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).

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

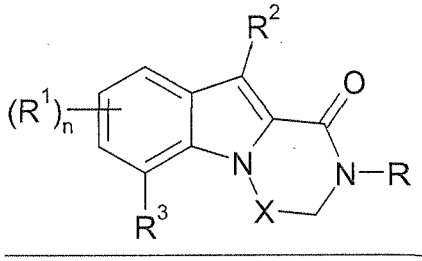
Therefore, the object of the ~~present invention~~embodiments disclosed herein was to identify compounds that modulate neurogenesis.

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, major 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, or abuse of neuro-active drugs, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.

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

The present invention relates to compounds of formula I and to their pharmaceutically acceptable salts, 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, major depression, bipolar disorders, anxiety disorders, normal aging, epilepsy, retinal degeneration, traumatic brain injury, spinal cord injury, post-traumatic stress disorder, Parkinson's disease, dementia, Alzheimer's disease, mild 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine, and to pharmaceutical compositions containing the compounds of formula I.

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



I

wherein

R^1 is hydrogen, halogen, lower alkyl, lower alkoxy, lower alkoxy substituted by halogen or cyano;

R^2 is hydrogen, lower alkyl or lower alkyl substituted by halogen;

R^3 is phenyl, benzo[1,3]dioxolyl, 2,3-dihydro-benzofuran-5-yl or a 5- and 6-membered heteroaryl, wherein phenyl and the 5- and 6-membered heteroaryl groups may be substituted by one or more substituents, selected from cyano, nitro, amino and lower di-alkylamino, lower alkyl sulfonyl, lower alkoxy, lower alkoxy substituted by halogen, halogen, lower alkyl, lower alkyl substituted by halogen or lower alkyl substituted by hydroxyl;

X is -CH(lower alkyl)-, $-CH_2-$, $-CH_2CH_2-$ or $-CH(\text{lower alkyl})CH_2-$;

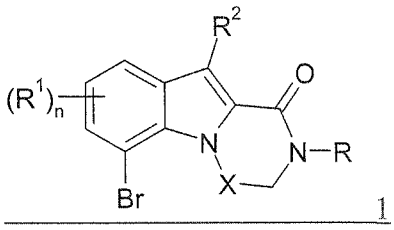
R is hydrogen or lower alkyl;

n is 1 or 2;

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

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

reacting a compound of formula

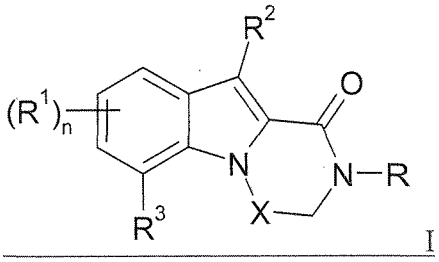


1

with a compound of formula

$R_3B(OH)_2$ 2

to a compound of formula



I

wherein the substituents are as described above

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

In another aspect, there is provided a compound as defined herein, when manufactured by a process as defined herein.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical acceptable carrier and/or adjuvant.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical acceptable carrier and/or adjuvant for use in the treatment of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.

In another aspect, there is provided compounds as defined herein for use as therapeutic active substances.

In another aspect, there is provided compounds as defined herein for use as therapeutic active substances in the treatment of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.

In another aspect, there is provided use of a compound as defined herein for the preparation of medicaments for the therapeutic and/or prophylactic treatment of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.

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

20. The use of a compound according to any one of claims 1 to 13 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.

~~21. A method for the treatment or prophylaxis of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine, which method comprises administering an effective amount of a compound as defined in any one of claim 1 to 13.~~

~~22. The use of a compound according to any one of claims 1 to 13 for the treatment or prophylaxis of of schizophrenia, obsessive-compulsive personality disorder, major 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, 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, such as alcohol, opiates, methamphetamine, phencyclidine and cocaine.~~