

2007/121319 for the treatment of anxiety and depression, from WO 2013/034761, WO 2012/104293 and WO2013/000924 for the treatment of neurological and psychiatric disorders, from WO 2006/072615, WO 2006/072612, WO 2006/024640 and WO 2005/113517 for the treatment of arthritis, cancer, edema and septic shock, 5 from WO 2005/063723 for the treatment of renal and liver failure, liver dysfunction, restless leg syndrome, rheumatic disorders, arthritis, rhinitis, asthma and obesity, from WO 2005/041957 for the treatment of cancer and thrombotic disorders, from WO 2006/102728 for the treatment of angina pectoris and hypertension from WO 2008/043461 for the treatment of cardiovascular disorders, erectile dysfunction, 10 inflammation and renal failure and from WO 2005/061497 for the treatment of e.g. dementia, memory disorders, cancer and osteoporosis.

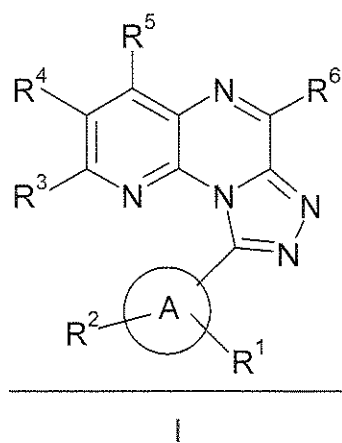
Finally, benzodiazepines are described in WO 2005/063723 for the general treatment of CNS diseases including anxiety, depression, ADHD, neurodegeneration, 15 Alzheimer's disease and psychosis.

Aim of the invention

It has now been found that compounds of the present ~~invention~~ disclosure according to general formula I are effective inhibitors of phosphodiesterase 2 and/or 10. 20 Besides the inhibition property toward phosphodiesterase 2 and/or 10 enzymes, the compounds of the present ~~disclosure invention~~ provide further advantageous pharmacokinetic properties. For example the compounds of the present ~~disclosure invention~~ show high concentration in cerebrospinal fluid (CSF) and have a high CSF to plasma ratio, which translates in lower efficacious doses of the compounds for 25 disease treatment and as a consequence in further potential advantages such as minimization of side effects . Furthermore, compounds of the present ~~disclosure inventions~~ show good metabolic stability and low potential of formation of biologically active metabolite and low hERG potassium channel inhibition.

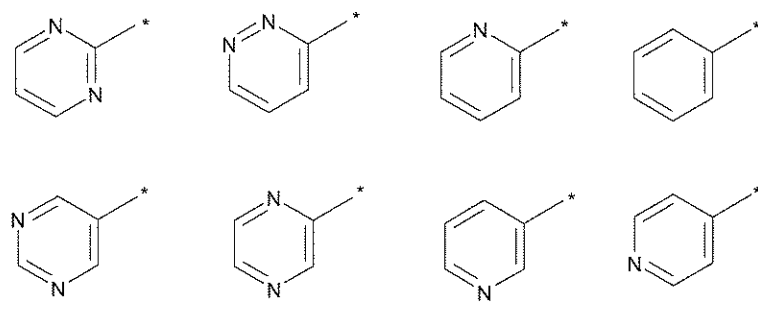
30 Accordingly, ~~one aspect of the disclosure invention~~ refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and salts thereof as inhibitors of phosphodiesterase 2 and/or 10.

According to a first aspect, there is provided compounds of formula I



wherein

A is selected from the group A^a consisting of



wherein above mentioned phenyl-, pyridinyl-, pyrimidinyl-, pyridazinyl and pyrazinyl groups are substituted with R¹ and R²;

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R¹ is selected from the group R^{1a} consisting of H, halogen, NC-, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4,

wherein above mentioned C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl and R⁸-(CH₂)_n-O- groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO- and optionally with 1 to 7 fluorine atoms substituted C₁₋₃-alkyl-;

R² is selected from the group R^{2a} consisting of

H, HO-, halogen, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl, heteroaryl, R⁸-(CH₂)_n-O- with n = 0, 1, 2, 3 or 4, and R⁸-(CH₂)_m-(CH)(CH₃)-(CH₂)_o-O- with m = 0, 1 or 2 and o = 0, 1 or 2,

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wherein above mentioned C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-6} -cycloalkyl-, heterocyclyl, heterocyclyl- C_{1-3} -alkyl-, phenyl, heteroaryl, R^8 -(CH_2)_n-O- and R^8 -(CH_2)_m-(CH)(CH_3)-(CH₂)_o-O-groups may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, HO-, optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-O-, and optionally with 1 to 7 fluorine atoms substituted C_{1-3} -alkyl-;

R³

is selected from the group R^{3a} consisting of H, halogen, NC-, C_{1-4} -alkyl- and C_{3-6} -cycloalkyl-, wherein the above mentioned C_{1-4} -alkyl- and C_{3-6} -cycloalkyl-groups may optionally be substituted with 1 to 9 substituents independently selected from the group consisting of halogen, NC-, HO-, C_{1-3} -alkyl- and C_{1-3} -alkyl-O-;

R⁴, R⁵

are selected independently of each other from the group R^{4a}/R^{5a} consisting of H, halogen, NC-, HO-, C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-8} -cycloalkyl-, C_{3-8} -cycloalkyl- C_{1-3} -alkyl-, C_{3-8} -cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R^7 -CH₂-O- and R^7 -(CH₂)₂-O-, wherein above mentioned C_{1-6} -alkyl-, C_{1-6} -alkyl-O-, C_{3-8} -cycloalkyl-, C_{3-8} -cycloalkyl- C_{1-3} -alkyl-, C_{3-8} -cycloalkyl-O-, heterocyclyl-O-, heterocyclyl, heteroaryl, R^7 -CH₂-O- and R^7 -(CH₂)₂-O-groups, may optionally be substituted with 1 to 5 substituents independently selected from the group consisting of halogen, optionally with 1 to 5 halogen atoms, substituted C_{1-2} -alkyl-, and optionally with 1 to 5 halogen atoms substituted C_{1-2} -alkyl-O-;

R⁶

is selected from the group R^{6a} consisting of H, NC-, C_{1-6} -alkyl-, C_{3-8} -cycloalkyl-, C_{3-8} -cycloalkyl- C_{1-3} -alkyl- and C_{3-8} -cycloalkyl-O- wherein above mentioned C_{1-6} -alkyl- groups may optionally be substituted with 1-3 halogen atoms;

R⁷ is selected from the group R^{7a} consisting of
H, carbocyclyl, heterocyclyl and heteroaryl,
wherein above mentioned carbocyclyl, heterocyclyl and heteroaryl-groups
may optionally be substituted with 1 to 4 substituents independently
selected from the group consisting of HO-, optionally with 1 to 3 halogen
atoms substituted C₁₋₄-alkyl-, optionally with 1 to 3 halogen atoms
substituted C₁₋₄-alkyl-O- and halogen;

R⁸ is selected from the group R^{8a} consisting of
C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-alkyl-, phenyl and pyridyl,
wherein above mentioned C₃₋₆-cycloalkyl, heterocyclyl, heterocyclyl-C₁₋₃-
alkyl-, phenyl and pyridyl groups may optionally be substituted with 1 to 5
substituents independently selected from the group consisting of HO-,
fluorine and optionally with 1 to 7 halogen atoms substituted C₁₋₃-alkyl-;

the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates
thereof, the hydrates thereof and the salts thereof

~~Another aspect of the invention~~ The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 and reaching high concentrations in cerebrospinal fluid (CSF) and/or having high CSF to plasma ratio.

~~Another aspect of the invention~~ The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 and showing good metabolic stability.

~~Another aspect of the invention~~ The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low hERG channel inhibition.

~~Another aspect of the invention~~ The disclosure also refers to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof as inhibitors of phosphodiesterase 2 and/or 10 with low potential of forming biologically active metabolite.

According to a second aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof for use as a medicament.

The disclosure also ~~In a further aspect this invention~~ relates to pharmaceutical compositions, containing at least one compound according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof optionally together with one or more inert carriers and/or diluents.

According to a third aspect, there is provided pharmaceutical compositions containing at least one compound as defined herein or a pharmaceutically acceptable tautomers thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof together with one or more pharmaceutically acceptable carrier.

The disclosure also ~~A further aspect of the present invention~~ relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the

tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of disorders associated with PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction.

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The disclosure also ~~Another aspect of the invention~~ relates to processes of manufacture of the compounds of the present ~~invention~~ disclosure.

The disclosure also ~~A further aspect of the present invention~~ relates to compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof or pharmaceutical compositions comprising compounds according to formula I, the tautomers thereof, the stereoisomers thereof, the mixtures thereof, the solvates thereof, the hydrates thereof and the physiologically acceptable salts thereof for the use in the prevention and/or treatment of diseases or conditions which can be influenced by inhibition of PDE2 and/or 10 hyperactivity and/or cAMP and/or cGMP hypofunction, such as (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood affective disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) including Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14) Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders.

30 In addition, the compounds of the present ~~invention~~ disclosure can be used for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In addition, the compounds of the present ~~invention~~ disclosure can be used for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis. In addition, the compounds of the present invention can be used for the treatment of Alzheimer's disease.

In addition compounds of the present ~~invention~~ disclosure can be used for the treatment of pain disorders, including but not limited to inflammatory, neuropatic and osteoarthritic pain.

In addition, the compounds of the present ~~disclosure~~ invention can be used for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

According to a fourth aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable tautomer thereof, stereoisomer thereof, mixtures thereof, solvate thereof, hydrate thereof or salt thereof or a pharmaceutical composition according to claim 22 for use in the prevention or treatment of (1) disorders comprising the symptom of cognitive deficiency; (2) organic, including symptomatic, mental disorders, dementia; (3) mental retardation; (4) mood [affective] disorders; (5) neurotic, stress-related and somatoform disorders including anxiety disorders; (6) behavioural and emotional disorders with onset usually occurring in childhood and adolescence, attention deficit hyperactivity syndrome (ADHD) and Autism spectrum disorders; (7) disorders of psychological development, developmental disorders of scholastic skills; (8) schizophrenia and other psychotic

disorders; (9) disorders of adult personality and behaviour; (10) mental and behavioural disorders due to psychoactive substance use; (11) extrapyramidal and movement disorders; (12) episodic and paroxysmal disorders, epilepsy; (13) Systemic atrophies primarily affecting the central nervous system, ataxia; (14)

- 5 Behavioural syndromes associated with physiological disturbances and physical factors; (15) sexual dysfunction comprising excessive sexual drive; (16) factitious disorders; (17) Treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory; (18) Treatment amelioration and / or prevention of cognitive impairment being related to
- 10 age-associated learning and memory impairments; (19) Age-associated memory losses; (20) Vascular dementia; (21) Craniocerebral trauma; (22) Stroke; (23) Dementia occurring after strokes (post stroke dementia); (24) Post-traumatic dementia; (25) General concentration impairments; (26) Concentration impairments in children with learning and memory problems; (27) Alzheimer's disease; (28) Lewy
- 15 body dementia; (29) Dementia with degeneration of the frontal lobes; including Pick's syndrome; (30) Parkinson's disease; (31) Progressive nuclear palsy; (32) Dementia with corticobasal degeneration; (33) Amyotrophic lateral sclerosis (ALS); (34) Huntington's disease; (35) Multiple sclerosis; (36) Thalamic degeneration; (37) Creutzfeld-Jacob dementia; (38) HIV dementia; (38) Schizophrenia with dementia or
- 20 Korsakoff's psychosis; (39) Sleep disorders; (40) Bipolar disorder; (41) Metabolic syndrome; (42) Obesity; (43) Diabetes mellitus; (44) Hyperglycemia; (45) Dyslipidemia; (46) Impaired glucose tolerance; (47) Disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen and (48) pain disorders.

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Other aims of the present disclosure invention will become apparent to the skilled man directly from the foregoing and following remarks.

Detailed description

- 30 In a first aspect the present invention relates to compounds of general formula I