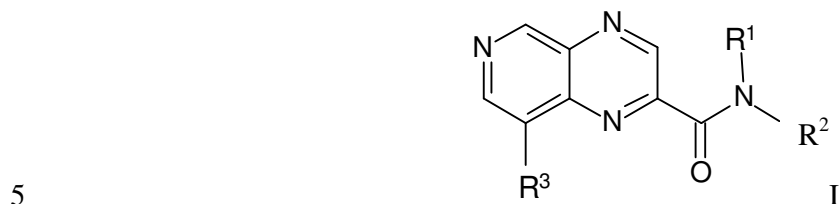


**PYRIDO[4,3-B]PYRAZINE-2-CARBOXAMIDES AS NEUROGENIC AGENTS FOR
THE TREATMENT OF NEURODEGENERATIVE DISORDERS**

The present invention relates to compounds of general formula



wherein

R¹ is hydrogen;

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

10 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,

15 phenyl optionally substituted by one or more halogen, cyano, lower alkyl substituted by halogen, lower alkoxy substituted by halogen or by 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;

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

Now it has been shown that the present compounds stimulate neurogenesis from neural stem cells (NSCs). Neurogenesis occurs in the developing and adult brain. Conceptually, this process of neurogenesis can be divided into four steps: (i) proliferation of NSCs; (ii) neuronal

fate determination of NSC; (iii) survival and maturation of new neurons; and (iv) functional integration of new neurons into the neuronal network.

Adult neurogenesis is a developmental process that occurs throughout life in the adult brain whereby new functional neurons are generated from adult neural stem cells. Constitutive adult neurogenesis under physiological conditions occurs mainly in two “neurogenic” brain regions, 1) the sub-granular zone (SGZ) in the dentate gyrus of the hippocampus, where new dentate granule cells are generated, 2) the sub-ventricular zone (SVZ) of the lateral ventricles, where new neurons are generated and then migrate through the rostral migratory stream (RMS) to the olfactory bulb to become interneurons.

Extensive evidence suggests that hippocampal adult neurogenesis plays an important role in cognitive and emotional states albeit the precise function remains elusive. It has been argued that the relatively small number of newborn granule neurons can affect global brain function because they innervate many interneurons within the dentate gyrus, each of which inhibits hundreds of mature granule cells leading to a neurogenesis-dependent feedback inhibition. In combination with a low threshold for firing the newborn neurons trigger responses to very subtle changes in context. Disturbances in this process may manifest behaviorally in deficits in pattern separation related to psychiatric diseases. For example, adult hippocampal neurogenesis correlates with cognitive and emotional capacity, e.g. physical exercise, exposure to an enriched environment and typical antidepressants concomitantly promote adult hippocampal neurogenesis and cognition and/or emotional states, while chronic stress, depression, sleep deprivation and aging decrease adult neurogenesis and associate with negative cognitive and/or emotional states (Neuron 70, May 26, 2011, pp 582 -588 and pp 687 – 702; WO 2008/046072). Interestingly, antidepressants promote hippocampal adult neurogenesis and their effects on certain behaviors require the stimulation of neurogenesis. Neurogenesis in other adult CNS regions is generally believed to be very limited under normal physiological conditions, but could be induced after injury such as stroke, and central and peripheral brain damage.

It is therefore believed that stimulation of adult neurogenesis represents a neuro-regenerative therapeutic target for normal aging and in particular for a variety of neurodegenerative and neuropsychiatric diseases, including schizophrenia, obsessive-compulsive personality disorder, major depression, bipolar disorders, anxiety disorders, 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 (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.

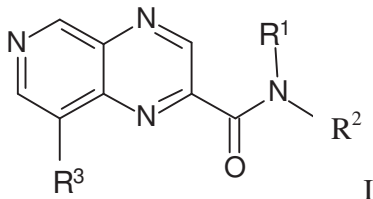
SUMMARY

The present 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

- R^1 is hydrogen;
- 10 R^2 is hydrogen, lower alkyl, benzyl, lower alkyl substituted by hydroxy or cycloalkyl optionally substituted by cyano;
or R^1 and R^2 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;
- 15 R^3 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
- 20 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 disclosure are pharmaceutical compositions, containing a compound of formula I. In another aspect, there is provided a pharmaceutical composition comprising a
25 compound of formula I as defined herein and pharmaceutically acceptable excipients.

One further object of the present 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 schizophrenia,

5 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,
10 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 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 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

8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

5 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-carboxamide

10 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-Benzyl-8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(3,4,5-Trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
5 8-(2-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
10 8-(3-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(3,6-Dihydro-2H-pyran-4-yl)pyrido[4,3-b]pyrazine-2-carboxamide
15 8-(3-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(3,4-Difluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
N-Benzyl-8-(pyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Cyanophenyl)pyrido[4,3-b]pyrazine-2-carboxamide
20 N-tert-Butyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(2,4-Dichlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(2-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxamide
8-(4-Chloro-3-fluorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-
25 carboxamide
N-(3-Hydroxy-3-methylbutan-2-yl)-8-(3,4,5-trifluorophenyl)pyrido[4,3-b]pyrazine-2-
carboxamide
N-(3-Hydroxy-3-methylbutan-2-yl)-8-(1-methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-
carboxamide
30 8-(1-Methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide
N-(3-Hydroxy-3-methylbutan-2-yl)-8-(6-methylpyridin-3-yl)pyrido[4,3-b]pyrazine-2-
carboxamide or

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 are compounds of formula I, wherein R¹ and R² form together with the N-atom to which they are attached a heterocycloalkyl group,

5 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

10 (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

15 (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

20 (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

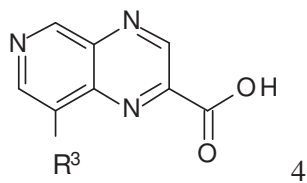
25 or

(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

30 a) reacting a compound of formula 4

-6a-



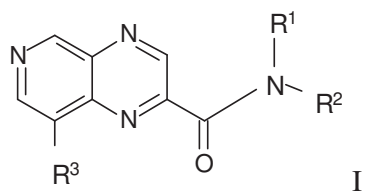
with a compound of formula 2

5



to a compound of formula I

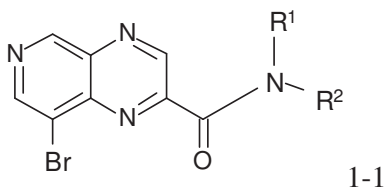
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and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

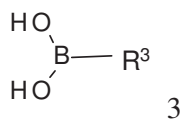
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b) reacting a compound of formula I-1

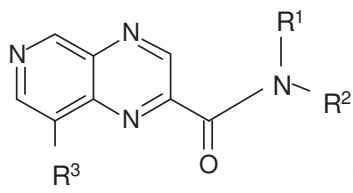


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with a compound of formula 3



to a compound of formula I



25

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.

The term “alkoxy” denotes a group -O-R' wherein R' is lower alkyl as defined above.

The term “lower alkyl substituted by halogen” denotes a lower alkyl group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom. The preferred group is CF₃.

5 The term “lower alkoxy substituted by halogen” denotes a lower alkoxy group as defined above, wherein at least one hydrogen atom is replaced by a halogen atom. The preferred group is OCF₃.

The term “lower alkyl substituted by hydroxy” denotes a lower alkyl group as defined above, wherein at least one hydrogen atom is replaced by a hydroxy group. The preferred group
10 is CH(CH₃)C(OH)(CH₃)₂.

The term “cycloalkyl” denotes a carbon ring with 3 – 7 carbon atoms.

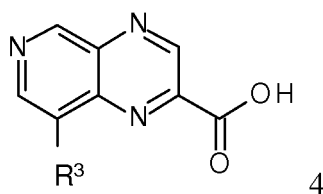
The term “heterocycloalkyl” comprises non aromatic rings, containing at least one heteroatom, selected from N, O or S. Such groups are piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or 1,1-di-oxo-thiomorpholinyl.

15 The term “heteroaryl” denotes a carbocyclic ring system, containing from 5 to 10 ring atoms forming one or more rings, wherein at least one carbon atom is replaced by a heteroatom, selected from the group consisting of O, N or S, and wherein at least one ring is aromatic in nature, for example oxazolyl, pyridyl, thiophenyl, quinolinyl, pyrrolyl, furyl, benzoimidazolyl, imidazolyl, pyrazolyl and the like. The most preferred groups are pyridyl and pyrazolyl

20 The term “halogen” denotes chlorine, bromine, fluorine or iodine.

The present new compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

25 a) reacting a compound of formula 4

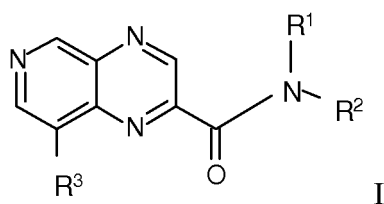


with a compound of formula 2

30 NHR^1R^2 2

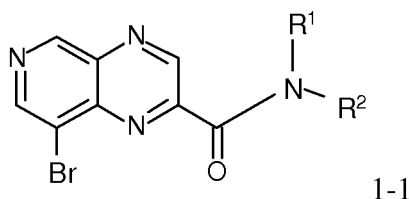
to a compound of formula I

-8-



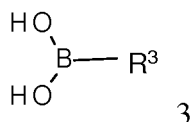
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

5 b) reacting a compound of formula I-1

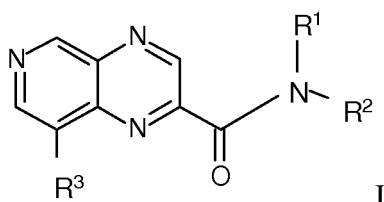


with a compound of formula 3

10



to a compound of formula I



15

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

The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following scheme 1. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

20

In more detail, the compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in scheme 1, however, depending on the starting

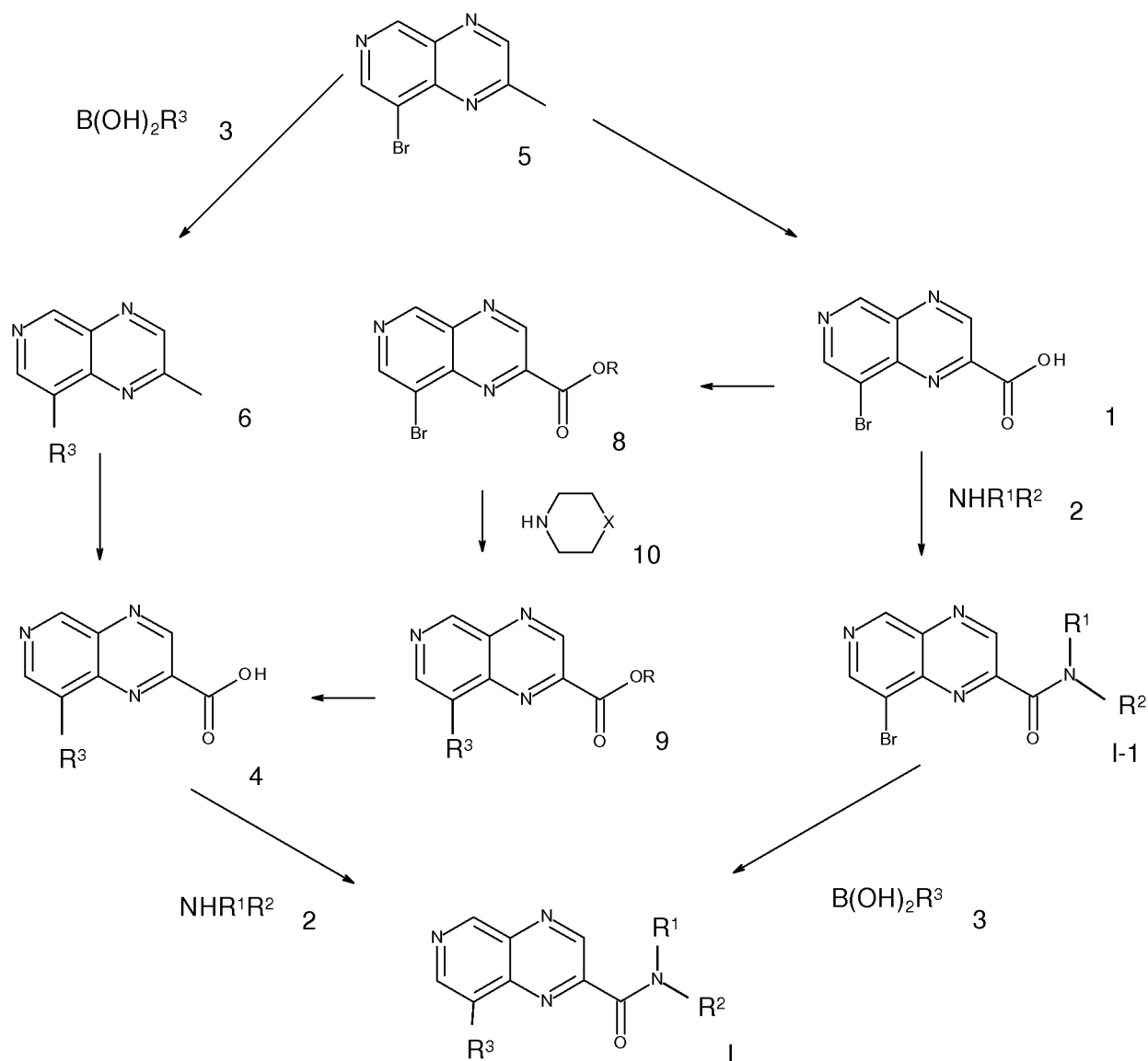
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materials and their respective reactivity the sequence of reaction steps can be freely altered.

Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

5

Scheme 1



The precursor compounds of formula 4 can be prepared by methods known in the art.

To a suspension of 8-bromo-2-methyl-pyrido[3,4-b]pyrazine (formula 5) and a boronic acid of formula 3 and cesium carbonate in dioxane and water is added
 10 bis(diphenylphosphino)ferrocene-palladium(II)dichloride. The mixture is stirred at 80 °C for 3 hours. Removal of the solvent by distillation and chromatography yields the compound of formula 6.

Furthermore, the 8-substituted 2-methylpyrido[4,3-b]pyrazine of formula **6** was combined with selenium dioxide in dioxane and was heated at 100 °C for 3 hours. The resulting aldehyde was combined with t-butanol, 2-methylbut-2-ene, sodium chlorite and sodium dihydrogen phosphate in water and was stirred at room temperature overnight to yield a compound of formula **4**.

- 5 Furthermore, the oxidation of 8-bromo-2-methyl-pyrido[3,4-b]pyrazine (formula **5**) for example with selenium dioxide followed by sodium chlorite oxidation to result in the formation of 8-bromo-pyrido[3,4b]pyrazine-2-carboxylic acid (formula **1**), followed by esterification to a compound of formula **8**, which is then reacted with a compound of formula **10** ($X=CF_2$) to a compound of formula **9** and ester cleavage results in the formation of a compound of
10 formula **4**.

- In more detail, a mixture of 8-bromo-2-methylpyrido[4,3-b]pyrazine (formula **5**) with selenium dioxide in dioxane and was heated at 100 °C for 3 hours. The resulting aldehyde was combined with t-butanol, 2-methylbut-2-ene, sodium chlorite and sodium dihydrogen phosphate in water and was stirred at room temperature 2 days to yield 8-bromo-pyrido[3,4-b]pyrazine-2-carboxylic
15 acid (formula **1**).

- A mixture of 8-bromo-pyrido[3,4-b]pyrazine-2-carboxylic acid of formula **1**, N, N-diisopropylethylamine and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) in dimethylformamide is stirred at room temperature for 10 minutes. The corresponding amine of formula **2** is added and stirring is continued over overnight
20 to yield a compound of formula **I-1**.

- Furthermore, to a suspension of 8-bromo-pyrido[3,4-b]pyrazine-2-carboxylic acid amide of formula **I-1** and a boronic acid of formula **3** and cesium carbonate in dioxane and water is added bis(diphenylphosphino)ferrocene-palladium(II)dichloride. The mixture is stirred at 80 °C for 3 hours. Removal of the solvent by distillation and chromatography yields the compound of
25 formula **I**.

Or, a mixture of 8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxylic acid of formula **4** and 1,1'-carbonyldiimidazole in dichloromethane was combined with the corresponding amine of formula **2**. The mixture was stirred at room temperature overnight to yield a compound of formula **I**.

- 30 A mixture of 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (formula **1**) and oxalyl chloride in dichloromethane was stirred at 0 °C for 1 hour and then at room temperature for 1 hour. The mixture was concentrated in vacuo and dissolved in dichloromethane. Methanol was added and

the mixture was concentrated in vacuo to yield methyl-8-bromopyrido[4,3-b]pyrazine-2-carboxylate (formula **8**).

A suspension of 8-bromopyrido[4,3-b]pyrazine-2-carboxylate (formula **8**) and cesium carbonate in toluene (6.0 ml) was combined with palladium(II)acetate and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and 4,4-difluoropiperidine. The reaction mixture was heated at 80 °C for 5 hours. Purification by chromatography yields the compound of formula **9**.

A solution of methyl 8-(4,4-difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxylate (compound of formula **9**) in dioxane and water was treated with aqueous lithium hydroxide. Acidification and extraction yields the compound of formula **4**.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

Salts of compounds of formula I

The compounds of formula I are basic and may be converted to a corresponding acid addition salt. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base

such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention have an activity as neurogenic agents. The compounds were investigated in accordance with the test given hereinafter.

Neurogenesis assay

Neural Stem Cell Proliferation Assay

- 10 Neurogenic properties of small molecules are determined based on the proliferation of human embryonic stem cell derived neural stem cells (NSCs) which were derived via a dual smad inhibition as previously described (Chambers, S.M., et al., *Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling*, Nature biotechnology, 2009. 27(3): p. 275-80.)
- 15 Compounds respond is measured by the increase in cells based on ATP levels (Promega:CellTiterGlo®) after an incubation period of 4 days.
- NSCs are thawed and expanded over 3 passages. On the 14th day, NSCs are seeded in Polyornithin/ Laminin coated 384 well plates at a cell density of 21'000 cells/cm² in a media volume of 38 µl.
- 20 4 hours after cell seeding, compound solutions are added at a volume of 2 µl. Stock solutions of the compounds (water, 5% DMSO) are diluted to obtain a dose response (11 points, dilution factor is 2), ranging from 8 µM to 8 nM. Controls are run to consistently determine the neurogenic properties of the cells:
- Negative (neutral) control is cell culture Media (final DMSO concentration: 0.25 %).
- 25 Positive controls are:
1. cell culture Media + 100 ng/ml FGF2 (final DMSO concentration: 0.1 %)
 2. cell culture Media + 20 ng/ml EGF (final DMSO concentration: 0.1 %)
 3. cell culture Media + 100 ng/ml Wnt3a (final DMSO concentration: 0.1 %)
- After 4 days incubation at 37° C, 5 % CO₂, the amount of ATP per well is quantified. The ATP concentration is proportional to the cell number. ATP is quantified by using the Promega CellTiterGlo® kit. The CellTiterGlo® reagents contain a cell lysis buffer, a thermo stable luciferase (UltraGlo™ recombinant luciferase), magnesium and luciferin. Luciferin reacts with
- 30

ATP producing oxyluciferin, AMP and light. The luminescence signal is proportional to the ATP content.

The value of negative (neutral) control is determined for each assay plate by taking the average of 16 negative control wells. The neurogenic compound response is calculated for each

5 compound as (compound/Negative Control)*100.

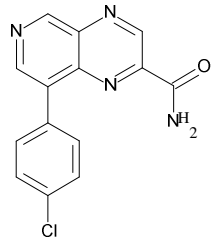
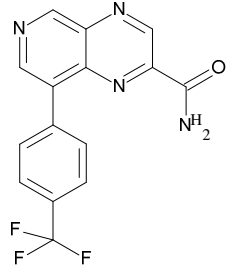
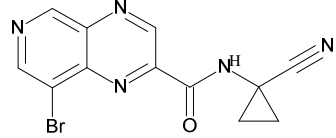
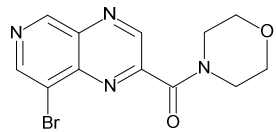
The values of EC₁₅₀ from the dose response curve are determined for each test compound. The EC₁₅₀ is the compound concentration at which 150 % activity of control (100 %) is reached.

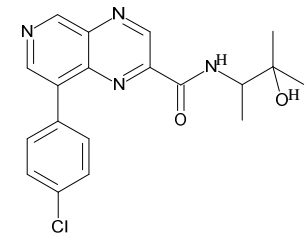
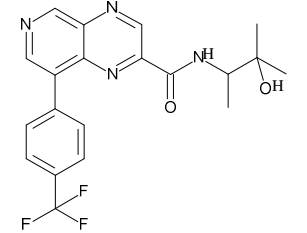
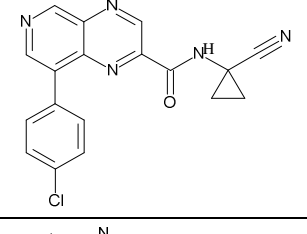
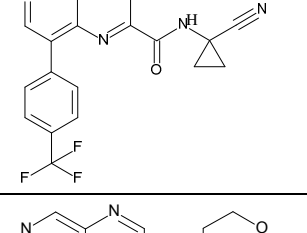
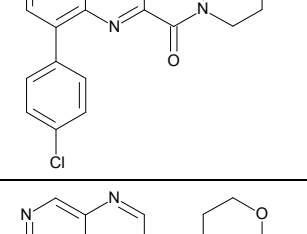
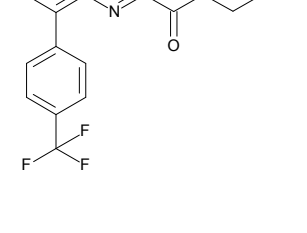
The preferred compounds show a EC₁₅₀ (μM) in the range of < 3.0 μM as shown in Table 1.

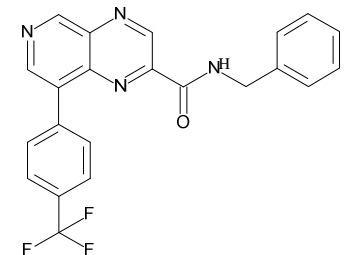
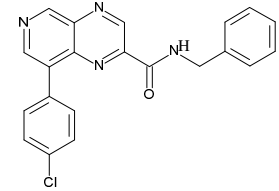
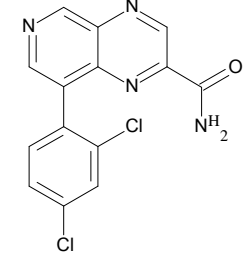
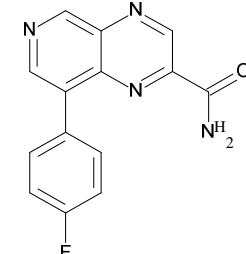
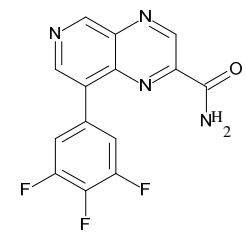
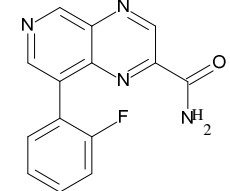
Table 1

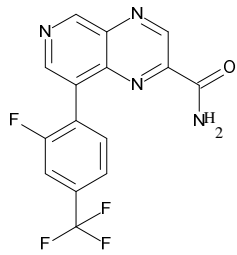
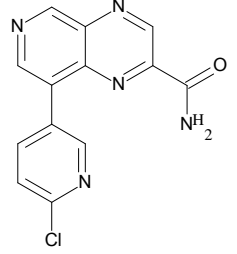
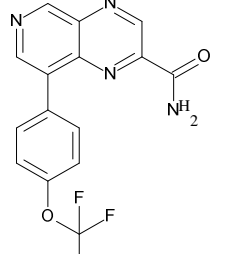
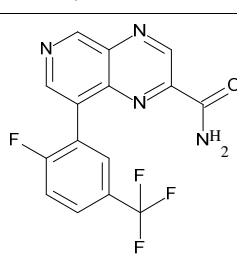
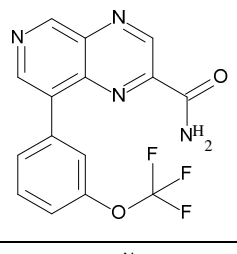
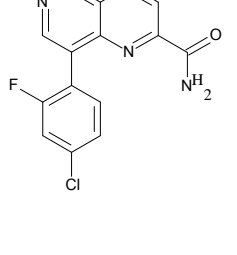
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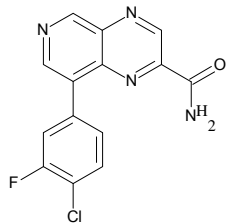
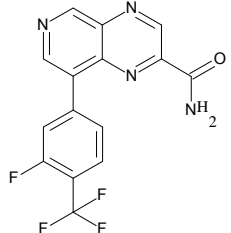
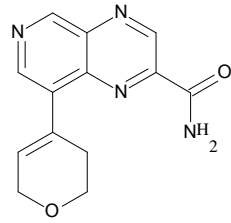
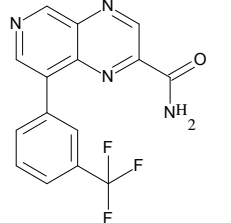
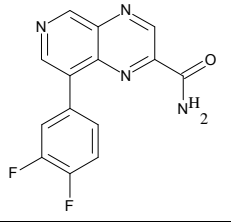
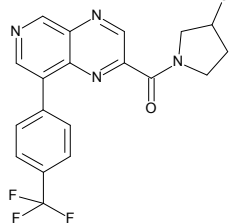
List of examples and EC₁₅₀ data

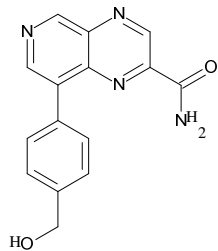
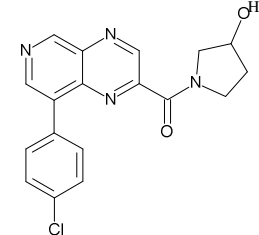
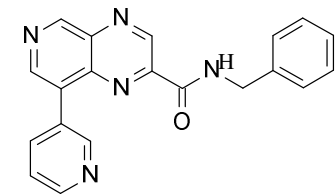
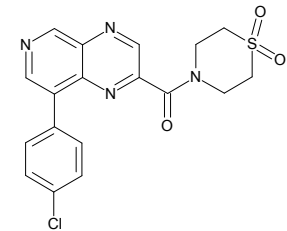
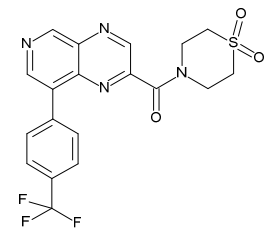
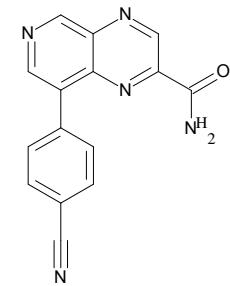
Example	Structure	Name	EC ₁₅₀ (uM)
1		8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.21
2		8-(4-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.30
3		8-Bromo-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide	2.32
4		(8-Bromopyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone	0.07

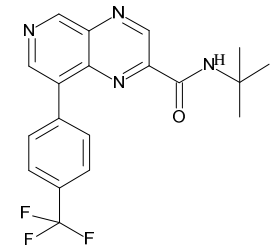
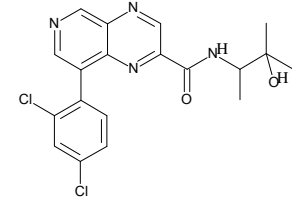
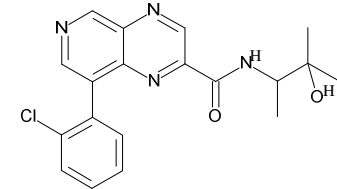
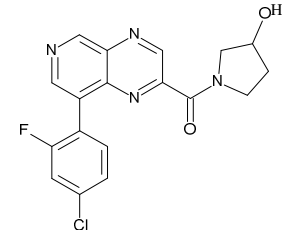
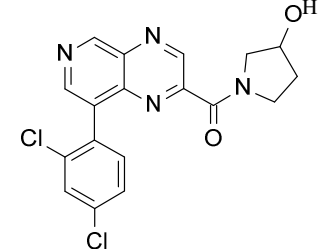
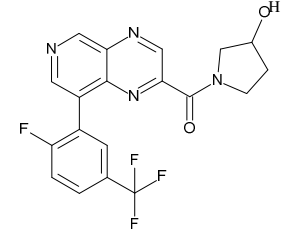
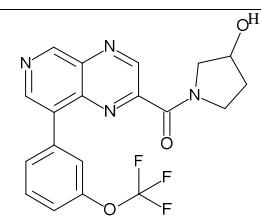
5		8-(4-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.89
6		N-(3-Hydroxy-3-methylbutan-2-yl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.38
7		8-(4-Chlorophenyl)-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.39
8		N-(1-Cyanocyclopropyl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.39
9		(8-(4-Chlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone	0.65
10		Morpholino(8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone	2.96

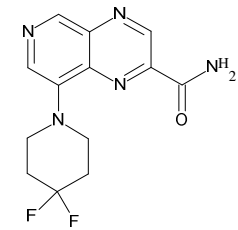
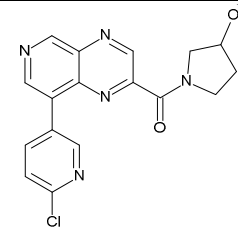
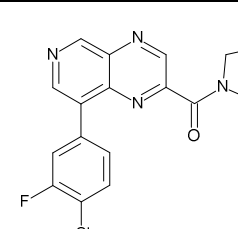
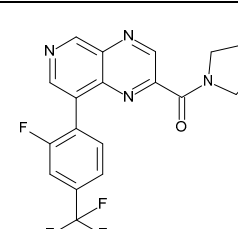
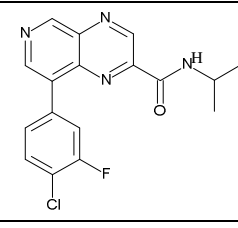
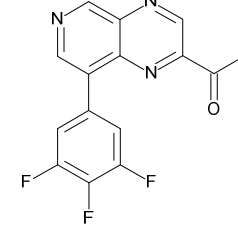
11		N-Benzyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.41
12		N-Benzyl-8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.26
13		8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.28
14		8-(4-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.10
15		8-(3,4,5-Trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.55
16		8-(2-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.06

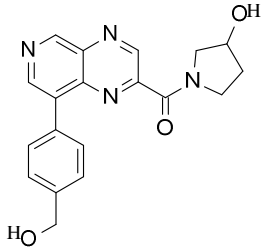
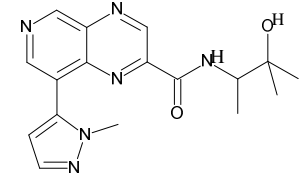
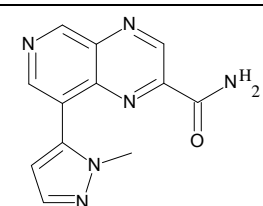
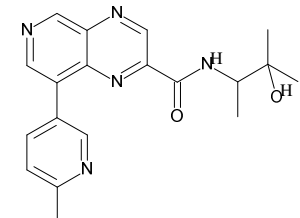
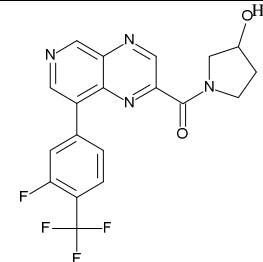
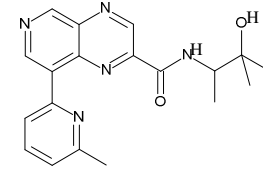
17		8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.08
18		8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.21
19		8-(4-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.09
20		8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.22
21		8-(3-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.21
22		8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.07

23		8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.10
24		8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.18
25		8-(3,6-Dihydro-2H-pyran-4-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.66
26		8-(3-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.43
27		8-(3,4-Difluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.12
28		(3-Hydroxypyrrolidin-1-yl)(8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone	0.29

29		8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.05
30		(8-(4-Chlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.69
31		N-Benzyl-8-(pyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.47
32		[8-(4-Chlorophenyl)pyrido[3,4-b]pyrazin-2-yl]-(1,1-dioxo-1,4-thiazinan-4-yl)methanone	0.84
33		(1,1-Dioxo-1,4-thiazinan-4-yl)-[8-[4-(trifluoromethyl)phenyl]pyrido[3,4-b]pyrazin-2-yl]methanone	1.65
34		8-(4-Cyanophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.15

35		N-tert-Butyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.32
36		8-(2,4-Dichlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide	1.50
37		8-(2-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide	1.13
38		(8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.10
39		(8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.11
40		(8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.93
41		(3-Hydroxypyrrolidin-1-yl)(8-(3-(trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone	0.60

42		8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.09
43		(8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.03
44		(8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.27
45		(8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	1.48
46		8-(4-Chloro-3-fluorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.29
47		N-(3-Hydroxy-3-methylbutan-2-yl)-8-(3,4,5-trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide	0.03

48		(8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.67
49		N-(3-Hydroxy-3-methylbutan-2-yl)-8-(1-methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.02
50		8-(1-Methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.02
51		N-(3-Hydroxy-3-methylbutan-2-yl)-8-(6-methylpyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.08
52		(8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone	0.07
53		N-(3-Hydroxy-3-methylbutan-2-yl)-8-(6-methylpyridin-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide	0.50

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration

can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those which include disorders of the central nervous system, for example the treatment or prevention of depression, psychosis, Parkinson's disease, anxiety, attention deficit hyperactivity disorder (ADHD) and diabetes.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500
				mg	
5	1. Compound of formula I	5	25	100	500
	2. Lactose Anhydrous DTG	125	105	30	150
	3. Sta-Rx 1500	6	6	6	30
	4. Microcrystalline Cellulose	30	30	30	150
	5. Magnesium Stearate	1	1	1	1
10	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
- 15 3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

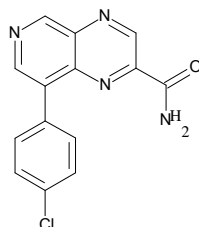
<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500
20				mg	
	1. Compound of formula I	5	25	100	500
	2. Hydrous Lactose	159	123	148	---
	3. Corn Starch	25	35	40	70
25	4. Talc	10	15	10	25
	5. Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

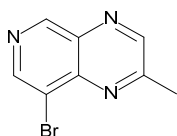
- 30 1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



a) 8-Bromo-2-methylpyrido[4,3-b]pyrazine

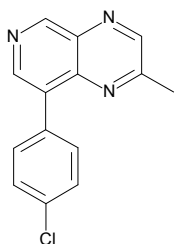


5

In a 50 ml round-bottomed flask, 5-bromopyridine-3,4-diamine (1.00 g, 5.32 mmol) and 2-oxopropanal (0.96 g, 5.32 mmol) were combined with dioxane (30.0 ml) to give a light brown solution.. The reaction mixture was heated at 100 °C for 5 days. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) to yield the title compound (1.00 g, 84 %) as light brown solid. MS: m/e = 224.3, 226.3 [M+H]⁺.

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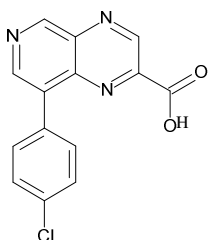
b) 8-(4-Chlorophenyl)-2-methylpyrido[4,3-b]pyrazine



15 In a 25 ml round-bottomed flask, 8-bromo-2-methylpyrido[4,3-b]pyrazine (500 mg, 2.23 mmol), 4-chlorophenylboronic acid (349 mg, 2.23 mmol) and cesium carbonate (800 mg, 2.45 mmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (81.6 mg, 112 µmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (618 mg, 92 %) as light yellow solid. MS: m/e = 256.4 [M+H]⁺.

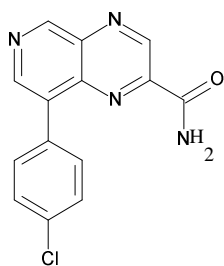
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c) 8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxylic acid



In a 25 ml round-bottomed flask, 8-(4-chlorophenyl)-2-methylpyrido[4,3-b]pyrazine (610 mg, 2.39 mmol) and selenium dioxide (1.48 g, 13.4 mmol) were combined with dioxane (13 ml) to give a light yellow mixture. The reaction mixture was heated at 100 °C for 3 hours. The mixture
5 was filtered through sintered glass and was concentrated in vacuo. The crude material was purified by chromatography (silica gel, methanol / dichloromethane = 0:100 to 2:98). The pure fractions were concentrated in vacuo and were combined with t-butanol (13 ml) and 2-methylbut-2-ene (4 ml) to give a light yellow solution. Sodium chlorite (1.6 g, 17.7 mmol) and sodium dihydrogen phosphate (1.6 g, 13.4 mmol) in water (13 ml) were added slowly and the
10 mixture was stirred at room temperature overnight. The crude reaction mixture was concentrated in vacuo, triturated with water (13 ml) and stirred for 30 minutes at room temperature. The residue was filtered off and dried in vacuo to yield the title compound (295 mg, 43 %) as light light yellow solid. MS: m/e = 284.4 [M-H]⁻.

15 d) 8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

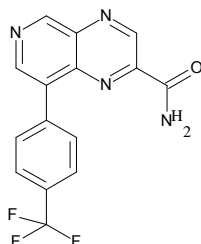


In a 25 ml round-bottomed flask, 8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxylic acid (195 mg, 683 μmol) and 1,1'-carbonyldiimidazole (133 mg, 819 μmol) were combined with dichloromethane (10 ml) to give a light yellow suspension. After 1 hour ammonium chloride
20 (183 mg, 3.41 mmol) and triethylamine (345 mg, 476 μl, 3.41 mmol) were added. The mixture was stirred at room temperature overnight. Then ammonium chloride (183 mg, 3.41 mmol) and triethylamine (345 mg, 476 μl, 3.41 mmol) were added again and the mixture was stirred at room temperature for 3 days. Chromatography (silica gel, ethyl acetate / heptane = 10:90 to 100:0) and

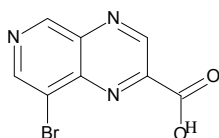
trituration with diethyl ether/pentane (0.5 ml / 0.5 ml yielded the title compound (126 mg, 65 %) as light yellow solid. MS: $m/e = 285.3$ $[M+H]^+$.

Example 2

5 8-(4-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

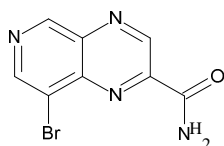


a) 8-Bromopyrido[4,3-b]pyrazine-2-carboxylic acid



In a 25 ml round-bottomed flask, 8-bromo-2-methylpyrido[4,3-b]pyrazine (500 mg, 2.23 mmol) and selenium dioxide (1.39 g, 12.5 mmol) were combined with dioxane (10 ml) to give a light yellow mixture. The reaction mixture was heated at 100 °C for 3 hours. The mixture was filtered and was concentrated in vacuo. The crude material was purified by chromatography (silica gel, methanol / dichloromethane = 0:100 to 2:98). The pure fractions were concentrated in vacuo and were combined with t-butanol (10 ml) and 2-methylbut-2-ene (3 ml) to give a light yellow solution. Sodium chlorite (1.5 g, 16.6 mmol) and sodium dihydrogen phosphate (1.5 g, 12.5 mmol) in water (10 ml) were added slowly and the mixture was stirred at room temperature over weekend. The crude reaction mixture was concentrated in vacuo, triturated with water at room temperature for 15 minutes. The residue was filtered off and dried in vacuo to yield the title compound (329 mg, 58 %) as light brown solid. MS: $m/e = 252.3, 254.3$ $[M-H]^-$.

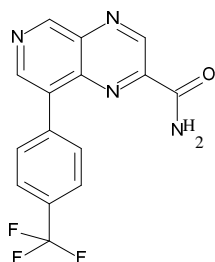
b) 8-Bromopyrido[4,3-b]pyrazine-2-carboxamide



In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (324 mg, 1.28 mmol) and 1,1'-carbonyldiimidazole (227 mg, 1.4 mmol) were combined with dichloromethane

(10 ml) to give a brown suspension. The mixture was stirred for 1 hour at room temperature. Then ammonium chloride (341 mg, 6.38 mmol) and triethylamine (645 mg, 889 μ l, 6.38 mmol) were added and stirring was continued for 3 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) to yield the title compound (65 mg, 20 %) as light brown solid. MS: m/e = 253.3, 255.3 $[M+H]^+$.

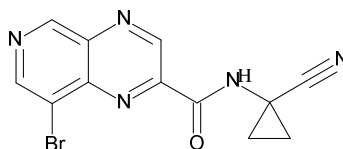
c) 8-(4-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (60 mg, 237 μ mol), 4-(trifluoromethyl)phenylboronic acid (45.0 mg, 237 μ mol) and cesium carbonate (77.3 mg, 237 μ mol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (173 mg, 237 μ mol) was added. The reaction mixture was heated to 80 $^{\circ}$ C and stirred for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0). Trituration with diethyl ether (1 ml) yielded the title compound (33 mg, 44 %) as off-white solid. MS: m/e = 319.4 $[M+H]^+$.

Example 3

8-Bromo-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide

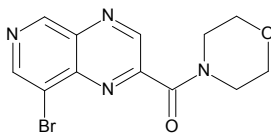


In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (300 mg, 1.18 mmol), 1-aminocyclopropanecarbonitrile (97.0 mg, 1.18 mmol) and triethylamine (179 mg, 247 μ l) were combined with dimethylformamide (10.0 ml) to give a light brown solution. O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 494 mg, 1.3 mmol) was added and stirring was continued at room temperature. The reaction was complete after 1 hour. The crude reaction mixture was concentrated in vacuo. Extraction and

chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) yielded the title compound (220 mg, 59 %) as off-white solid. MS: $m/e = 319.4 [M+H]^+$.

Example 4

5 (8-Bromopyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone

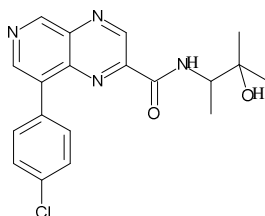


In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (300 mg, 1.18 mmol), morpholine (103 mg, 103 μ l 1.18 mmol) and triethylamine (179 mg, 247 μ l, 1.77 mmol) were combined with dimethylformamide (10 ml) to give a light brown suspension. O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 494 mg, 1.3 mmol) was added and stirring was continued at room temperature. The reaction was complete after 1 hour. Extraction with ethyl acetate and chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) yielded the title compound (240 mg, 63 %) as off-white solid. MS: $m/e = 323.4, 235.4 [M+H]^+$.

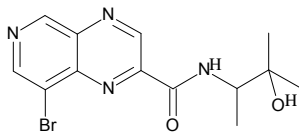
15

Example 5

8-(4-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



a) 8-Bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



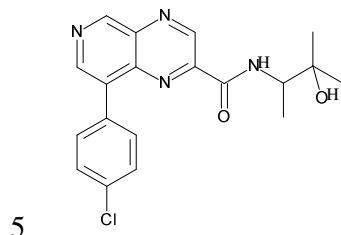
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In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (300 mg, 1.18 mmol), 3-amino-2-methylbutan-2-ol (122 mg, 1.18 mmol) and triethylamine (179 mg, 247 μ l, 1.77 mmol) were combined with dimethylformamide (10 ml) to give a light brown solution. Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 494 mg, 1.3 mmol) was added and stirring was continued at room temperature overnight. Extraction with

25

ethyl acetate and chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) yielded the title compound (218 mg, 54 %) as light brown solid. MS: $m/e = 339.0, 341.0 [M+H]^+$.

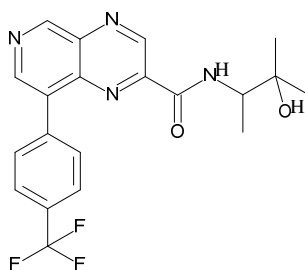
b) 8-(4-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 4-chlorophenylboronic acid (23.1 mg, 147 μmol) and cesium carbonate (96.1 mg, 295 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (10.8 mg, 14.7 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (52.3 mg, 96 %) as yellow solid. MS: $m/e = 371.5 [M+H]^+$.

Example 6

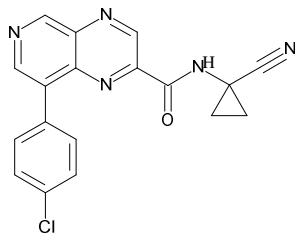
15 N-(3-Hydroxy-3-methylbutan-2-yl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 4-(trifluoromethyl)phenylboronic acid (28.0 mg, 147 μmol) and cesium carbonate (96.1 mg, 295 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (10.8 mg, 14.7 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (58.2 mg, 98 %) as yellow solid. MS: $m/e = 405.6 [M+H]^+$.

Example 7

8-(4-Chlorophenyl)-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide

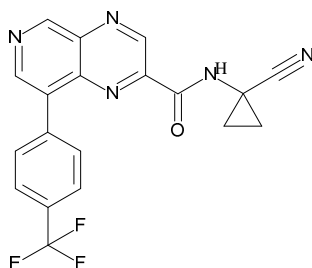


In a 25 ml round-bottomed flask, 8-bromo-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 157 μ mol), 4-chlorophenylboronic acid (24.6 mg, 157 μ mol) and cesium carbonate (102 mg, 314 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a colorless solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (11.5 mg, 15.7 μ mol) was added. The reaction mixture was heated at 80 $^{\circ}$ C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (48.5 mg, 88 %) as off-white solid. MS: m/e = 350.5 [M+H]⁺.

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Example 8

N-(1-Cyanocyclopropyl)-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



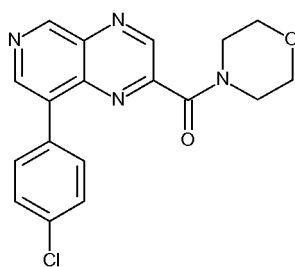
15 In a 25 ml round-bottomed flask, 8-bromo-N-(1-cyanocyclopropyl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 157 μ mol), 4-(trifluoromethyl)phenylboronic acid (29.9 mg, 157 μ mol) and cesium carbonate (102 mg, 314 μ mol, Eq: 2.00) were combined with dioxane (2.0 ml) and water (200 μ l) to give a colorless solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (11.5 mg, 15.7 μ mol) was added. The reaction mixture was heated at 80 $^{\circ}$ C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (54.7 mg, 76 %) as off-white solid. MS: m/e = 384.5 [M+H]⁺.

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Example 9

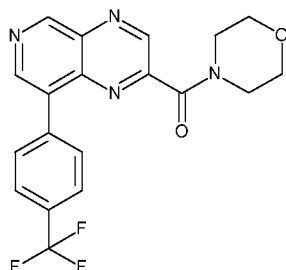
(8-(4-Chlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(morpholino)methanone

-31-



In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(morpholino) methanone (50 mg, 155 μ mol), 4-chlorophenylboronic acid (24.2 mg, 155 μ mol) and cesium carbonate (101 mg, 309 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (11.3 mg, 15.5 μ mol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (44.7 mg, 81 %) as off-white solid. MS: $m/e = 355.5 [M+H]^+$.

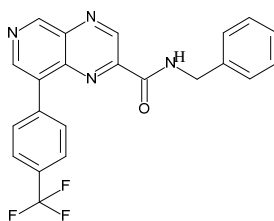
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Example 10**Morpholino(8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone**

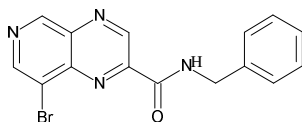
In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(morpholino) methanone (50 mg, 155 μ mol), 4-(trifluoromethyl)phenylboronic acid (29.4 mg, 155 μ mol) and cesium carbonate (101 mg, 309 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (11.3 mg, 15.5 μ mol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (51.7 mg, 86 %) as off-white solid. MS: $m/e = 389.5 [M+H]^+$.

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Example 11**N-Benzyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide**

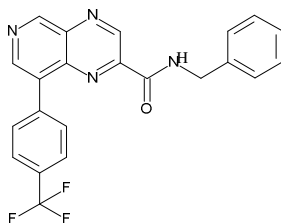


a) N-Benzyl-8-bromopyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (170 mg, 669 μmol) and 3 drops of dimethylformamide were combined with dichloromethane (10 ml) to give a light brown suspension. Oxalyl chloride (849 mg, 586 μl , 6.69 mmol) was added and stirring was continued for 1 hour. The crude reaction mixture was concentrated in vacuo, taken up in dichloromethane (10 ml) and was added to a mix of phenylmethanamine (71.7 mg, 669 μmol) and triethylamine (135 mg, 187 μl , 1.34 mmol) in dichloromethane (10 ml). The reaction mixture was then stirred at room temperature over night. Extraction with dichloromethane and chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) yielded the title compound (159 mg, 69 %) as light brown solid. MS: $m/e = 343.5, 345.4 [M+H]^+$.

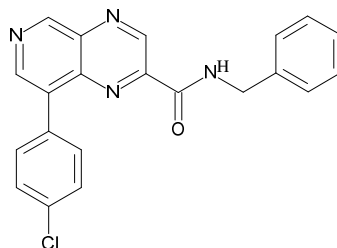
b) N-Benzyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, N-benzyl-8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 146 μmol), 4-(trifluoromethyl)phenylboronic acid (27.7 mg, 146 μmol) and cesium carbonate (94.9 mg, 291 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light yellow solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (10.7 mg, 14.6 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 15 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (56.3 mg, 95 %) as off-white solid. MS: $m/e = 409.6 [M+H]^+$.

Example 12

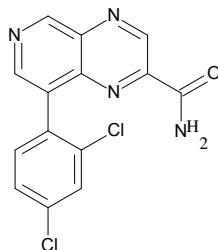
N-Benzyl-8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, N-benzyl-8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 146 μ mol), 4-chlorophenylboronic acid (22.8 mg, 146 μ mol) and cesium carbonate (94.9 mg, 291 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (10.7 mg, 14.6 μ mol) was added. The reaction mixture was heated at 80°C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (37.8 mg, 69 %) as off-white solid. MS: m/e = 375.5 [M+H]⁺.

Example 13

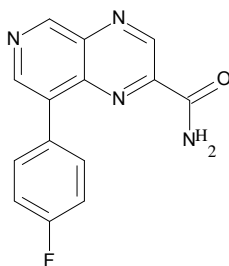
8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μ mol), 2,4-dichlorophenylboronic acid (37.7 mg, 198 μ mol) and cesium carbonate (129 mg, 395 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μ mol) was added. The reaction mixture was heated at 80 °C and stirred for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (51.2 mg, 81 %) as off-white solid. MS: m/e = 319.4, 321.4 [M+H]⁺.

Example 14

8-(4-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



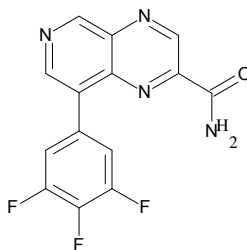
In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-fluorophenylboronic acid (27.6 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution.

- 5 Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (33.4 mg, 63 %) as yellow solid. MS: $m/e = 269.1$ $[\text{M}+\text{H}]^+$.

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Example 15

8-(3,4,5-Trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



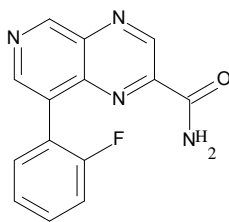
In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3,4,5-trifluorophenylboronic acid (34.8 mg, 198 μmol) and cesium carbonate (129 mg,

- 15 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (49.6 mg, 83 %) as light brown solid. MS: $m/e = 305.1$ $[\text{M}+\text{H}]^+$.

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Example 16

8-(2-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



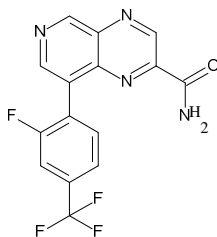
In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 2-fluorophenylboronic acid (27.6 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution.

- 5 Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (33 mg, 62 %) as off-white solid. MS: $m/e = 269.1$ $[\text{M}+\text{H}]^+$.

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Example 17

8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



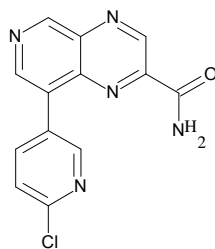
In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 2-fluoro-4-(trifluoromethyl)phenylboronic acid (41.1 mg, 198 μmol) and cesium

- 15 carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (2x, silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (26 mg, 39 %) as off-white solid. MS: $m/e = 337.1$ $[\text{M}+\text{H}]^+$.

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Example 18

8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide

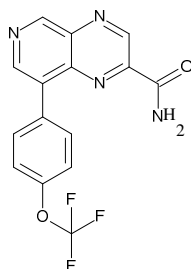


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 6-chloropyridin-3-ylboronic acid (31.1 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (48 mg, 85 %) as light yellow solid. MS: $m/e = 286.1$ $[\text{M}+\text{H}]^+$.

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Example 19

8-(4-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

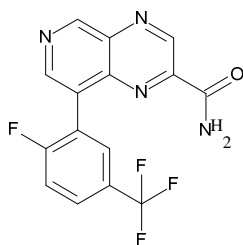


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-(trifluoromethoxy)phenylboronic acid (40.7 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (2x, silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (21 mg, 32 %) as off-white solid. MS: $m/e = 286.1$ $[\text{M}+\text{H}]^+$.

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Example 20

8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

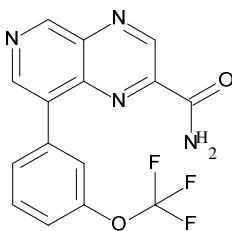


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 2-fluoro-5-(trifluoromethyl)phenylboronic acid (41.1 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (40 mg, 60 %) as off-white solid. MS: $m/e = 337.1$ $[\text{M}+\text{H}]^{+}$.

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Example 21

8-(3-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

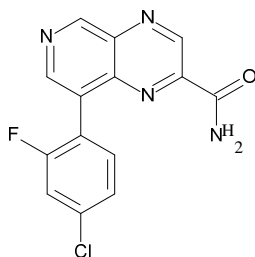


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3-(trifluoromethoxy)phenylboronic acid (40.7 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (40 mg, 61 %) as off-white solid. MS: $m/e = 335.1$ $[\text{M}+\text{H}]^{+}$.

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Example 22

8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

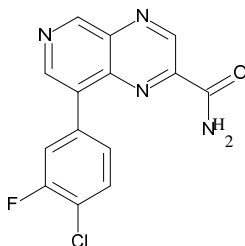


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-chloro-2-fluorophenylboronic acid (34.5 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (2x, silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (33 mg, 55 %) as off-white solid. MS: $m/e = 303.1$ $[\text{M}+\text{H}]^{+}$.

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Example 23

8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

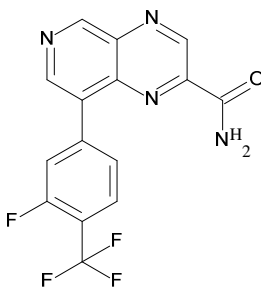


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-chloro-3-fluorophenylboronic acid (34.5 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (43.1 mg, 72 %) as light brown solid. MS: $m/e = 303.1$ $[\text{M}+\text{H}]^{+}$.

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Example 24

8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

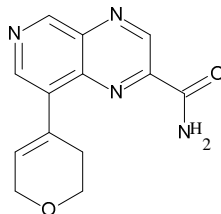


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3-fluoro-4-(trifluoromethyl)phenylboronic acid (41.1 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (34.1 mg, 51 %) as off-white solid. MS: $m/e = 337.1[\text{M}+\text{H}]^{+}$.

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Example 25

8-(3,6-Dihydro-2H-pyran-4-yl)pyrido[4,3-b]pyrazine-2-carboxamide

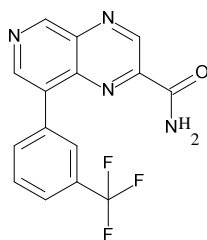


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3,6-dihydro-2H-pyran-4-ylboronic acid (25.3 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (30 mg, 59 %) as light yellow oil. MS: $m/e = 257.2[\text{M}+\text{H}]^{+}$.

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Example 26

8-(3-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

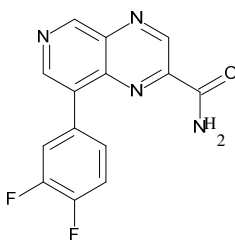


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3-(trifluoromethyl)phenylboronic acid (37.5 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 min. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (25 mg, 40 %) as off-white solid. MS: $m/e = 319.2[\text{M}+\text{H}]^{+}$.

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Example 27

8-(3,4-Difluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

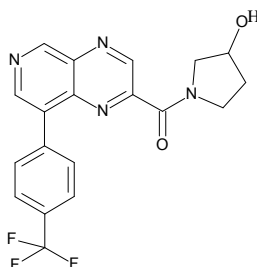


In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 3,4-difluorophenylboronic acid (31.2 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (37.8 mg, 67 %) as light yellow solid. MS: $m/e = 287.1 [\text{M}+\text{H}]^{+}$.

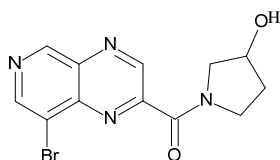
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Example 28

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

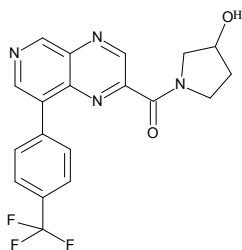


a) (8-Bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (800 mg, 3.15 mmol), pyrrolidin-3-ol (274 mg, 3.15 mmol) and triethylamine (478 mg, 658 μ l, 4.72 mmol) were combined with dimethylformamide (25.0 ml) to give a light brown solution. Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 1.32 g, 3.46 mmol) was added and stirring was continued at room temperature over night. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0). Trituration with diethyl ether (2 ml) yielded the title compound (104 mg, 10 %) as off-white solid. MS: m/e = 323.0, 325.0 [M+H]⁺.

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



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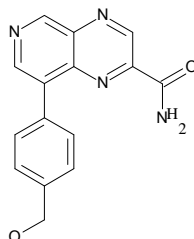
In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (50 mg, 155 μ mol), 4-(trifluoromethyl)phenylboronic acid (29.4 mg, 155 μ mol) and cesium carbonate (55.5 mg, 170 μ mol) were combined with dioxane (5.0 ml) and water (0.5 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (5.66 mg, 7.74 μ mol) was added under Argon. The reaction mixture was heated at 90 °C for 1 hour. The crude material was concentrated in vacuo and purified by chromatography (silica gel,

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ethyl acetate / heptane = 50:50 to 100:0) to yield the title compound (44.3 mg, 74 %) as off-white solid. MS: $m/e = 389.2$ $[M+H]^+$.

Example 29

8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



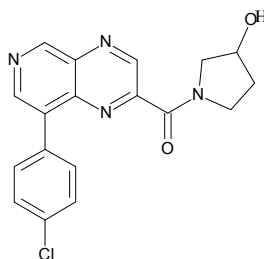
5

In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-(hydroxymethyl)phenylboronic acid (30.0 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.00 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (18 mg, 33 %) as light yellow solid. MS: $m/e = 281.2$ $[M+H]^+$.

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Example 30

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



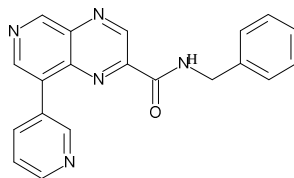
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In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (54 mg, 167 μmol), 4-chlorophenylboronic acid (26.1 mg, 167 μmol) and cesium carbonate (59.9 mg, 184 μmol) were combined with dioxane (5.0 ml) and water (0.5 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (6.11 mg, 8.36 μmol) was added under Argon. The reaction mixture was heated at 90 °C for 1 hour. The crude material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 25:75 to 100:0) to yield the title compound (36.5 mg, 61 %) as off-white solid. MS: $m/e = 355.2$ $[M+H]^+$.

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Example 31

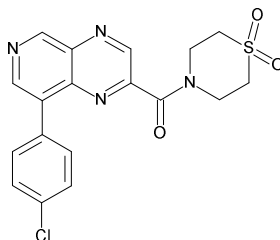
N-Benzyl-8-(pyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide



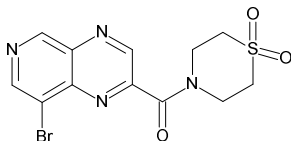
In a 25 ml round-bottomed flask, N-benzyl-8-bromopyrido[4,3-b]pyrazine-2-carboxamide (45 mg, 131 μ mol), pyridin-3-ylboronic acid (16.1 mg, 131 μ mol) and cesium carbonate (47.0 mg, 144 μ mol) were combined with dioxane (12.9 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (4.8 mg, 6.56 μ mol) was added. The reaction mixture was heated at 80 °C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (35 mg, 78 %) as off-white solid. MS: m/e = 342.2 [M+H]⁺.

Example 32

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

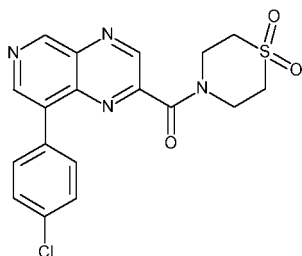


15 a) (8-Bromopyrido[3,4-b]pyrazin-2-yl)-(1,1-dioxo-1,4-thiazinan-4-yl)methanone



In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (300 mg, 1.18 mmol), thiomorpholine-1,1-dioxide (160 mg, 1.18 mmol) and triethylamine (179 mg, 247 μ l, 1.77 mmol) were combined with dimethylformamide (10.0 ml) to give a light brown suspension. Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 494 mg, 1.3 mmol) was added and stirring was continued at room temperature for 4 hours. The crude reaction mixture was concentrated in vacuo and extracted with ethyl acetate / water. Purification by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) yielded the title compound (213 mg, 49 %) as light brown solid. MS: m/e = 373.1 [M+H]⁺.

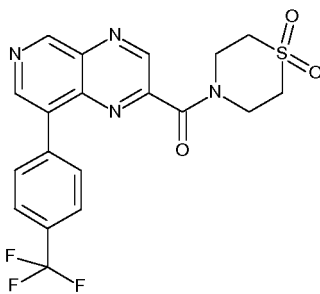
b) [8-(4-Chlorophenyl)pyrido[3,4-b]pyrazin-2-yl]-(1,1-dioxo-1,4-thiazinan-4-yl)methanone



In a 25 ml round-bottomed flask, (8-bromopyrido[3,4-b]pyrazin-2-yl)-(1,1-dioxo-1,4-thiazinan-4-yl)methanone (70 mg, 189 μmol), 4-chlorophenylboronic acid (29.5 mg, 189 μmol) and cesium carbonate (67.6 mg, 207 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (6.9 mg, 9.43 μmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (72 mg, 95 %) as off-white solid. MS: $m/e = 403.1$ $[\text{M}+\text{H}]^+$.

Example 33

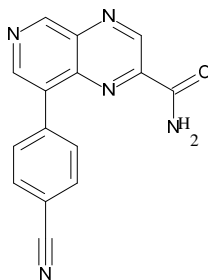
(1,1-Dioxo-1,4-thiazinan-4-yl)-[8-[4-(trifluoromethyl)phenyl]pyrido[3,4-b]pyrazin-2-yl]methanone



In a 25 ml round-bottomed flask, (8-bromopyrido[3,4-b]pyrazin-2-yl)-(1,1-dioxo-1,4-thiazinan-4-yl)methanone (70 mg, 189 μmol), 4-(trifluoromethyl)phenylboronic acid (35.8 mg, 189 μmol) and cesium carbonate (67.6 mg, 207 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (6.9 mg, 9.43 μmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (60 mg, 73 %) as light brown solid. MS: $m/e = 437.1$ $[\text{M}+\text{H}]^+$.

Example 34

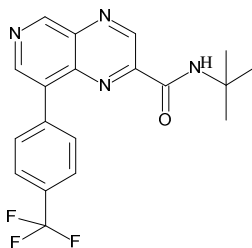
8-(4-Cyanophenyl)pyrido[4,3-b]pyrazine-2-carboxamide



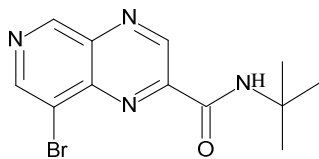
In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 198 μmol), 4-cyanophenylboronic acid (29.0 mg, 198 μmol) and cesium carbonate (129 mg, 395 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (14.5 mg, 19.8 μmol) was added. The reaction mixture was heated at 80 °C for 30 minutes. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (19.4 mg, 36 %) as light brown solid. MS: $m/e = 276.1$ $[\text{M}+\text{H}]^+$.

Example 35

N-tert-Butyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide



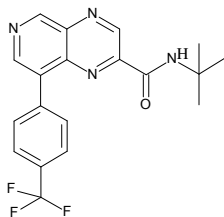
15 a) 8-Bromo-N-tert-butylpyrido[4,3-b]pyrazine-2-carboxamide



In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (200 mg, 787 μmol), 2-methylpropan-2-amine (57.6 mg, 82.7 μl , 787 μmol) and triethylamine (119 mg, 165 μl , 1.18 mmol) were combined with dimethylformamide (10 ml) to give a light brown suspension. Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 329 mg, 866 μmol) was added and stirring was continued at room temperature. The crude reaction

mixture was concentrated in vacuo and extracted with ethyl acetate / water. Chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) yielded the title compound (156 mg, 64 %) as white solid. MS: $m/e = 309.1, 311.1 [M+H]^+$.

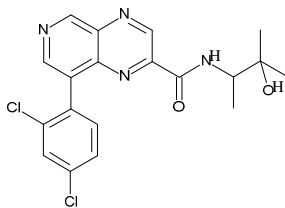
5 **b) N-tert-Butyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide**



In a 25 ml round-bottomed flask, 8-bromo-N-tert-butylpyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 162 μmol), 4-(trifluoromethyl)phenylboronic acid (30.7 mg, 162 μmol) and cesium carbonate (52.7 mg, 162 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light yellow solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (118 mg, 162 μmol) was added. The reaction mixture was heated at 80 °C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (50 mg, 83 %) as off-white solid. MS: $m/e = 375.2 [M+H]^+$.

15 **Example 36**

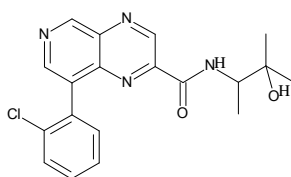
8-(2,4-Dichlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 2,4-dichlorophenylboronic acid (28.1 mg, 147 μmol) and cesium carbonate (52.8 mg, 162 μmol) were combined with dioxane (10.0 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (5.39 mg, 7.37 μmol) was added. The reaction mixture was heated at 80°C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) to yield the title compound (41 mg, 69%) as light brown solid. MS: $m/e = 405.6, 407.7 [M+H]^+$.

Example 37

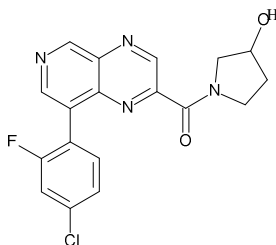
8-(2-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



- 5 In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 2-chlorophenylboronic acid (23.1 mg, 147 μmol) and cesium carbonate (52.8 mg, 162 μmol) were combined with dioxane (10.0 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (5.39 mg, 7.37 μmol) was added. The reaction mixture was heated at
- 10 80°C for 2 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) to yield the title compound (50 mg, 92 %) as off-white solid. MS: $m/e = 371.7 [\text{M}+\text{H}]^+$.

Example 38

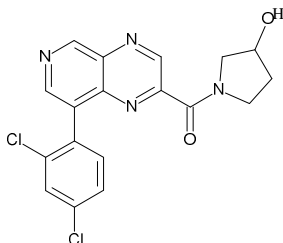
- 15 (8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



- In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μmol), 4-chloro-2-fluorophenylboronic acid (18.9 mg, 108 μmol) and cesium carbonate (38.8 mg, 119 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (3.96 mg, 5.42 μmol) was added. The reaction mixture was heated at 90 °C for 4 hours. The crude material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 25:75 to 100:0) to yield the title compound (9.2 mg, 23 %) as off-white solid. MS: $m/e = 373.2 [\text{M}+\text{H}]^+$.
- 25

Example 39

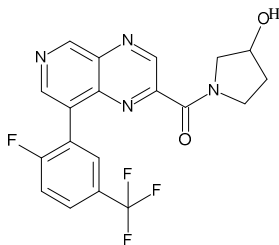
(8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μ mol), 2,4-dichlorophenylboronic acid (20.7 mg, 108 μ mol) and cesium carbonate (38.8 mg, 119 μ mol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (3.96 mg, 5.42 μ mol) was added. The reaction mixture was heated at 90 °C for 4 hours. The crude material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (29 mg, 69 %) as light brown solid. MS: m/e = 389.2, 391.2 [M+H]⁺.

Example 40

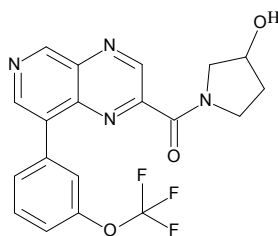
(8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μ mol), 2-fluoro-5-(trifluoromethyl)phenylboronic acid (22.5 mg, 108 μ mol) and cesium carbonate (70.6 mg, 217 μ mol) were combined with dioxane (2.0 ml) and water (200 μ l) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (7.93 mg, 10.8 μ mol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (20.1 mg, 46 %) as colorless oil. MS: m/e = 407.3 [M+H]⁺.

Example 41

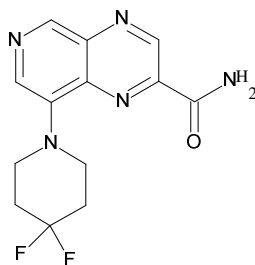
(3-Hydroxypyrrolidin-1-yl)(8-(3-(trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazin-2-yl)methanone



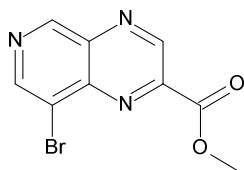
- 5 In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μmol), 3-(trifluoromethoxy)phenylboronic acid (22.3 mg, 108 μmol) and cesium carbonate (70.6 mg, 217 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (7.93 mg, 10.8 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 1 hour. The crude
- 10 material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (19.5 mg, 45 %) as colorless oil. MS: $m/e = 405.3[\text{M}+\text{H}]^{+}$.

Example 42

8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxamide



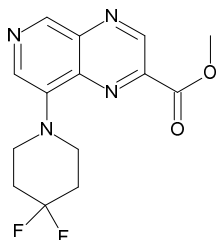
- 15
- a) Methyl 8-bromopyrido[4,3-b]pyrazine-2-carboxylate



- In a 50 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxylic acid (300 mg, 1.18 mmol) was combined with dichloromethane (10 ml) and 10 drops of dimethylformamide to give
- 20 a light brown suspension. The mixture was cooled to 0 $^{\circ}\text{C}$ and oxalyl chloride (749 mg, 517 μl , 5.9 mmol) was added. The reaction mixture was stirred at 0 $^{\circ}\text{C}$ for 1 hour and then at room temperature for 1 hour. The mixture was concentrated in vacuo and dissolved in

dichloromethane (10 ml). It was then slowly added to excess methanol at 0 °C. After 1 hour of stirring the mixture was concentrated in vacuo to yield the title compound (148 mg, 47 %) as off-white solid. MS: m/e = 268.0, 270.0 [M+H]⁺.

5 b) Methyl 8-(4,4-difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxylate

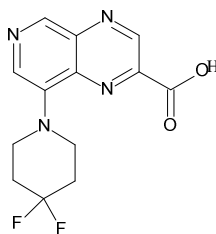


In a 25 ml three-necked flask, methyl 8-bromopyrido[4,3-b]pyrazine-2-carboxylate (100 mg, 373 μmol) and cesium carbonate (365 mg, 1.12 mmol) were combined with toluene (6.0 ml) to give a light brown suspension. Palladium(II)acetate (8.38 mg, 37.3 μmol) and 2,2'-

- 10 bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 46.5 mg, 74.6 μmol) and 4,4-difluoropiperidine (45.2 mg, 373 μmol) were added. The reaction mixture was heated at 80 °C for 5 hours. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (82 mg, 71 %) as light red solid. MS: m/e = 309.2 [M+H]⁺.

15

c) 8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxylic acid

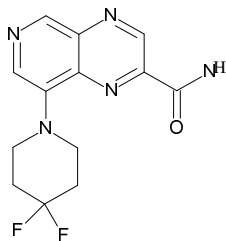


In a 25 ml round-bottomed flask, methyl 8-(4,4-difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxylate (80 mg, 260 μmol) was combined with dioxane (5.0 ml) to give a light red solution.

- 20 Lithium hydroxide (7.46 mg, 311 μmol) in water (1.0 ml) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 5 ml water, acidified with aqueous hydrochloric acid (2N) and extracted with ethyl acetate (5 x 25 ml). The organic layers were dried over magnesium sulfate, concentrated and dried in vacuo to yield the title compound (79 mg, 93 %) as light red solid. MS: m/e = 293.3 [M-H]⁻.

25

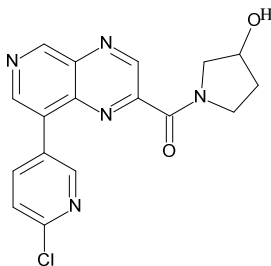
d) 8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxamide



- In a 25 ml round-bottomed flask, 8-(4,4-difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxylic acid (70 mg, 238 μmol) was combined with dichloromethane (5.0 ml) and 3 drops of dimethylformamide to give a red suspension. The mixture was cooled to 0 °C and then oxalyl chloride (302 mg, 208 μl , 2.38 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 20 minutes and then for 30 minutes at room temperature. The mixture was concentrated in vacuo, taken up in dichloromethane (5.0 ml) and added to a mixture of triethylamine (72.2 mg, 99.5 μl , 714 μmol) and ammonium hydroxide (25 % in water, 4.5 g, 5 ml, 128 mmol) at 0 °C. The mixture was stirred overnight at room temperature. Extraction with dichloromethane/water and chromatography (silica gel, ethyl acetate / heptane = 50:50 to 100:0) yielded the title compound (9 mg, 13 %) as orange solid. MS: $m/e = 294.2$ $[\text{M}+\text{H}]^+$.

Example 43

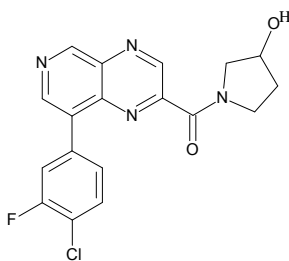
- 15 **(8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone**



- In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μmol), 6-chloropyridin-3-ylboronic acid (17.0 mg, 108 μmol) and cesium carbonate (70.6 mg, 217 μmol) were combined with dioxane (2.0 ml) and water (200 μl) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (7.93 mg, 10.8 μmol) was added. The reaction mixture was heated at 80 °C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (32 mg, 83 %) as off-white solid. MS: $m/e = 356.2$ $[\text{M}+\text{H}]^+$.

Example 44

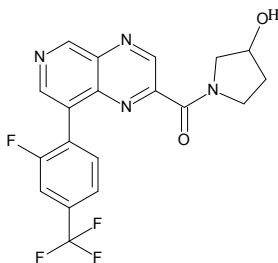
(8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



- 5 In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μ mol), 4-chloro-3-fluorophenylboronic acid (18.9 mg, 108 μ mol) and cesium carbonate (38.8 mg, 119 μ mol) were combined with dioxane (10.0 ml) and water (0.5 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (3.96 mg, 5.42 μ mol) was added. The reaction mixture was heated at 90 °C for 1 hour. The crude
- 10 material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 25:75 to 100:0) to yield the title compound (6 mg, 15 %) as light brown solid. MS: $m/e = 373.2 [M+H]^+$.

Example 45

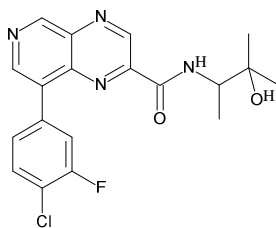
- (8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone**
- 15



- In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (35 mg, 108 μ mol), 2-fluoro-4-(trifluoromethyl)phenylboronic acid (22.5 mg, 108 μ mol) and cesium carbonate (70.6 mg, 217 μ mol) were combined with dioxane (2.0 ml) and
- 20 water (200 μ l) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (7.93 mg, 10.8 μ mol) was added. The reaction mixture was heated at 80°C for 1 hour. The crude material was purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (11.2 mg, 25 %) as off-white solid. MS: $m/e = 407.3 [M+H]^+$.

Example 46

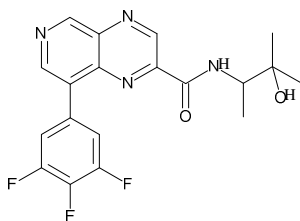
8-(4-Chloro-3-fluorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide



- 5 In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 4-chloro-3-fluorophenylboronic acid (25.7 mg, 147 μmol) and cesium carbonate (96.1 mg, 295 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-
- 10 palladium(II)dichloride (10.8 mg, 14.7 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 1 hour. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (34 mg, 59 %) as off-white solid. MS: $m/e = 389.3$ $[\text{M}+\text{H}]^{+}$.

Example 47

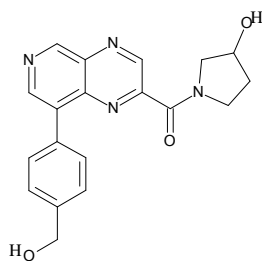
- 15 **N-(3-Hydroxy-3-methylbutan-2-yl)-8-(3,4,5-trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide**



- In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (50 mg, 147 μmol), 3,4,5-trifluorophenylboronic acid (25.9 mg, 147 μmol) and cesium carbonate (96.1 mg, 295 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-
- 20 palladium(II)dichloride (10.8 mg, 14.7 μmol) was added. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 1 hour. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound
- 25 (50 mg, 87 %) as off-white solid. MS: $m/e = 391.2$ $[\text{M}+\text{H}]^{+}$.

Example 48

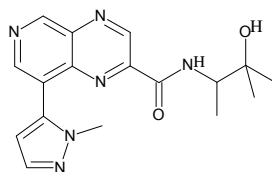
(8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



- 5 In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (40 mg, 124 μ mol), 4-(hydroxymethyl)phenylboronic acid (18.8 mg, 124 μ mol) and cesium carbonate (44.4 mg, 136 μ mol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (4.53 mg, 6.19 μ mol) was added. The reaction mixture was heated at 90 °C for 1 hour. The crude
- 10 reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, methanol / dichloromethane = 2:98 to 7:93) to yield the title compound (30.6 mg, 71 %) as brown solid. MS: m/e = 351.2 [M+H]⁺.

Example 49

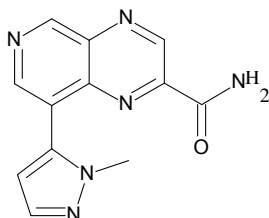
- 15 **N-(3-Hydroxy-3-methylbutan-2-yl)-8-(1-methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide**



- In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (40 mg, 118 μ mol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (24.5 mg, 118 μ mol) and cesium carbonate (42.3 mg, 130 μ mol)
- 20 were combined with dioxane (10 ml) and water (1.0 ml) to give a light yellow suspension. Bis(diphenylphosphino)ferrocene-palladium(II)dichloride (4.31 mg, 5.9 μ mol) was added. The reaction mixture was heated at 90 °C overnight. The crude material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0; then silica gel, methanol / dichloromethane = 2:98 to 5:95) to yield the title compound (12.5 mg, 31 %) as
- 25 light grey solid. MS: m/e = 341.2 [M+H]⁺.

Example 50

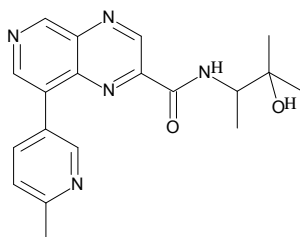
8-(1-Methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide



In a 25 ml round-bottomed flask, 8-bromopyrido[4,3-b]pyrazine-2-carboxamide (100 mg, 395
5 μmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (82.2 mg, 395
 μmol) and cesium carbonate (258 mg, 790 μmol) were combined with dioxane (10.0 ml) and
water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-
palladium(II)dichloride (28.9 mg, 39.5 μmol) was added. The reaction mixture was heated at
80 °C for 1 hour. The crude reaction mixture was concentrated in vacuo and purified by
10 chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound
(41 mg, 41 %) as light grey solid. MS: $m/e = 255.2$ $[\text{M}+\text{H}]^+$.

Example 51

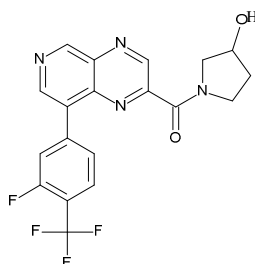
15 N-(3-Hydroxy-3-methylbutan-2-yl)-8-(6-methylpyridin-3-yl)pyrido[4,3-b]pyrazine-2- carboxamide



In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-
b]pyrazine-2-carboxamide (50 mg, 147 μmol), 6-methylpyridin-3-ylboronic acid (20.2 mg, 147
 μmol) and cesium carbonate (96.1 mg, 295 μmol) were combined with dioxane (10.0 ml) and
20 water (1.0 ml) to give a light brown solution. Bis(diphenylphosphino)ferrocene-
palladium(II)dichloride (10.8 mg, 14.7 μmol) was added. The reaction mixture was heated at 80
°C for 1 hour. The crude reaction mixture was concentrated in vacuo and purified by
chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound
(16 mg, 31 %) as light brown solid. MS: $m/e = 352.3$ $[\text{M}+\text{H}]^+$.

Example 52

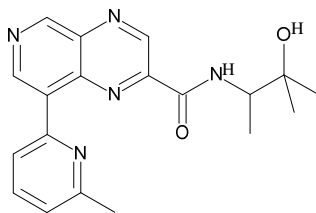
(8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone



- 5 In a 25 ml round-bottomed flask, (8-bromopyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone (40 mg, 124 μmol), 3-fluoro-4-(trifluoromethyl)phenylboronic acid (25.7 mg, 124 μmol) and cesium carbonate (44.4 mg, 136 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light brown suspension. Bis(diphenylphosphino)ferrocene-
- 10 palladium(II)dichloride (4.53 mg, 6.19 μmol) was added. The reaction mixture was heated at 90 $^{\circ}\text{C}$ for 1 hour. The crude reaction mixture was concentrated in vacuo and purified by chromatography (silica gel, methanol / dichloromethane = 2:98 to 7:93) to yield the title compound (20.7 mg, 41 %) as off-white solid. MS: $m/e = 407.3$ $[\text{M}+\text{H}]^{+}$.

Example 53

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



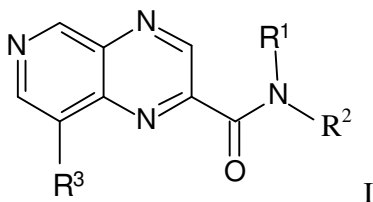
- In a 25 ml round-bottomed flask, 8-bromo-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide (70 mg, 206 μmol), 6-methylpyridin-2-ylboronic acid (28.3 mg, 206 μmol) and cesium carbonate (74.0 mg, 227 μmol) were combined with dioxane (10 ml) and water (1.0 ml) to give a light yellow solution. Bis(diphenylphosphino)ferrocene-
- 20 palladium(II)dichloride (7.55 mg, 10.3 μmol) was added. The reaction mixture was heated at 90 $^{\circ}\text{C}$ for 3 hours. Again, 6-methylpyridin-2-ylboronic acid (28.3 mg, 206 μmol) and cesium carbonate (74.0 mg, 227 μmol ,) and bis(diphenylphosphino)ferrocene-palladium(II)dichloride
- 25 (7.55 mg, 10.3 μmol) were added. The reaction mixture stirred over night at 90 $^{\circ}\text{C}$. A third time

6-methylpyridin-2-ylboronic acid (28.3 mg, 206 μmol) and cesium carbonate (74.0 mg, 227 μmol) and bis(diphenylphosphino)ferrocene-palladium(II)dichloride (7.55 mg, 10.3 μmol) were added. The reaction mixture was heated at 100 °C for 5 days. The crude material was concentrated in vacuo and purified by chromatography (silica gel, ethyl acetate / heptane = 20:80 to 100:0) to yield the title compound (8.8 mg, 12 %) as light grey solid. MS: $m/e = 352.3[\text{M}+\text{H}]^+$.

5

Claims

1. A compound of formula I



wherein

5 R^1 is hydrogen;

R^2 is hydrogen, lower alkyl, benzyl, lower alkyl substituted by hydroxy or cycloalkyl optionally substituted by cyano;

or R^1 and R^2 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;

10

R^3 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

15 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.

2. A compound of formula I according to claim 1, wherein R^1 is hydrogen, R^2 is hydrogen, lower alkyl, benzyl lower alkyl substituted by hydroxy or cycloalkyl optionally substituted by cyano, and R^3 is as described in claim 1.

20

3. A compound of formula I according to any one of claims 1 or 2, wherein the compounds are

8-(4-Chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

25 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-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-Benzyl-8-(4-chlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2,4-Dichlorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3,4,5-Trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2-Fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(6-Chloropyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2-Fluoro-5-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3-(Trifluoromethoxy)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-Chloro-2-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3,6-Dihydro-2H-pyran-4-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3-(Trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(3,4-Difluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-(Hydroxymethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

N-Benzyl-8-(pyridin-3-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-Cyanophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

N-tert-Butyl-8-(4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2,4-Dichlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(2-Chlorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4,4-Difluoropiperidin-1-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(4-Chloro-3-fluorophenyl)-N-(3-hydroxy-3-methylbutan-2-yl)pyrido[4,3-b]pyrazine-2-carboxamide

N-(3-Hydroxy-3-methylbutan-2-yl)-8-(3,4,5-trifluorophenyl)pyrido[4,3-b]pyrazine-2-carboxamide

N-(3-Hydroxy-3-methylbutan-2-yl)-8-(1-methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide

8-(1-Methyl-1H-pyrazol-5-yl)pyrido[4,3-b]pyrazine-2-carboxamide

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

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

4. A compound of formula I according to claim 1, 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, and R³ is as defined in claim 1.

5. A compound of formula I according to any one of claims 1 or 4, wherein the compounds are

(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

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(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

5 (8-(4-Chloro-3-fluorophenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

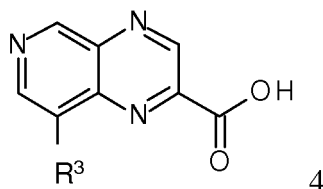
(8-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrido[4,3-b]pyrazin-2-yl)(3-hydroxypyrrolidin-1-yl)methanone

10 (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.

6. A process for the manufacture of a compound of formula I as defined in any one of claims 1 to 5, which process comprises

15 a) reacting a compound of formula

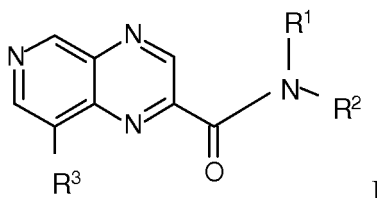


with a compound of formula

20



to a compound of formula

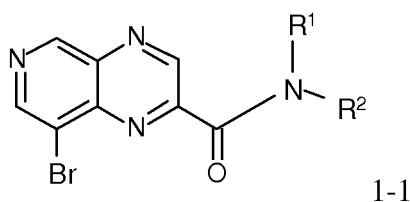


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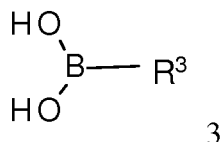
and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or

b) reacting a compound of formula I-1

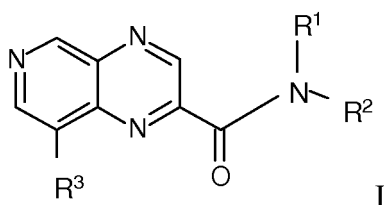
-62-



with a compound of formula



to a compound of formula



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

7. A compound of formula I according to any one of claims 1 - 5 for use as therapeutically active substances.

8. A compound of formula I according to any one of claims 1- 5 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, 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.

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

5 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,
10 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.

15