R2 is selected from the group consisting of hydrogen, linear or branched C_1-C_8 alkyl, phenyl, saturated monocyclic C_3-C_8 cycloalkyl, oxetanyl, benzo[*d*][1,3]dioxolyl, tetrahydrofuranyl and tetrahydropyranyl; or

R2 is phenyl or pyridyl substituted with one or more substituents selected from the group consisting of hydroxyl, amino, cyano, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_5 cycloalkoxy, C_3-C_5 cycloalkyl-methoxy, C_1-C_3 fluoroalkoxy, and -NC(O)CH_3; or

R2 is a 5-membered heteroaryl which can be substituted one or more times with C_1-C_3 alkyl;

R3 is selected from the group consisting of hydrogen, halogen, C_1-C_5 alkyl, C_3-C_5 cycloalkyl and phenyl; or

R3 is selected from the group consisting of phenyl substituted one or more times with C_1-C_3 alkyl; methyl substituted one, two or three times with fluorine; ethyl substituted one, two or three times with fluorine;

R4 is hydrogen;

and tautomers and pharmaceutically acceptable addition salts thereof;

with the proviso that R2 and R3 cannot be hydrogen at the same time; and

2) a second compound, which compound is useful in the treatment of a psychiatric disorder;

wherein 1) and 2) are for combined use in the treatment of a psychiatric and/or cognitive disorder.

Reference to Compound (I) includes the free base of Compound (I), pharmaceutically acceptable salts of Compound (I), such as acid addition salts of Compound (I), racemic mixtures of Compound (I), or the corresponding enantiomer and/or optical isomer of Compound (I), and polymorphic and amorphic forms of Compound (I) as well as tautomeric forms of Compound (I). Furthermore, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

In one aspect, the present disclosure relates to a pharmaceutical composition comprising

1) a compound according formula (I); and

2) a second compound, which compound is useful in the treatment of a psychiatric disorder; and

one or more pharmaceutically acceptable carrier or excipient.

In one aspect, the present disclosure relates to a method for the treatment of a psychiatric and/or cognitive disorder, which method comprises the administration of:

1) a therapeutically effective amount of a compound according to Formula (I); and

2) a therapeutically effective amount of:

a second compound, which compound is useful in the treatment of a psychiatric disorder, to a patient in need thereof.

In one aspect, the present disclosure relates to the use of a compound of Formula (I) as described herein in the manufacture of a medicament for the treatment of a psychiatric and/or cognitive disorder; wherein said medicament is to be used in combination with a second compound, which compound is useful in the treatment of a psychiatric disorder.

In one aspect, the present disclosure relates to the use of:

1) a compound of Formula (I); and

2) a second compound, which compound is useful in the treatment of a psychiatric disorder;

in the manufacture of a medicament for use in the treatment of a psychiatric and/or cognitive disorder.

In another aspect, the present disclosure relates to a use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a psychiatric and/or cognitive disorder.

DETAILED DESCRIPTION OF THE INVENTION

EMBODIMENTS OF THE INVENTION

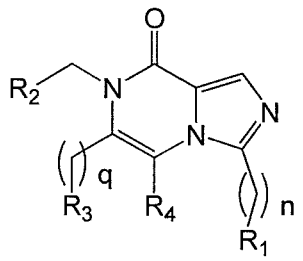
The following notation is applied: an embodiment of the invention is identified as Ei, where i is an integer indicating the number of the embodiment. An embodiment Ei' specifying a specific embodiment a previously listed embodiment Ei is identified as Ei'(Ei), e.g. E2(E1) means "in an embodiment E2 of embodiment E1".

Where an embodiment is a combination of two embodiments the notation is similarly Ei''(Ei and Ei'), e.g. E3(E1 and E2) means "in an embodiment E3 according to any of embodiments E2 and E1"

Where an embodiment is a combination of more than two embodiments the notation is similarly Ei'''(Ei, Ei' and Ei'') or (Ei-Ei''), e.g. E4(E1, E2 and E3) or E4(E1-E3), means "in an embodiment E4 according to any of embodiments E1, E2 and E3"

Claims

1. Use of a compound of Formula (I)



(I)

wherein

n is 0 or 1;

q is 0 or 1;

R1 is selected from the group consisting of benzyl, indanyl, indoline and 5-membered heteroaryls; all of which can be substituted with a substituent selected from the group consisting of halogen and C_1-C_3 alkyl; or

R1 is selected from the group consisting of saturated monocyclic rings containing 4-6 carbon atoms and 1-2 nitrogen atoms; all of which can be substituted one or more times with one or more substituents selected from the group consisting of methyl, fluorine and sulfonamide; or

R1 is selected from the group consisting of lactams containing 4-6 carbon atoms; all of which can be substituted one or more times with one or more substituents selected from the group consisting of methyl and fluorine; or

R1 is selected from the group consisting of bicyclic ethers such as, 7-oxabicyclo[2.2.1]heptane; all of which can be substituted one or more times with one or more substituents selected from the group consisting of methyl and fluorine; or

R1 is selected from the group consisting of linear or branched C_1-C_8 alkyl, saturated monocyclic C_3-C_8 cycloalkyl, oxetanyl, tetrahydrofuranyl and tetrahydropyranyl; all of which can be substituted one or more times with one or more substituents selected from the group consisting of methyl, fluorine, hydroxy, cyano or methoxy; or

R1 is a linear or branched C_1-C_3 alkyl, which is substituted with a substituent selected from phenyl and 5-membered heteroaryl, wherein said 5-membered heteroaryl can be substituted with one or more C_1-C_3 alkyls; or

R1 is selected from the group consisting of morpholine, tetrahydrofuran-3-amine, hexahydro-2*H*-furo[3,2-b]pyrrole and homomorpholine; all of which can be subsituted with one or more substituents selected from the group consisting of C_1-C_3 alkyl;

R2 is selected from the group consisting of hydrogen, linear or branched C_1-C_8 alkyl, phenyl, saturated monocyclic C_3-C_8 cycloalkyl, oxetanyl, benzo[*d*][1,3]dioxolyl, tetrahydrofuranyl and tetrahydropyranyl; or

R2 is phenyl or pyridyl substituted with one or more substituents selected from the group consisting of hydroxyl, amino, cyano, halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_5 cycloalkoxy, C_3-C_5 cycloalkyl-methoxy, C_1-C_3 fluoroalkoxy, and -NC(O)CH_3; or

R2 is a 5-membered heteroaryl which can be substituted with one or more C_1-C_3 alkyl;

R3 is selected from the group consisting of hydrogen, halogen, C_1-C_5 alkyl, C_3-C_5 cycloalkyl and phenyl; or

R3 is selected from the group consisting of phenyl substituted one or more times with C_1-C_3 alkyl; methyl substituted one, two or three times with fluorine; ethyl substituted one, two or three times with fluorine;

R4 is hydrogen;

and tautomers and pharmaceutically acceptable addition salts thereof;

with the proviso that R2 and R3 cannot be hydrogen at the same time; in the manufacture of a medicament for the treatment of a psychiatric and/ or cognitive disorder; wherein said medicament is to be used in combination with a second compound, which compound is useful in the treatment of a psychiatric disorder.

2. The use according to claim 1, wherein

R1 is selected from the group consisting of linear or branched C_1-C_8 alkyl, saturated monocyclic C_3-C_8 cycloalkyl, oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl;

R2 is selected from the group consisting of, linear or branched C_1-C_8 alkyl, phenyl, and saturated monocyclic C_3-C_8 cycloalkyl; or

R2 is selected from the group consisting of phenyl substituted with a substituent selected from the group consisting of halogen, C_1-C_3 alkyl and methoxy;

R3 is selected from the group consisting of hydrogen, C_1-C_3 alkyl and halogen;

R4 is hydrogen.

3. The use according to claim 1, wherein said compound of formula (I) is selected from the group consisting of:

7-(3-Fluorobenzyl)-3-propylimidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Benzyl-7-(3-fluorobenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Benzyl-7-(cyclohexylmethyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cyclohexylmethyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-Fluorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

3-Cyclopropyl-7-(3-fluorobenzyl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cyclopentylmethyl)-3-cyclopropylimidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cyclohexylmethyl)-3-cyclopropylimidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-Fluorobenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cyclopentylmethyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cyclohexylmethyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cycloheptylmethyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(Cycloheptylmethyl)-3-cyclopropylimidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(4-Chlorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Bromo-7-(3-fluorobenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-Benzyl-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(2-Fluorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-Chlorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(2-Chlorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-Methoxybenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Methyl-7-(2-methylbenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Methyl-7-(4-methylbenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(4-Methoxybenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(4-Fluorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

6-Methyl-7-(3-methylbenzyl)-3-(tetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-fluorobenzyl)-6-methyl-3-(4-methyltetrahydro-2*H*-pyran-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(4-methoxybenzyl)-6-methyl-3-((tetrahydrofuran-3-yl)amino)imidazo[1,5-a]pyrazin-8(7*H*)-one;

(*R*)-7-(4-methoxybenzyl)-6-methyl-3-(3-methylmorpholino)imidazo[1,5-a]pyrazin-8(7*H*)-one;

(S)-7-(4-methoxybenzyl)-6-methyl-3-(3-methylmorpholino)imidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(4-methoxybenzyl)-6-methyl-3-(1,4-oxazepan-4-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

3-(2,2-dimethylmorpholino)-7-(4-methoxybenzyl)-6-methylimidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-fluorobenzyl)-3-((3a*S*,6a*S*)-hexahydro-4*H*-furo[3,2-b]pyrrol-4-yl)-6-methylimidazo[1,5-a]pyrazin-8(7*H*)-one;

7-(3-fluorobenzyl)-3-((3a*R*,6a*R*)-hexahydro-4*H*-furo[3,2-b]pyrrol-4-yl)-6-methylimidazo[1,5-a]pyrazin-8(7*H*)-one;

(*R*)-7-(3-fluorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

(*S*)-7-(3-fluorobenzyl)-6-methyl-3-(tetrahydro-2*H*-pyran-3-yl)imidazo[1,5-a]pyrazin-8(7*H*)-one;

or a pharmaceutically acceptable salt of any of these compounds.

4. The use according to any of claims 1-3, wherein said psychiatric and/or cognitive disorder is selected from the group consisting of Attention Deficit Hyperactivity Disorder (ADHD), depression, anxiety, narcolepsy, schizophrenia, cognitive impairment and cognitive impairment associated with schizophrenia (CIAS).

5. The use according to any of claims 1-4, wherein said second compound, which compound is useful in the treatment of a psychiatric disorder, has a pharmacological activity selected from one or more of the following mechanisms: antagonist/inverse agonist/negative modulator/partial agonist/inhibitor of one or more of the targets dopamine D1 receptor, dopamine D2 receptor, dopamine D3 receptor, phosphodiesterase PDE10, serotonin 5-HT2A receptor, serotonin 5-HT6 receptor, and glycine transporter GlyT1; or agonist/positive modulator/partial agonist of one or more of the targets KCNQ channel, NMDA receptor, AMPA receptor and nicotinic alpha-7 receptor.

6. The use according to any of claims 1-4, wherein said second compound, which compound is useful in the treatment of a psychiatric disorder, is selected from the list

7-(4-methoxybenzyl)-6-methyl-3-((tetrahydrofuran-3-yl)amino)imidazo[1,5-a]pyrazin-8(7H)-one;

(R)-7-(4-methoxybenzyl)-6-methyl-3-(3-methylmorpholino)imidazo[1,5-a]pyrazin-8(7H)-one;

(S)-7-(4-methoxybenzyl)-6-methyl-3-(3-methylmorpholino)imidazo[1,5-a]pyrazin-8(7H)-one;

7-(4-methoxybenzyl)-6-methyl-3-(1,4-oxazepan-4-yl)imidazo[1,5-a]pyrazin-8(7H)-one;

3-(2,2-dimethylmorpholino)-7-(4-methoxybenzyl)-6-methylimidazo[1,5-a]pyrazin-8(7H)-one;

7-(3-fluorobenzyl)-3-((3aS,6aS)-hexahydro-4H-furo[3,2-b]pyrrol-4-yl)-6-methylimidazo[1,5-a]pyrazin-8(7H)-one;

7-(3-fluorobenzyl)-3-((3aR,6aR)-hexahydro-4H-furo[3,2-b]pyrrol-4-yl)-6-methylimidazo[1,5-a]pyrazin-8(7H)-one;

(R)-7-(3-fluorobenzyl)-6-methyl-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-8(7H)-one;

(S)-7-(3-fluorobenzyl)-6-methyl-3-(tetrahydro-2H-pyran-3-yl)imidazo[1,5-a]pyrazin-8(7H)-one;

or a pharmaceutically acceptable salt of any of these compounds.

10. The pharmaceutical composition according to any of claims 7-9, comprising the compound of formula (I) and any of the compounds listed under item 2) in claim 1, in therapeutically effective amounts.

11. Use of the pharmaceutical composition according to any of claims 7-10 in the manufacture of a medicament for the treatment of a psychiatric and/or cognitive disorder.

12. The use according to claim 11, wherein said psychiatric and/or cognitive disorder is selected from the group consisting of Attention Deficit Hyperactivity Disorder (ADHD), depression, anxiety, narcolepsy, schizophrenia, cognitive impairment and cognitive impairment associated with schizophrenia (CIAS),

13. The pharmaceutical composition according to any of claims 7-10, wherein said second compound, which compound is useful in the treatment of a psychiatric disorder, has a pharmacological activity selected from one or more of the following mechanisms: antagonist/inverse agonist/negative modulator/partial agonist/inhibitor of one or more of the

targets dopamine D1 receptor, dopamine D2 receptor, dopamine D3 receptor, phosphodiesterase PDE10, serotonin 5-HT2A receptor, serotonin 5-HT6 receptor, and glycine transporter GlyT1; or agonist/positive modulator/partial agonist of one or more of the targets KCNQ channel, NMDA receptor, AMPA receptor and nicotinic alpha-7 receptor.

14. The pharmaceutical composition according to any of claims 7-10, wherein said second compound, which compound is useful in the treatment of a psychiatric disorder, is selected from the list comprising clozapine, risperidone, paliperidone, olanzapine, quetiapine, amisulpride, ziprasidone, aripiprazole, brexpiprazole, asenapine, haloperidole, iloperidone, lurasidone, chlorpromazine, blonanserin, perphenazine, levomepromazine, sulpiride, fluphenazine, zuclopenthixol, flupenthixol and cariprazine.

15. The use according to any of claims 11-12, wherein said second compound of the composition , which compound is useful in the treatment of a psychiatric disorder, has a pharmacological activity selected from one or more of the following mechanisms: antagonist/inverse agonist/negative modulator/partial agonist/inhibitor of one or more of the targets dopamine D1 receptor, dopamine D2 receptor, dopamine D3 receptor, phosphodiesterase PDE10, serotonin 5-HT2A receptor, serotonin 5-HT6 receptor, and glycine transporter GlyT1; or agonist/positive modulator/partial agonist of one or more of the targets KCNQ channel, NMDA receptor, AMPA receptor and nicotinic alpha-7 receptor.

16. The use according to any of claims 11-12, wherein said second compound of the composition, which compound is useful in the treatment of a psychiatric disorder, is selected from the list comprising clozapine, risperidone, paliperidone, olanzapine, quetiapine, amisulpride, ziprasidone, aripiprazole, brexpiprazole, asenapine, haloperidole, iloperidone, lurasidone, chlorpromazine, blonanserin, perphenazine, levomepromazine, sulpiride, fluphenazine, zuclopenthixol, flupenthixol and cariprazine.