1-PROPYL AZETIDINE,
 3-[FLUORO(2,3,5,6-TETRAFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(PENTAFLUOROPHENYL)METHYL]AZETIDINE,
 3-[FLUORO(2,3,5,6-TETRAFLUOROPHENYL)METHYL]-1-METHYL AZETIDINE,
 1-ETHYL-3-[FLUORO(2,3,5,6-TETRAFLUOROPHENYL)METHYL]-AZETIDINE, and

3-[FLUORO(2,3,5,6-TETRAFLUOROPHENYL)METHYL]-1-PROPYLAZETIDINE

or a pharmaceutically acceptable salt of any of the foregoing compounds.

10. A compound according to claim 1, which is:

(-)-3-[(2,3-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,

(-)-3-[(3,5-DIFLUOROPHENYL)(FLUORO)METHYL]AZETIDINE,

(-)-3-[FLUORO(2,3,5-TRIFLUOROPHENYL)METHYL]AZETIDINE,

or a pharmaceutically acceptable salt of any of the foregoing compounds.

11. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula I is a (-)-enantiomer.

12. A pharmaceutical composition, comprising a therapeutically effective amount of a compound according to any one of claims 1-11, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient and/or diluent.

13. A compound according to any one of claims 1-11 or a pharmaceutically acceptable salt thereof, for use as a medicament.

14. Use of a compound according to any one of claims 1-11 for the manufacture of a medicament for the treatment and/or prevention of a disease, disorder and/or condition which is responsive to modulation of monoamines in the cerebral cortex, wherein said disease, disorder and/or condition is selected from the group consisting of dementia, age-related cognitive impairment, cognitive impairment associated with neurodegenerative disorders and/or diseases, autism spectrum disorders, affective disorders, schizophrenia, anxiety disorders, attention deficit hyperactivity disorder (ADHD) and movement disorders.

15. Use according to claim 14, wherein said disease, disorder and/or condition is selected from the group consisting of dementia, age-related cognitive impairment and schizophrenia.