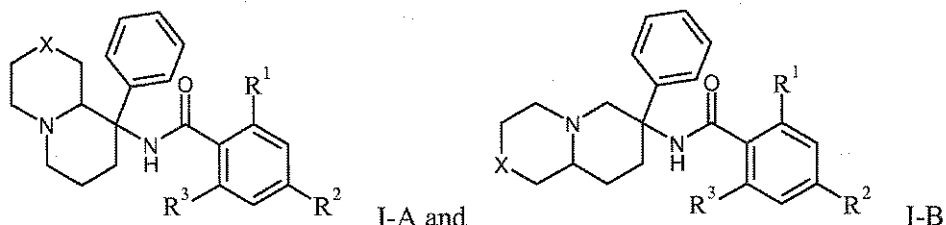


QUINOLIZIDINE AND INDOLIZIDINE DERIVATIVES

The present invention relates to a compound of general formula I-A or I-B



wherein

X is a bond or a $-\text{CH}_2-$ group;

- 5 R^1 , R^2 and R^3 are independently from each other hydrogen, lower alkoxy, lower alkyl substituted by halogen or S-lower alkyl;
or to a pharmaceutically acceptable acid addition salt, to a racemic mixture, or to its corresponding enantiomer and/or optical isomer thereof.

- 10 Furthermore, the present invention relates to pharmaceutical compositions containing the compounds of formulas I-A and I-B and to their use in the treatment of neurological and neuropsychiatric disorders.

- It has surprisingly been found that the compounds of general formulas I-A and I-B are good inhibitors of the glycine transporter 1 (GlyT-1), and that they have a good selectivity to
15 glycine transporter 2 (GlyT-2) inhibitors.

- Schizophrenia is a progressive and devastating neurological disease characterized by episodic positive symptoms such as delusions, hallucinations, thought disorders and psychosis and persistent negative symptoms such as flattened affect, impaired attention and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, *Neuron*, 2000, 28:325-33).
20 For decades research has focused on the "dopaminergic hyperactivity" hypothesis which has led to therapeutic interventions involving blockade of the dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets*, 2001, 5(4): 507-518; Nakazato A and Okuyama S, et al., 2000, *Exp. Opin. Ther. Patents*, 10(1): 75-98). This pharmacological approach poorly address negative and cognitive symptoms which are the best predictors of functional outcome (Sharma
25 T., *Br.J. Psychiatry*, 1999, 174(suppl. 28): 44-51).

A complementary model of schizophrenia was proposed in the mid-1960' based upon the psychotomimetic action caused by the blockade of the glutamate system by compounds like phencyclidine (PCP) and related agents (ketamine) which are non-competitive NMDA receptor antagonists. Interestingly in healthy volunteers, PCP-induced psychotomimetic action
5 incorporates positive and negative symptoms as well as cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al., 1999, *Biol. Psychiatry*, 45: 668-679 and refs. herein). Furthermore transgenic mice expressing reduced levels of the NMDAR1 subunit displays behavioral abnormalities similar to those observed in pharmacologically induced models of schizophrenia, supporting a model in which reduced NMDA receptor activity results
10 in schizophrenia-like behavior (Mohn AR et al., 1999, *Cell*, 98: 427-236).

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such as the NMDA receptors appears to serve as a graded switch for gating the threshold of synaptic plasticity and memory formation (Hebb DO, 1949, *The organization of behavior*, Wiley, NY; Bliss TV and Collingridge GL, 1993, *Nature*,
15 361: 31-39). Transgenic mice over-expressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., 1999, *Nature*: 401- 63-69).

Thus, if a glutamate deficit is implicate in the pathophysiology of schizophrenia, enhancing glutamate transmission, in particular via NMDA receptor activation, would be
20 predicted to produce both anti-psychotic and cognitive enhancing effects.

The amino acid glycine is known to have at least two important functions in the CNS. It acts as an inhibitory amino acid, binding to strychnine sensitive glycine receptors, and it also influences excitatory activity, acting as an essential co-agonist with glutamate for N-methyl-D-aspartate (NMDA) receptor function. While glutamate is released in an activity-dependent
25 manner from synaptic terminals, glycine is apparently present at a more constant level and seems to modulate/control the receptor for its response to glutamate.

One of the most effective ways to control synaptic concentrations of neurotransmitter is to influence their re-uptake at the synapses. Neurotransmitter transporters by removing neurotransmitters from the extracellular space, can control their extracellular lifetime and
30 thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, 2002, *Trends in Pharm. Sci.*, 23(8): 367-373).

Glycine transporters, which form part of the sodium and chloride family of neurotransmitter transporters, play an important role in the termination of post-synaptic

glycinergic actions and maintenance of low extracellular glycine concentration by re-uptake of glycine into presynaptic nerve terminals and surrounding fine glial processes.

Two distinct glycine transporter genes have been cloned (GlyT-1 and GlyT-2) from mammalian brain, which give rise to two transporters with ~50 % amino acid sequence homology. GlyT-1 presents four isoforms arising from alternative splicing and alternative promoter usage (1a, 1b, 1c and 1d). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-1b). GlyT-2 also presents some degree of heterogeneity. Two GlyT-2 isoforms (2a and 2b) have been identified in rodent brains. GlyT-1 is known to be located in CNS and in peripheral tissues, whereas GlyT-2 is specific to the CNS. GlyT-1 has a predominantly glial distribution and is found not only in areas corresponding to strychnine sensitive glycine receptors but also outside these areas, where it has been postulated to be involved in modulation of NMDA receptor function (Lopez-Corcuera B et al., 2001, *Mol. Mem. Biol.*, 18: 13-20). Thus, one strategy to enhance NMDA receptor activity is to elevate the glycine concentration in the local microenvironment of synaptic NMDA receptors by inhibition of GlyT-1 transporter (Bergereon R. Et al., 1998, *Proc. Natl. Acad. Sci. USA*, 95: 15730-15734; Chen L et al., 2003, *J. Neurophysiol.*, 89 (2): 691-703).

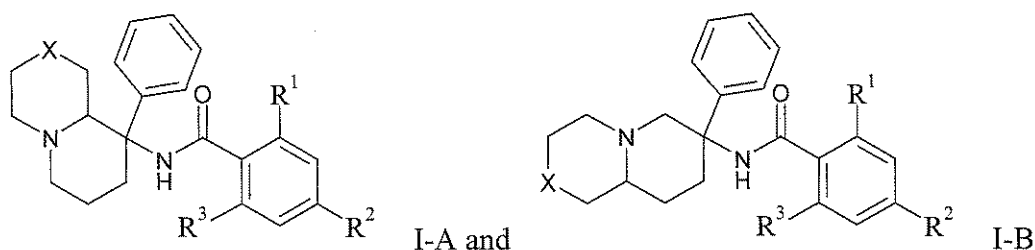
Glycine transporters inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572), psychotic mood disorders such as severe major depressive disorder, mood disorders associated with psychotic disorders such as acute mania or depression associated with bipolar disorders and mood disorders associated with schizophrenia, (Pralong ET et al., 2002, *Prog. Neurobiol.*, 67: 173-202), autistic disorders (Carlsson ML, 1998, *J. Neural Transm.* 105: 525-535), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572).

Thus, increasing activation of NMDA receptors via GlyT-1 inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

Objects of the embodiments disclosed herein are the compounds of formulas I-a and I-B per se, the use of compounds of formulas I-A and I-B and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 inhibition, their manufacture, medicaments based on a compound in

accordance with the disclosure and their production as well as the use of compounds of formulas I-A and I-B in the control or prevention of illnesses such as psychoses, dysfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

5 In a first aspect, there is provided a compound of general formula I-A or I-B



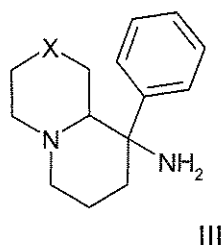
wherein

X is a bond or a $-\text{CH}_2-$ group;

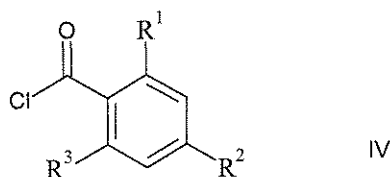
10 R^1 , R^2 and R^3 are independently from each other hydrogen, lower alkoxy, lower alkyl substituted by halogen or S-lower alkyl;
or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer thereof.

In a second aspect, there is provided a process for preparation of a compound of formula I-A or I-B as disclosed above and its pharmaceutically acceptable salt, which process comprises

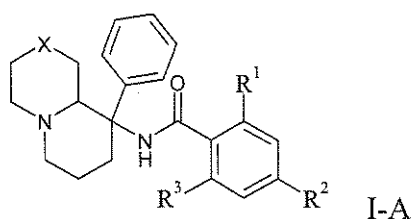
15 a) reacting a compound of formula



with a compound of formula

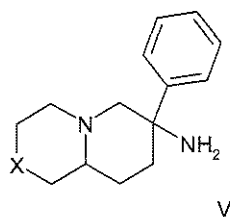


20 in the presence of a base like N-ethyl-diisopropylamine
to a compound of formula

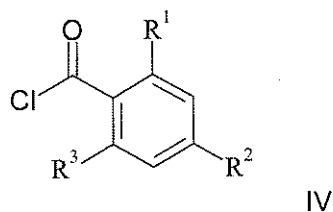


wherein the substituents are as defined above, or

b) reacting a compound of formula

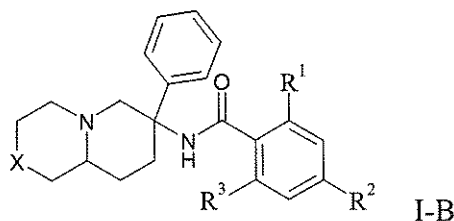


with a compound of formula



5

in the presence of a base like N-ethyldiisopropylamine
to a compound of formula



10 wherein the substituents are as defined above.

In a third aspect, there is provided a compound as defined above, when manufactured according to a process as defined above.

In a fourth aspect, there is provided a compound of formula I-A or I-B as defined above for use as therapeutically active substance.

15 In a fifth aspect, there is provided a compound of formula I-A or I-B as defined above for use in the treatment or prophylaxis of psychoses, pain, dysfunction in memory and learning, attention deficit, schizophrenia, dementia disorders or Alzheimer's disease.

In a sixth aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a therapeutically inert carrier.

In a seventh aspect, there is provided the use of a compound as defined above for the preparation of a medicament for the treatment or prophylaxis of psychoses, pain, dysfunction in memory and learning, attention deficit, schizophrenia, dementia disorders or Alzheimer's disease.

A further object of the embodiments disclosed herein is a method for the treatment or prophylaxis of psychoses, pain, dysfunction in memory and learning, attention deficit, schizophrenia, dementia disorders or Alzheimer's disease, which method comprises administering an effective amount of a compound of formula I-A or I-B to a mammal in need.

The preferred indications using the compounds of the present disclosure are schizophrenia, cognitive impairment and Alzheimer's disease.

Furthermore, the disclosure includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers.

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "lower alkoxy" denotes a lower alkyl group as defined above, which is linked with an O atom.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

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, for example the following groups: CF₃, CHF₂, CH₂F, CH₂CF₃, CH₂CHF₂, CH₂CH₂F, CH₂CH₂CF₃, CH₂CH₂CH₂CF₃, CH₂CH₂Cl, CH₂CF₂CF₃, CH₂CF₂CHF₂, CF₂CHFCF₃, C(CH₃)₂CF₃, CH(CH₃)CF₃ or CH(CH₂F)CH₂F. The preferred "lower alkyl substituted by halogen" group is CF₃.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

One embodiment of the invention are compounds of formula I-A, wherein X is CH₂, for example 2-methoxy-6-methylsulfanyl-N-((1S,R;9aR,S)-1-phenyl-octahydro-quinolizin-1-yl)-4-trifluoromethyl-benzamide.

A further embodiment of the invention are compounds of formula I-A, wherein X is a bond, for example

2-methoxy-6-methylsulfanyl-N-((8S,R; 8aR,S)-8-phenyl-octahydro-indolizin-8-yl)-4-trifluoromethyl-benzamide

5 One embodiment of the invention are compounds of formula I-B, wherein X is CH₂, for example

2-methoxy-6-methylsulfanyl-N-(3-phenyl-octahydro-quinolizin-3-yl)-4-trifluoromethyl-benzamide

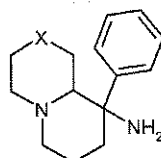
10 One embodiment of the invention are compounds of formula I-B, wherein X is a bond, for example

2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide (diastereoisomer 1) or

2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide (diastereoisomer 2).

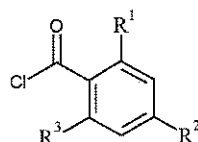
15 The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



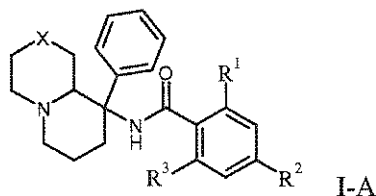
III

20 with a compound of formula



IV

in the presence of a base like N-ethyldiisopropylamine
to a compound of formula



I-A

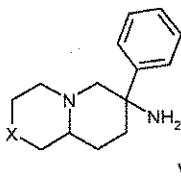
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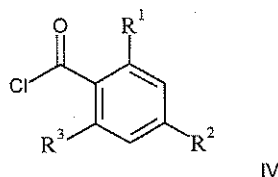
wherein the substituents are as defined above

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

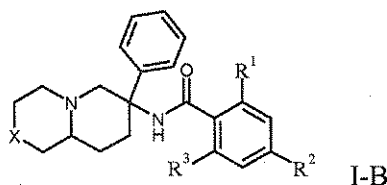
- 5 a) reacting a compound of formula



with a compound of formula



- 10 in the presence of a base like N-ethyldiisopropylamine
to a compound of formula



wherein the substituents are as defined above.

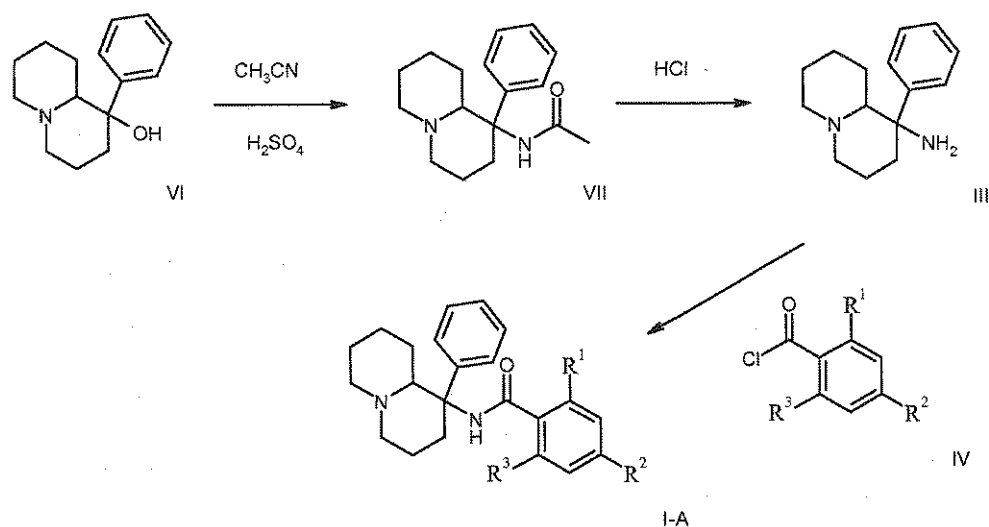
- The compounds of formula I-A wherein X is a $-CH_2-$ group may be prepared in accordance with
15 process variant a) and with the following scheme 1. The starting material is commercially
available or may be prepared in accordance with known methods.

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-7-

Scheme 1



Compounds of general formula I-A wherein X is a $-\text{CH}_2-$ group can be prepared by reacting amino-quinazolidine derivative of formula III with acid chloride of formula IV in the presence of a base like N-ethyldiisopropylamine. Amino-quinazolidine derivative of formula III can be prepared by reacting quinolizidinol VI with acetonitrile in the presence of an acid like sulfuric acid to provide acetamide derivative VII which is transformed into III in the presence of an acid like HCl.

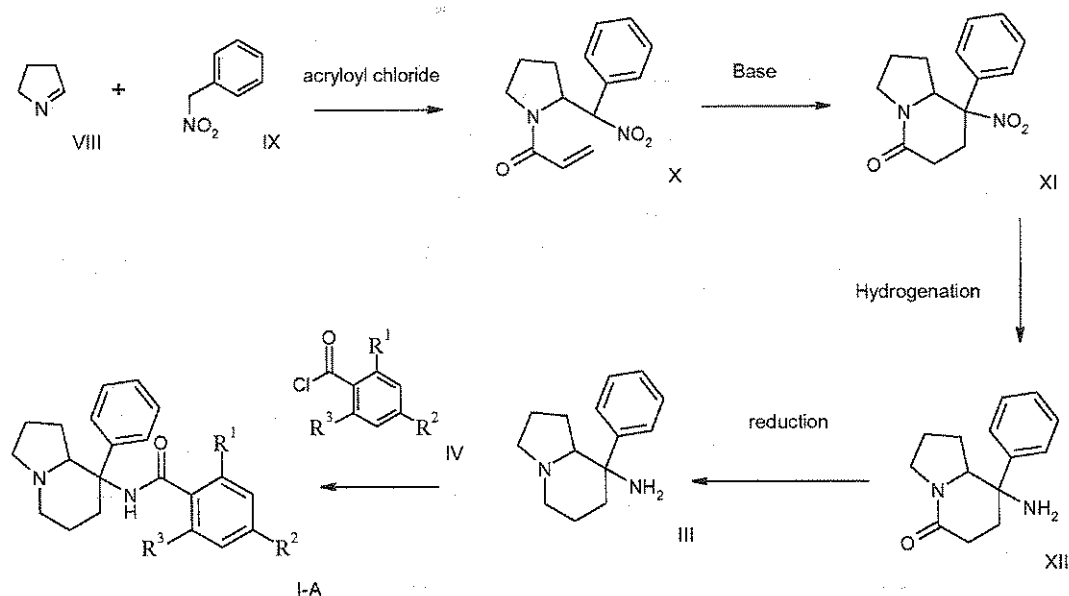
- 10 The compounds of formula I-A wherein X is a bond may be prepared in accordance with process variant b) and with the following scheme 2. The starting material is commercially available or may be prepared in accordance with known methods.

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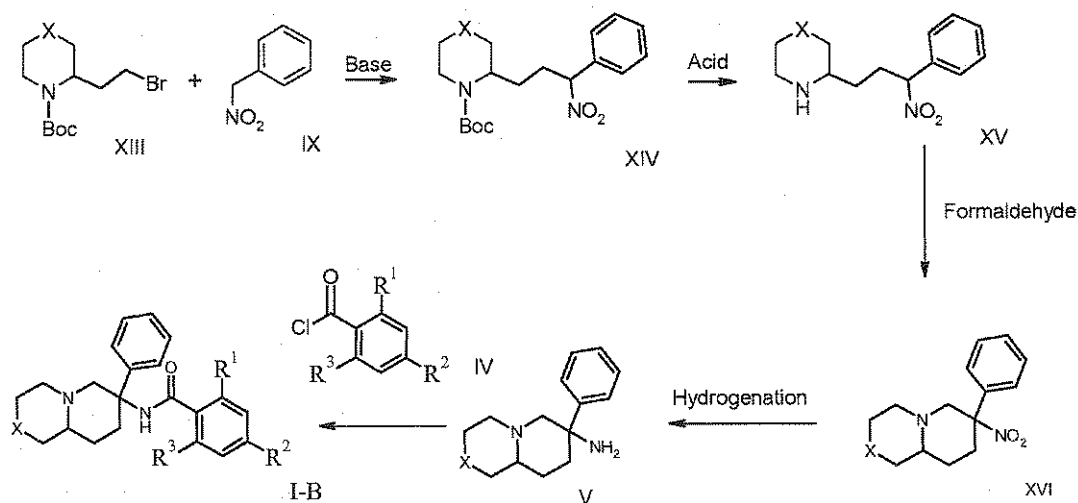
-8-

Scheme 2



- Compounds of general formula I-A wherein X is a bond can be prepared by reacting amino-indolizidine derivative of formula III with acid chloride of formula IV in the presence of a base like N-ethyldiisopropylamine. Amino-indolizidine derivative of formula III can be prepared by reacting 1H-pyrroline VIII with nitro-benzyl derivative IX to provide the corresponding Mannich adduct which can be trapped in situ with acryloyl chloride to provide X which undergoes an intramolecular Michael reaction in the presence of a base such as Amberlyst A21 to provide indolizidone XI. XI can be reduced to amino-indolizidone derivative XII upon hydrogenation in the presence of a metal catalyst such as Raney-Nickel. Reaction of XII with a reducing agent such as lithium aluminium hydride provides amino-indolizidine derivative of formula III
- The compounds of formula I-B wherein X is a $-\text{CH}_2-$ group or a bond may be prepared in accordance with process variant c) and with the following scheme 3. The starting material is commercially available or may be prepared in accordance with known methods.

Scheme 3



Compounds of general formula I-B wherein X is a bond or a $-\text{CH}_2-$ group can be prepared by
 5 reacting amino-indolizidine ($\text{X} = \text{bond}$) or quinolizidine ($\text{X} = -\text{CH}_2-$) derivative of formula V
 with acid chloride of formula IV in the presence of a base like N-ethyl-diisopropylamine. V can
 be prepared by reacting boc-protected bromo derivative XIII with nitro-benzyl derivative IX in
 the presence of a base like butyl lithium to provide adduct XIV, followed by removal of the Boc-
 protective group in the presence of acid such as HCl, intramolecular Mannich reaction with
 10 formaldehyde and finally hydrogenation of the nitro group in the presence of a metal catalyst
 such as Raney-Nickel.

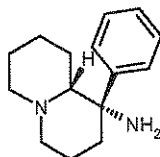
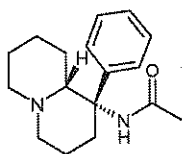
Racemic mixtures of chiral compound I can be separated using chiral HPLC.

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

Experimental part:

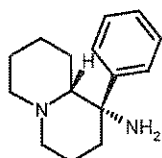
Abbreviations

HATU O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
 20 DMF Dimethylformamide
 DMSO Dimethylsulfoxide
 THF Tetrahydrofuran
 TMEDA Tetramethylethylenediamine

Preparation of intermediates**Example A.1****Preparation of (1R,S; 9S,R)-1-Phenyl-octahydro-quinolizin-1-ylamine**5 a) step 1: N-((1R,S; 9S,R)-1-Phenyl-octahydro-quinolizin-1-yl)-acetamide

To a suspension of 710 mg (3.069 mmol) 1-phenyl-octahydro-quinolizin-1-ol (CAS: 22525-61-7) in 5.3 ml acetonitrile was added dropwise 1.8 ml sulfuric acid (98 %) at 0 °C over a period of 15 minutes. The colorless solution was then stirred at room temperature for 48 hours. The solution was poured onto ice. The mixture was basified with NaOH 5N and extracted 3 times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 100 %) to provide 625 mg (74.8 %) of the title compound as a white solid. MS(m/e): 273.4 (M+H⁺).

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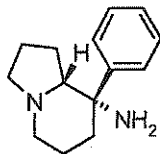
b) step 2: (1R,S;9S,R)-1-Phenyl-octahydro-quinolizin-1-ylamine

A solution of 270 mg (0.991 mmol) N-((1R,S;9S,R)-1-phenyl-octahydro-quinolizin-1-yl)-acetamide in 5.0 ml HCl 5N was heated in a 105 °C oil bath for 6 days. The solution was cooled in an ice bath and basified with a NaOH 5N solution. The aqueous layer was extracted 6 times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica eluting with a gradient formed from ethyl acetate and methanol (0 to 50 %) to provide 90 mg (40 %) of the title compound as a yellow solid. MS(m/e): 231.4 (M+H⁺).

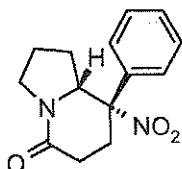
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Example A.2

Preparation of (8R,S; 8aS,R)-8-Phenyl-octahydro-indolizin-8-ylamine



a) step 1: (8R,S; 8aS,R)-8-Nitro-8-phenyl-hexahydro-indolizin-5-one

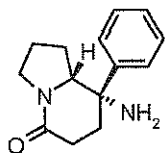


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To a room temperature solution of 280 mg (2.042 mmol) nitromethyl-benzene in 3 ml dioxane was added a solution of 141 mg (2.042 mmol) 3,4-dihydro-2H-pyrrole (CAS: 638-31-3) in 0.5 ml dioxane. The mixture was stirred at room temperature for 10 min then at 60 °C for 2.5 hours then cooled to 5-10 °C and 198.2 ul (2.45 mmol) acryloyl chloride was added dropwise. The mixture was then warm to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated sodium bicarbonate and ethylacetate. The aqueous phase was extracted two times with ethylacetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to provide 511 mg of light yellow oil. The crude compound was purified with flash column chromatography on silica eluting from n-heptane and ethyl acetate (0 to 40 %) to provide 332 mg of an oil that was dissolved in 3 ml dioxane and 816 mg of amberlyst A-21 was added. The reaction mixture was heated to 70 °C overnight cooled to room temperature, amberlyst was filtered and washed with ethylacetate. The filtrate was concentrated in vacuo. The crude compound was purified with flash column chromatography on silica eluting from n-heptane and ethyl acetate (0 to 100 %) to provide 329 mg (y: 62 %) of title compound as a colorless oil. (M+H+: 261.1)

20

b) step 2: (8R,S; 8aS,R)-8-Amino-8-phenyl-hexahydro-indolizin-5-one



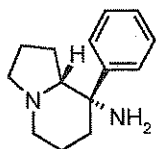
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To a solution of 60 mg (0.231 mmol) (8R,S;8aS,R)-8-nitro-8-phenyl-hexahydro-indolizin-5-one in 1ml THF were added 100 ul of Raney Nickel (55 % in water). The mixture was stirred at

room temperature under a hydrogen atmosphere for 90 hours. The apparatus was purged with argon. The catalyst was filtered (under argon), washed with THF and the filtrate was concentrated in vacuo to provide 38 mg (y: 72 %) of title compound as a colorless oil. (M+H⁺: 231.3).

5

c) step 3: (8R,S; 8aS,R)-8-Phenyl-octahydro-indolizin-8-ylamine

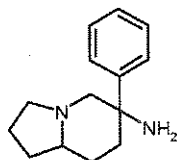


To a slurry of 14 mg (0.33 mmol) LiAlH₄ in 0.4 ml THF was added drop-wise a solution of 38 mg (0.165 mmol) (8R,S; 8aS,R)-8-amino-8-phenyl-hexahydro-indolizin-5-one in 0.4 ml THF at room temperature. The mixture was stirred at room temperature for 15 minutes and then refluxed for 30 minutes, cooled in an ice bath and quenched carefully with 15 ul water, 15 ul 5N NaOH and finally with 45 ul water. Ethyl acetate was added. The mixture was filtered and the filtrate was concentrated in vacuo to provide 30 mg (y: 84 %) of the title compound as a colorless oil. (M+H⁺: 217.4).

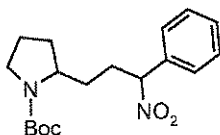
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Example A.3

Preparation of 6-Phenyl-octahydro-indolizin-6-ylamine



a) step 1: 2-(3-Nitro-3-phenyl-propyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

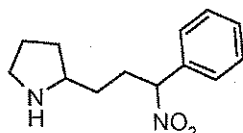


To a -78 °C solution of 200 mg (1.460 mmol) 2-(2-bromo-ethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (CAS: 958026-65-8) in 4.3 ml tetrahydrofuran over mol-sieves and 851.0 ul HMPA, was added drop-wise 1.92 ml (3.064 mmol) n-BuLi (1.6 M in hexane). After 45 minutes at -78 °C, a solution of 406.2 mg (1.460 mmol) nitromethyl-benzene in 0.6 ml tetrahydrofuran over mol-sieves was added drop-wise. After 1 hour at -78 °C, the reaction mixture was allowed to warm up slowly (during 5 hours) to -2 °C. The mixture was then cooled again to -78 °C and quenched at this temperature with 0.4 ml of acetic acid, then with 8 ml

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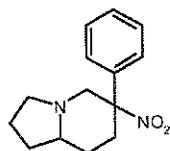
saturated ammonium chloride. Back to room temperature, the aqueous phase was extracted 2 times with ethylacetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude yellow oil (993 mg) was purified with flash column chromatography on silica eluting from n-heptane and ethyl acetate (0 to 15 %) to provide
5 242 mg (y: 49.6 %) of the title compound as a colorless oil. MS(m/e): 335.2 (M+H⁺).

b) step 2: 2-(3-Nitro-3-phenyl-propyl)-pyrrolidine



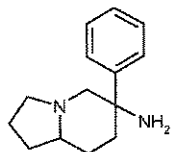
To a solution of 230 mg (0.688 mmol) 2-(3-nitro-3-phenyl-propyl)-pyrrolidine-1-carboxylic acid
10 tert-butyl ester in 3.5ml methanol were added 860 ul (0.344 mmol) of a 4M HCl solution in dioxane. The mixture was stirred at room temperature for 17 hours. The solvent was removed in vacuo. The residue was dissolved in water. The mixture was basified with a saturated sodium bicarbonate solution and extracted 6 times with dichloromethane. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo to provide 96 mg (y: 59.6 %) of the
15 title compound as a white solid. MS(m/e): 235.2 (M+H⁺).

c) step 3: 6-Nitro-6-phenyl-octahydro-indolizine



To a suspension of 95 mg (0.405mmol) 2-(3-nitro-3-phenyl-propyl)-pyrrolidine in 1.5ml dioxane
20 was added 32.5ul (0.446 mmol) formaldehyde (37 % in water). The mixture was stirred at room temperature for 30 minutes to get a solution, and then heated in a 65 °C oil bath for 4 hours. The mixture was cooled to room temperature and diluted with ethyl acetate. Sodium sulfate was added. The mixture was filtered and the filtrate was concentrated in vacuo. The residue (993 mg) was purified with flash column chromatography on silica eluting from n-heptane and ethyl
25 acetate (0 to 10 %) to provide 66 mg (y: 66.1 %) of the title compound as a colorless oil. MS(m/e): 247.3 (M+H⁺).

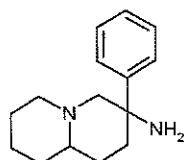
d) step 4: 6-Phenyl-octahydro-indolizin-6-ylamine



To a solution of 62mg (0.252 mmol) 6-nitro-6-phenyl-octahydro-indolizine in 2.0 ml THF was added 150 μ l Raney Nickel (50 % in water). The mixture was stirred under a hydrogen atmosphere for 2 hours. The apparatus was purged with argon. The catalyst was filtered, washed with THF and the filtrate was concentrated in vacuo to provide 57 mg (y: 100 %) of the title compound as a colorless oil. MS(m/e): 217.4 ($M+H^+$).

Example A.4

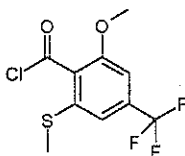
Preparation of 3-Phenyl-octahydro-quinolizin-3-ylamine



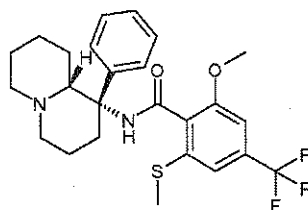
Title compound (colorless oil, MS(m/e): 231.4 ($M+H^+$)), was prepared following the same sequence of reaction as described for the preparation of example A3 using 2-(2-bromo-ethyl)-piperidine-1-carboxylic acid tert-butyl ester (CAS: 210564-52-6) as starting material.

Example B.1

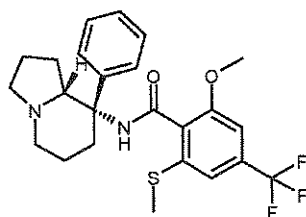
Preparation of 2-Methoxy-6-methylsulfanyl-4-trifluoromethyl-benzoyl chloride



A mixture of 51mg (0.191mmol) 2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzoic acid (CAS 1208984-79-5) and 140 μ l (1.91 mmol) thionylchloride in toluene (0.5 ml) was heated in a 80 $^{\circ}$ C oil bath for 4 hours. The solvent was removed in vacuo to provide the title compound.

Description of active examples:**Example 1****2-Methoxy-6-methylsulfanyl-N-((1S,R;9aR,S)-1-phenyl-octahydro-quinolizin-1-yl)-4-trifluoromethyl-benzamide**

To a solution of 33 mg (0.143 mmol) (1R,S; 9S,R)-1-phenyl-octahydro-quinolizin-1-ylamine (Example A1) and 74 μ l (0.429 mmol) N-ethyl-diisopropylamine in dichloromethane (0.33 ml) was added drop-wise a solution of 53 mg (0.186 mmol) 2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzoyl chloride (Example B1) in dichloromethane (0.3 ml) at room temperature. The mixture was stirred at room temperature overnight. The solution was washed once with a 2M sodium bicarbonate solution. The aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica eluting from n-heptane and ethyl acetate (0 to 50 %) to provide 44 mg (y: 64.2 %) of the title compound as a light yellow oil. MS(m/e): 479.1 ($M+H^+$).

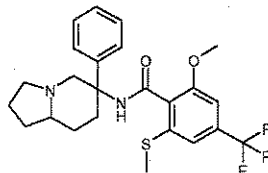
Example 2**2-Methoxy-6-methylsulfanyl-N-((8S,R; 8aR,S)-8-phenyl-octahydro-indolizin-8-yl)-4-trifluoromethyl-benzamide**

Title compound (colorless gum, MS(m/e): 465.2 ($M+H^+$)) was prepared according to the procedure described for example 1 using (8R,S; 8aS,R)-8-phenyl-octahydro-indolizin-8-ylamine (example A.2) as starting material.

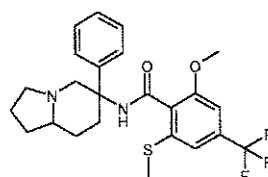
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Example 3

2-Methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide (diastereoisomer 1)

**Example 4**

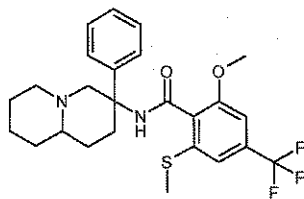
2-Methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide (diastereoisomer 2)



To a solution of 55 mg (0.254 mmol) 6-phenyl-octahydro-indolizin-6-ylamine (example A.3) and 130 μ l (0.762 mmol) N-ethyldiisopropylamine in dichloromethane (0.9 ml) was added dropwise a solution of 63 mg (0.22 mmol) 2-methoxy-6-methylsulfanyl-4-trifluoromethyl-benzoyl chloride (example B.1) in dichloromethane (0.6 ml) at room temperature. The mixture was stirred at room temperature for 1 hour. The solution was washed once with a 2M sodium carbonate solution. The aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified with flash column chromatography on silica eluting from n-heptane and ethyl acetate (0 to 50 %) to provide 26 mg (y: 22 %) of example 3 (2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide, diastereoisomer 1, first running compound) as a light yellow gum, MS (m/e): 465.2 ($M+H^+$) and 49 mg (y: 41.5 %) of example 4 (2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-benzamide, diastereoisomer 2, second running compound) as a white solid, MS(m/e): 465.2 ($M+H^+$).

Example 5

2-Methoxy-6-methylsulfanyl-N-(3-phenyl-octahydro-quinolizin-3-yl)-4-trifluoromethyl-benzamide



Title compound (white foam, MS(m/e): 479.1 (M+H⁺)) was prepared according to the procedure described for example 1 using 3-phenyl-octahydro-quinolizin-3-ylamine (example A.4) as starting material.

5

The compounds of formula IA and I-B and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are good inhibitors of the glycine transporter I (GlyT-1). The compounds were investigated in accordance with the test given hereinafter.

10

Solutions and materials

DMEM complete medium: Nutrient mixture F-12 (Gibco Life-technologies), fetal bovine serum (FBS) 5 %, (Gibco life technologies), Penicillin/Streptomycin 1 % (Gibco life technologies), Hygromycin 0.6 mg/ml (Gibco life technologies), Glutamine 1 mM (Gibco life technologies)

15 Uptake buffer (UB): 150 mM NaCl, 10 mM Hepes-Tris, pH 7.4, 1 mM CaCl_2 , 2.5 mM KCl, 2.5 mM MgSO_4 , 10 mM (+) D-glucose.

Flp-inTM-CHO (Invitrogen Cat n° R758-07) cells stably transfected with mGlyT1b cDNA.

Glycine uptake inhibition assay (mGlyT-1b)

On day 1 mammalian cells, (Flp-in™-CHO), transfected with mGlyT-1b cDNA, were plated at the density of 40,000 cells/well in complete F-12 medium, without hygromycin in 96-well culture plates. On day 2, the medium was aspirated and the cells were washed twice with uptake buffer (UB). The cells were then incubated for 20 min at 22 °C with either (i) no potential competitor, (ii) 10 mM non-radioactive glycine, (iii) a concentration of a potential inhibitor. A range of concentrations of the potential inhibitor was used to generate data for calculating the concentration of inhibitor resulting in 50 % of the effect (e.g. IC₅₀, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [³H]-glycine 60 nM (11-16 Ci/mmol) and 25 μM non-radioactive glycine. The plates were incubated with gentle shaking and the reaction was stopped by aspiration of the mixture and washing (three times) with ice-cold UB. The cells were lysed with scintillation liquid, shaken 3 hours and the radioactivity in the cells was counted using a scintillation counter.

The compounds described in examples 1 – 5 have an IC_{50} data $<0.1 \mu M$. The IC_{50} data for compounds of formula I-A and I-B are provided in table 1.

Table 1

Example	IC_{50} data (μM)
1	0.080
2	0.025
3	0.017
4	0.013
5	0.028

5

The compounds of formula I-A and I-B 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, parenterally, e.g. in the form of injection solutions.

10

The compounds of formula I-A and I-B 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.

15

Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

20

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.

25

Medicaments containing a compound of formula I-A and I-B 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-a and I-B 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.

5 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 schizophrenia, cognitive impairment and Alzheimer's disease.

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-a and I-B 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.

15 **Tablet Formulation (Wet Granulation)**

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

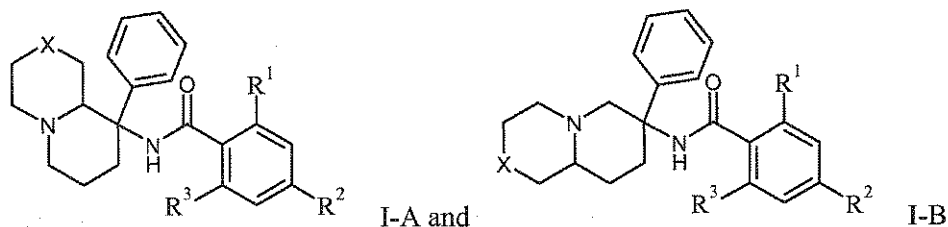
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Manufacturing Procedure

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.

Claims

1. A compound of general formula I-A or I-B



5 wherein

X is a bond or a $-\text{CH}_2-$ group;

R^1 , R^2 and R^3 are independently from each other hydrogen, lower alkoxy, lower alkyl substituted by halogen or S-lower alkyl;

or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding

10 enantiomer and/or optical isomer thereof.

2. A compound of formula I-A, wherein X is CH_2 .

3. A compound of formula I-A according to claim 2, wherein the compound is
15 2-methoxy-6-methylsulfanyl-N-((1S,R;9aR,S)-1-phenyl-octahydro-quinolizin-1-yl)-4-trifluoromethyl-benzamide.

4. A compound of formula I-A, wherein X is a bond.

20 5. A compound of formula I-A according to claim 4, wherein the compound is 2-methoxy-6-methylsulfanyl-N-((8S,R; 8aR,S)-8-phenyl-octahydro-indolizin-8-yl)-4-trifluoromethyl-benzamide.

6. A compound of formula I-B, wherein X is CH_2 .

25

7. A compound of formula I-B according to claim 6, wherein the compound is 2-methoxy-6-methylsulfanyl-N-(3-phenyl-octahydro-quinolizin-3-yl)-4-trifluoromethyl-benzamide.

8. A compound of formula I-B, wherein X is a bond.

9. A compound of formula I-B according to claim 8, wherein the compounds are
2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-

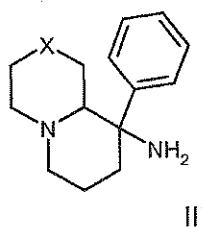
5 benzamide (diastereoisomer 1) or

2-methoxy-6-methylsulfanyl-N-(6-phenyl-octahydro-indolizin-6-yl)-4-trifluoromethyl-
benzamide (diastereoisomer 2).

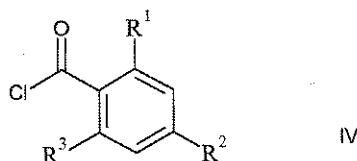
10. A process for preparation of a compound of formula I-A or I-B as disclosed in claim

10 1 and its pharmaceutically acceptable salt, which process comprises

a) reacting a compound of formula

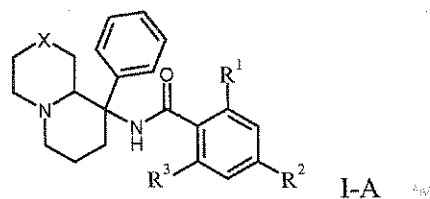


with a compound of formula



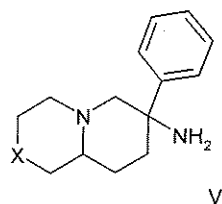
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in the presence of a base like N-ethyldiisopropylamine
to a compound of formula

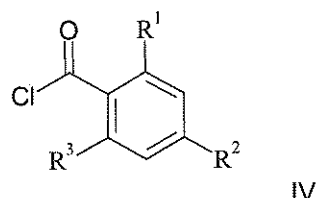


20 wherein the substituents are as defined in claim 1, or

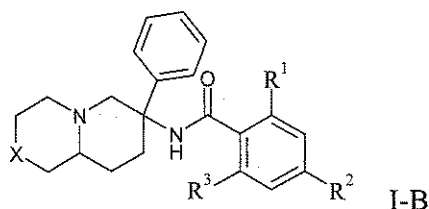
b) reacting a compound of formula



with a compound of formula



- 5 in the presence of a base like N-ethyldiisopropylamine
to a compound of formula



wherein the substituents are as defined in claim 1.

11. A compound according to any one of claims 1 to 9, when manufactured according to a
10 process of claim 10.

12. A compound of formula I-A or I-B according to any one of claims 1 to 9 for use as
therapeutically active substance.

- 15 13. A compound of formula I-A or I-B according to any one of claims 1 to 9 for use in
the treatment or prophylaxis of psychoses, pain, dysfunction in memory and learning, attention
deficit, schizophrenia, dementia disorders or Alzheimer's disease.

14. A pharmaceutical composition comprising a compound in accordance with any one of
20 claims 1 to 9 and a therapeutically inert carrier.

15. The use of a compound according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of psychoses, pain, dysfunction in memory and learning, attention deficit, schizophrenia, dementia disorders or Alzheimer's disease.