

under development for the treatment of Alzheimer's disease. This compound is reported to inhibit human (IC₅₀ = 55 nM) and murine (IC₅₀ = 100 nM) PDE9 activity in vitro.

Over the years convincing experimental evidence has accumulated supporting the cognition-enhancing properties of several classes of PDE-inhibitors (Blokland et al., 2006: "Improving memory; a role for phosphodiesterases", Current Pharmacological Design 12, 2511-2523).

In a later study van der Staay et al. (F. Josef van der Staay, Neuropharmacology Volume 55, Issue 5, October 2008, pages 908-918) concludes that the PDE9 inhibitor 1-(2-chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one may act as a putative cognition enhancer.

WO 2012/040230 (Envivo Pharmaceuticals, Inc) is directed to imidazotriazinone compounds which are claimed to be inhibitors of phosphodiesterase 9.

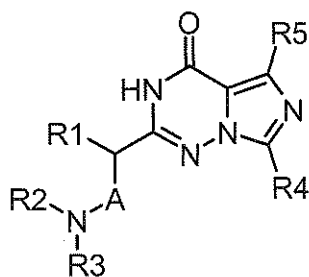
Alzheimer's disease is the most common form of dementia, it is incurable, degenerative, and terminal. The typical symptoms are cognitive difficulties, difficulties with executive functioning (such as planning, organization, mental flexibility and task coordination) as well as with perception (agnosia) and execution of movements (apraxia).

Because AD cannot be cured and is degenerative, palliative treatment of patients is essential.

SUMMARY OF THE INVENTION

The present invention discloses herein novel PDE9 inhibitors for the use as a medicament, such as in the treatment of patients suffering from cognitive impairments, in particular cognitive impairments that relate to neurodegenerative diseases such as cortical dementia (e.g. Alzheimer's disease) or subcortical dementia, e.g. AIDS related dementia.

The PDE9 inhibitors of the present invention-disclosure have the structure I (i.e. a 3H-imidazo[5,1-f][1,2,4]triazin-4-one backbone):



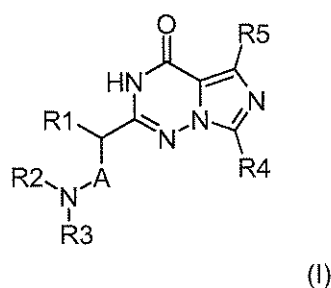
(I)

wherein R2 is cyclized with either R1 or R3.

The ~~invention disclosure~~ relates to methods of improving conditions involving PDE9, such as cognition, in particular the ~~invention disclosure~~ relates to a method of treating diseases involving cognitive difficulties, difficulties with executive functioning (such as planning, organization, mental flexibility and task coordination) as well as with perception (agnosia). The methods of improving conditions involving PDE9 and/or treating diseases involving PDE9 comprises the administration of a compound ~~of the present invention~~ disclosed herein or a pharmaceutically acceptable salt, solvate or prodrug thereof to a patient in need thereof. The disclosed compound ~~of the present invention~~ or a pharmaceutically acceptable salt, solvate or prodrug thereof may be in the form of a pharmaceutical composition.

In a further ~~aspect embodiment~~, the ~~invention disclosure~~ relates to an improved pharmaceutical composition comprising a compound ~~of the present invention~~ disclosed herein particularly useful for the treatment of cognitive difficulties, difficulties with executive functioning (such as planning, organization, mental flexibility and task coordination) as well as with perception (agnosia), in particular when associated neurodegenerative diseases, such as cortical or sub-cortical dementias, e.g. Alzheimer's disease (AD).

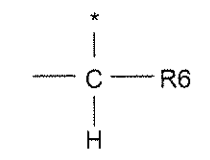
In one aspect, there is provided a compound having the structure (I)



wherein R2 is cyclized with either R1 or R3,

wherein R1, R2 and R3 are:

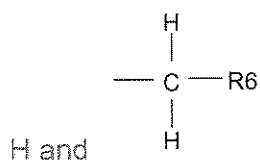
R1, when cyclized with R2, is

3a

wherein R6 is selected from the group consisting of H, -CH₃, -C₂H₅, and -C₃H₇,

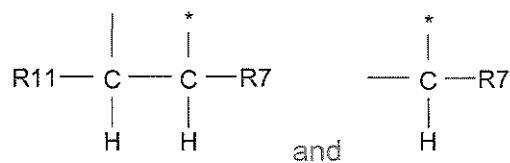
wherein * denotes the cyclization point, and

R1, when not cyclized, is selected from the group consisting of



wherein R6 is selected from the group consisting of H, -CH₃, -C₂H₅, and -C₃H₇

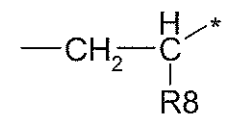
R2 is a compound selected from the group consisting of



wherein R7 and R11 independently are selected from the group consisting of H, -CH₃, -C₂H₅, and -C₃H₇

wherein * denotes the cyclization point, and

R3, when cyclized with R2, is



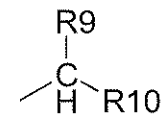
wherein * denotes the cyclization point, and

wherein R8 is selected from the group consisting of H, C₁-C₆ alkyl, branched C₃-C₆ alkyl, C₃-C₆ cycloalkyl, C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, C₃-C₉ heteroaryl, substituted C₃-C₉ heteroaryl, C₁-C₆ alkoxy, branched C₃-C₆ alkoxy, C₃-

3b

C₆ cycloalkoxy, C₆-C₁₀ aryloxy, substituted C₆-C₁₀ aryloxy, C₃-C₉ heteroaryloxy, substituted C₃-C₉ heteroaryloxy; and

R₃, when not cyclized, is



wherein

R₉ is selected from the group consisting of H, -CH₃, and -C₂H₅; and

R₁₀ is selected from the group consisting of C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, C₃-C₉ heteroaryl, substituted C₃-C₉ heteroaryl

R₄ is selected from the group consisting of C₆-C₁₀ aryl, substituted C₆-C₁₀ aryl, C₃-C₉ heteroaryl, substituted C₃-C₉ heteroaryl, C₃-C₆ heterocyclyl, substituted C₃-C₆ heterocyclyl, C₃-C₆ cycloalkyl, and substituted C₃-C₆ cycloalkyl;

R₅ is selected from the group consisting of hydrogen, F, Cl, CN, -CH₃, -C₂H₅, -C₃H₇, and -CF₃;

A is absent or -CH₂-

and tautomers and pharmaceutically acceptable acid addition salts thereof, and polymorphic forms thereof provided that the compound is not 2-[1-[(4-fluorophenyl)methyl]-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-(1-benzyl-4-methyl-pyrrolidin-3-yl)-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-(4-methylpyrrolidin-3-yl)-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[1-[(6-methoxy-2-pyridyl)methyl]-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3S,4S)-1-benzyl-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3R,4R)-1-benzyl-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3S,4S)-4-methylpyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one;

2-[(3R,4R)-4-methylpyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-7-

3c

tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3R,4R)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 4-[3-methyl-4-(4-oxo-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-2-yl)pyrrolidin-1-yl]benzonitrile; 2-[(3S,4S)-1-[(4-fluorophenyl)methyl]-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one; 2-[(3R,4R)-1-[(4-fluorophenyl)methyl]-4-methyl-pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one or 2-[4-methyl-1-(pyrazin-2-ylmethyl)pyrrolidin-3-yl]-7-tetrahydropyran-4-yl-3H-imidazo[5,1-f][1,2,4]triazin-4-one.

In another aspect, there is provided the use of a compound as defined above in the preparation of a medicament for the treatment of a neurodegenerative disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, mental retardation; CIAS, attention-deficit/hyperactivity disorder; and age-related cognitive decline, substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine.

In still another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above, and one or more pharmaceutically acceptable carriers, diluents and excipients.

DETAILED DESCRIPTION OF THE INVENTION

Cognitive impairment includes a decline in cognitive functions or cognitive domains, such as, e.g., difficulties with attention, learning, memory and executive function (relevant reactions to external stimuli). Cognitive impairment also may include: deficits in attention, disorganized thinking, slow thinking, difficulty in understanding, poor concentration, impairment of problem solving, poor memory, difficulty in expressing thoughts and/or integrating thoughts, feelings and behaviour, and/or extinction of irrelevant thoughts, and difficulty in attention and vigilance, verbal learning and memory, visual learning and memory, speed of processing, social cognition, reasoning and problem solving, e.g., executive functioning. There are presently no effective drugs for the treatment of cognitive disorders on the market and there is a great need and demand for drugs effective in the treatment of such disorders.

Without being limited to any specific theory it is believed that the mode of action of PDE9 inhibitors can be understood in the light of the following neurological processes: guanylyl cyclase (alt. guanylate cyclase) converts guanosine triphosphate (GTP) to cyclic guanosine

5. Use of Aa compound of any one of claims 1 to 4 in the manufacture of a medicament for ~~use in the~~ treatment of a neurodegenerative disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, mental retardation; CIAS, attention-deficit/hyperactivity disorder; and age-related cognitive decline, substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine.

~~6. A compound of any one of claims 1 to 4 for the preparation of a medicament for use in the treatment of a disorder selected from the group consisting of Alzheimer's disease, mental retardation; CIAS, attention-deficit/hyperactivity disorder; and age-related cognitive decline, substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine.~~

~~7. A method of treating a subject suffering from a disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, mental retardation; CIAS, attention-deficit/hyperactivity disorder; and age-related cognitive decline, substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine.~~

~~8.6.~~ A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 4, and one or more pharmaceutically acceptable carriers, diluents and excipients.