

autism spectrum disorders, hearing loss (Neuroscience, 167 (2010) 1216-1226; Nature Medicine, Vol. 11, number 3, (2005), 271-276) tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine (US 2012/0022096).

The stimulation of adult neurogenesis represents also a therapeutic target for optic neuropathy (S. Isenmann, A. Kretz, A. Cellerino, Progress in Retinal and Eye Research, 22, (2003) 483) and macular degeneration (G. Landa, O. Butovsky, J. Shoshani, M. Schwartz, A. Pollack, Current Eye Research 33, (2008) 1011).

Hence, chemical stimulation of adult neurogenesis offers new regenerative avenues and opportunities to develop novel drugs for treating neurological diseases and neuropsychiatric disorders.

Therefore, the object of the present invention was to identify compounds that modulate neurogenesis. It has been found that the compounds of formula I are active in this area and they may therefore be used for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, chemotherapy-induced cognitive dysfunction ("chemobrain"), Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, optic neuropathy or macular degeneration, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine or cocaine.

The most preferred indications for compounds of formula I are Alzheimer's disease, depression, anxiety disorders and stroke.

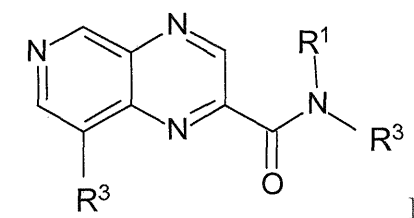
SUMMARY

The present ~~invention~~-disclosure relates to compounds of formula I and to their pharmaceutically acceptable salts, in cases where this applies to mixtures of enantiomers or diastereomers or their enantiomerically or diastereomerically pure forms, to these compounds as pharmaceutically active substances, to the processes for their production, as well as to the use in the treatment or prevention of disorders, relating to neurogenesis, schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal

aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment,

chemotherapy-induced cognitive dysfunction ("chemobrain"), Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, and disturbances due to radiation therapy, chronic stress, optic neuropathy or macular degeneration, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine or cocaine.

In one aspect, there is provided a compound of formula I



wherein

R¹ is hydrogen;

R² is hydrogen, lower alkyl, benzyl, lower alkyl substituted by hydroxy or cycloalkyl optionally substituted by cyano;

or R¹ and R² form together with the N-atom to which they are attached a heterocycloalkyl group, optionally containing an additional N, O or S ring atom, and which is optionally substituted by hydroxy;

R³ is halogen,

phenyl optionally substituted by one or more halogen, cyano, lower alkyl substituted by halogen, lower alkoxy substituted by halogen, lower alkyl substituted by hydroxy, or is heteroaryl, optionally substituted by lower alkyl or halogen, or is 3,6-dihydro-pyran-4-yl, or is

piperidin-1-yl optionally substituted by one or more halogen;

or to a pharmaceutically acceptable acid addition salt, to a racemic mixture or to its corresponding enantiomer and/or optical isomer thereof.

One object of the invention-disclosure are pharmaceutical compositions, containing a compound of formula I. In another aspect, there is provided a pharmaceutical composition comprising a compound of formula I as defined herein and pharmaceutically acceptable excipients.

One further object of the present ~~invention~~ disclosure is the use of a compound of formula I for the preparation of medicaments for the therapeutic and/or prophylactic treatment of the above-mentioned diseases. In another aspect, there is provided the use of a compound of formula I as defined herein for the preparation of a medicament for the treatment of

5 schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia,

10 amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

In another aspect, there is provided a compound of formula I as defined herein for use as therapeutically active substances. In another aspect, there is provided a compound of formula I

15 as defined herein for use in the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders,

20 hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

A further object of the ~~disclosure~~ invention is a method for the treatment of schizophrenia, obsessive-compulsive personality disorder, major depression, bipolar disorders, anxiety

25 disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation

30 therapy, chronic stress, abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine, which method comprises administering an effective amount of a compound of formula I.

One embodiment of the ~~disclosure~~^{invention} are compounds of formula I, wherein R¹ is hydrogen, R² is hydrogen, lower alkyl, benzyl, lower alkyl substituted by hydroxy or cycloalkyl optionally substituted by cyano, and R³ is as described above, for example the following compounds

- 5 8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-Bromo-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide
N-(3-Hydroxy-3-methylbutan-2-yl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-
10 carboxamide
8-(4-Chlorophenyl)-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide
N-(1-Cyanocyclopropyl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
N-Benzyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

N-(3-Hydroxy-3-methylbutan-2-yl)-8-(6-methylpyridin-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide.

One further embodiment of the ~~disclosure~~invention are compounds of formula I, wherein R¹ and R² form together with the N-atom to which they are attached a heterocycloalkyl group, optionally containing an additional N, O or S ring atom, and which is optionally substituted by hydroxy, for example the following compounds:

(8-Bromopyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone

(8-(4-Chlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone

Morpholino(8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone

(3-Hydroxypyrrolidin-1-yl)(8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone

(8-(4-Chlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

[8-(4-Chlorophenyl)pyrido[3,4-b]pyrazin-2-yl]-(1,1-dioxo-1,4-thiazinan-4-yl)methanone

(1,1-Dioxo-1,4-thiazinan-4-yl)-[8-[4-(trifluoromethyl)phenyl]pyrido[3,4-b]pyrazin-2-yl]methanone

(8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

(8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

(3-Hydroxypyrrolidin-1-yl)(8-(3-(trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone

(8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

(8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

(8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

(8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

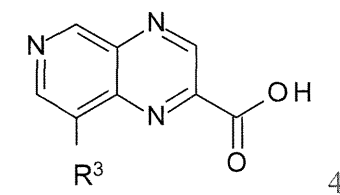
or

(8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone.

In another aspect there is provided a process for the manufacture of a compound of formula I as defined herein, which process comprises

a) reacting a compound of formula 4

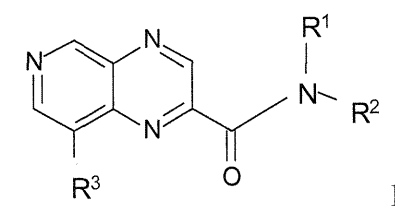
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with a compound of formula 2

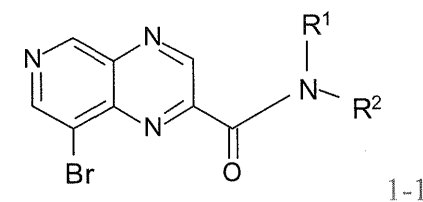


to a compound of formula I

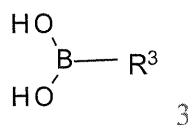


and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

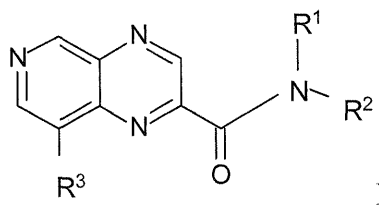
b) reacting a compound of formula I-1



with a compound of formula 3



to a compound of formula I



and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 – 7 carbon atoms. Examples for “alkyl” are

5 methyl, ethyl, n-propyl, and isopropyl.

9. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claim 1 – 5 and pharmaceutically acceptable excipients.

10. The use of a compound of formula I according to any one of claims 1 - 5 for the preparation of a medicament for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine.

~~11. A method for the treatment of schizophrenia, obsessive-compulsive personality disorder, depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, panic disorder, Parkinson's disease, dementia, Alzheimer's disease, cognitive impairment, chemotherapy-induced cognitive dysfunction, Down syndrome, autism spectrum disorders, hearing loss, tinnitus, spinocerebellar ataxia, amyotrophic lateral sclerosis, multiple sclerosis, Huntington's disease, stroke, radiation therapy, chronic stress, abuse of neuro-active drugs, selected from alcohol, opiates, methamphetamine, phencyclidine and cocaine, which method comprises administering an effective amount of a compound of formula I as claimed in any one of claims 1–5.~~