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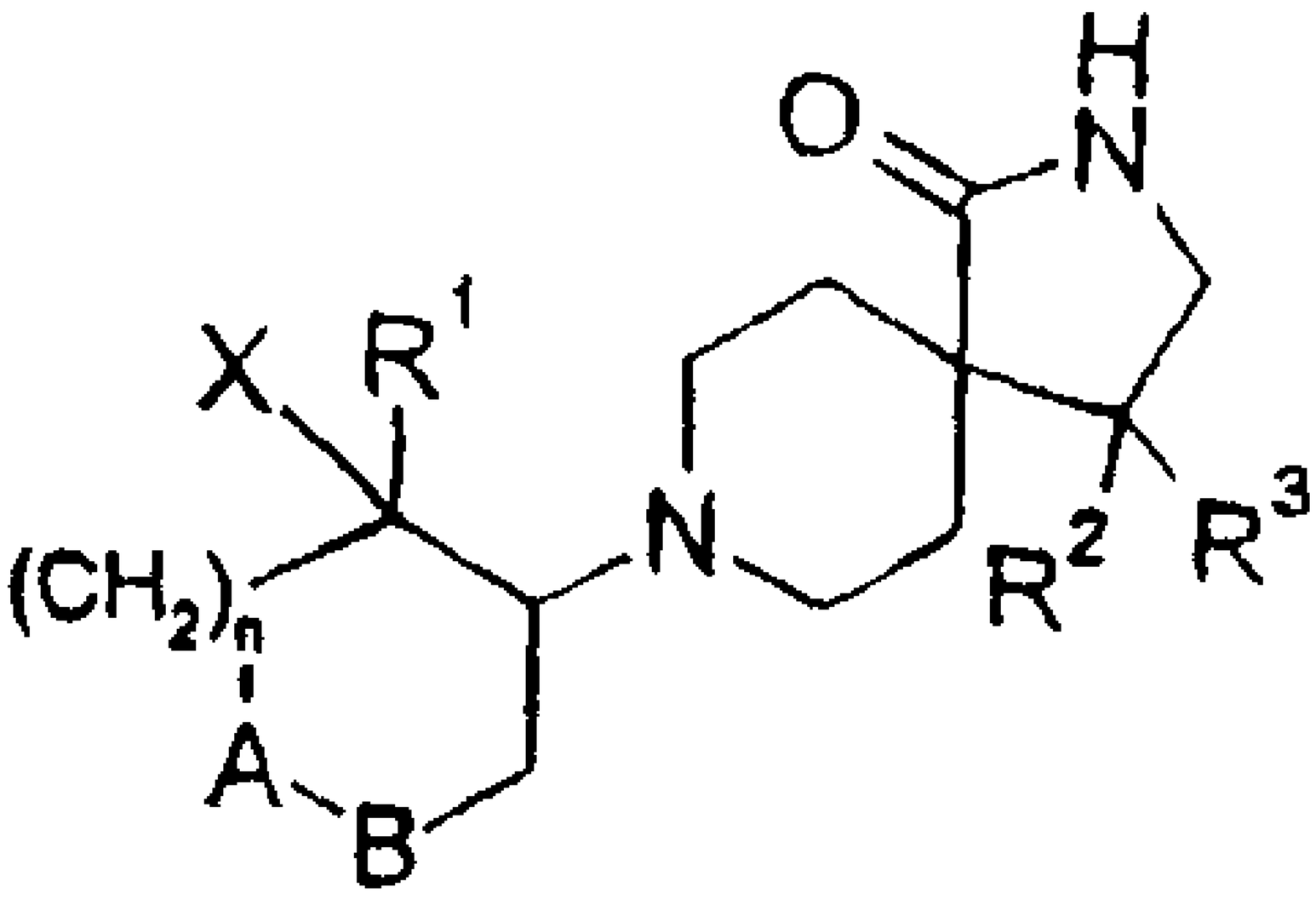
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(54) Title: DIAZA-SPIROPIPERIDINE DERIVATIVES



I

(57) Abrégé/Abstract:
The present invention relates to compounds of formula (I); wherein A-B is $-CH_2-CH_2-$, $-CH_2-O-$ or $-O-CH_2-$; X is hydrogen or hydroxy; R^1 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, cyano, CF_3, $-OCF_3$, lower alkoxy, $-SO_2$-lower alkyl or by heteroaryl, R^2 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, CF_3 or lower alkoxy; R^3 is hydrogen or lower alkyl; n is 0, 1 or 2; and to their pharmaceutically active salts. The compounds of formula I may be used in the treatment of neurological and neuropsychiatric disorders.

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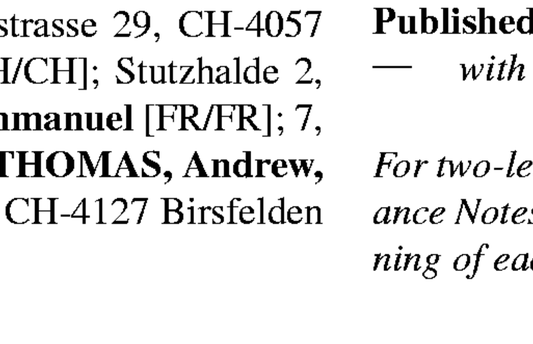
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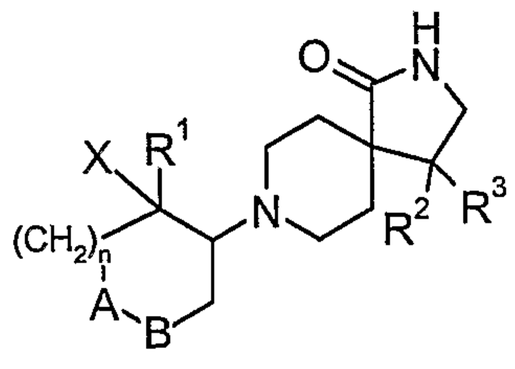
(I)

(57) Abstract: The present invention relates to compounds of formula (I); wherein A-B is $-CH_2-CH_2-$, $-CH_2-O-$ or $-O-CH_2-$; X is hydrogen or hydroxy; R^1 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, cyano, CF_3, $-OCF_3$, lower alkoxy, $-SO_2$-lower alkyl or by heteroaryl, R^2 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, CF_3 or lower alkoxy; R^3 is hydrogen or lower alkyl; n is 0, 1 or 2; and to their pharmaceutically active salts. The compounds of formula I may be used in the treatment of neurological and neuropsychiatric disorders.

WO 2005/068463 A1

Diaza-spiropiperidine derivatives

The present invention relates to compounds of formula



I

wherein

A-B is $-CH_2-CH_2-$, $-CH_2-O-$ or $-O-CH_2-$;

X is hydrogen or hydroxy;

R^1 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, cyano, CF_3, $-OCF_3$, lower alkoxy, $-SO_2$-lower alkyl or by heteroaryl,

R^2 is aryl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, CF_3 or lower alkoxy;

R^3 is hydrogen or lower alkyl;

n is 0, 1 or 2;

and to their pharmaceutically active salts.

The present invention related to compounds of general formula I, to pharmaceutical composition containing them and their use in the treatment of neurological and neuropsychiatric disorders.

It has surprisingly been found that the compounds of general formula I are good inhibitors of the glycine transporter 1 (GlyT-1), and that they have a good selectivity to 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). 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 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 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 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*, 361: 31-39). Transgenic mice overexpressing 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 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 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 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 neuroligical 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 present invention are the compounds of formula I per se, the use of compounds of formula I 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 invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as psychoses, disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

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

Furthermore, the invention 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.

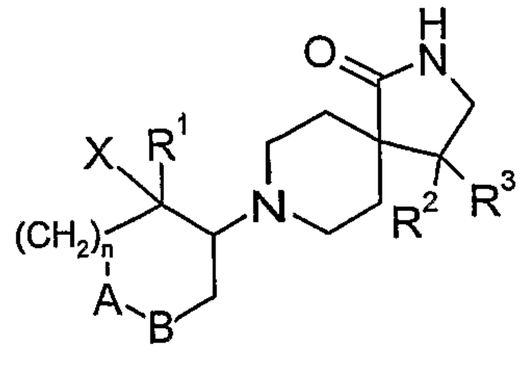
The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, for example phenyl or naphthyl.

The term "heteroaryl" denotes a cyclic aromatic hydrocarbon radical, containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen, for example pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isothiazolyl or isoxazolyl.

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.

Preferred compounds of formula I are those of formula



I

wherein

A-B is $-CH_2-CH_2-$ or $-CH_2-O-$;

X is hydrogen or hydroxy;

R^1 is phenyl, optionally substituted by one or two substituents, selected from the group consisting of halogen, lower alkyl, cyano, CF_3, $-OCF_3$, lower alkoxy, $-SO_2$-lower alkyl or by heteroaryl,

R^2 is phenyl, optionally substituted by one or two substituents, selected from the group consisting of halogen or lower alkoxy;

R^3 is hydrogen;

n is 1;

and their pharmaceutically active salts.

Most preferred are compounds, wherein n is 1 and A-B is $-CH_2-CH_2-$. Especially preferred compounds from this group are those, wherein R^1 and R^2 are both phenyl, optionally substituted by lower alkyl, halogen or CF_3, for example the following compounds:

cis-rac-4-phenyl-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one,

cis-rac4-phenyl-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one,

cis-rac-8-[2-(4-fluoro-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one,

cis-rac-4-(4-fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,

cis-rac-4-(4-fluoro-phenyl)-8-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,

8-[2-(4-fluoro-phenyl)-2-hydroxy-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one,

4-(4-fluoro-phenyl)-8-[2-(3-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,

4-(4-fluoro-phenyl)-8-[2-(2-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,

8-[2-(3-chloro-phenyl)-2-hydroxy-cyclohexyl]-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one or

4-(4-fluoro-phenyl)-8-*trans*-(4-hydroxy-4-phenyl-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one.

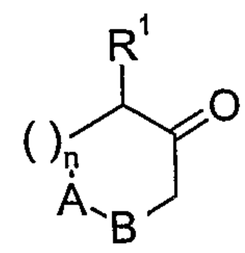
Preferred are further compounds, wherein X is hydrogen.

The invention relates also to compounds, wherein X is hydroxy.

Objects of the present invention are further compounds, wherein n is 1 and A-B is $-CH_2-O-$.

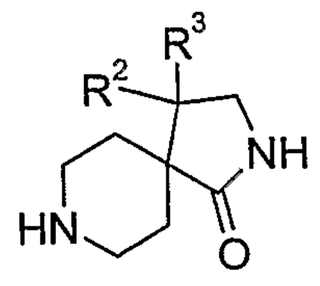
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



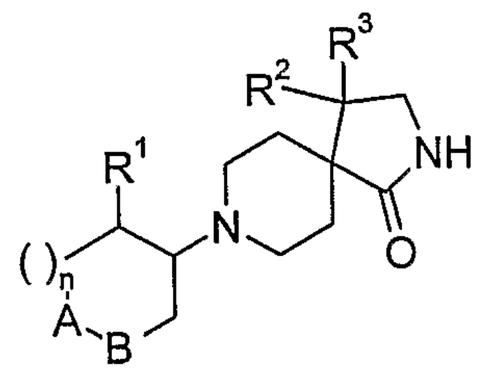
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with a compound of formula



7

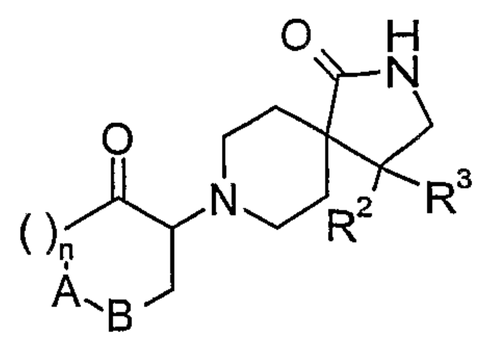
to a compound of formula



I for X = hydrogen,

wherein the substituents are as defined above, or

b) reacting a compound of formula

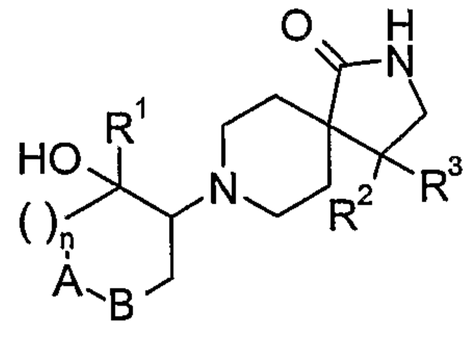


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with a compound of formula

R^1Br 8

to a compound of formula



I for X = hydroxy

wherein the substituents are as defined above, or

c) if desired, separating the obtained racemic forms into corresponding enantiomers, and

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

The compounds of formula I may be prepared in accordance with process variant a), b) or c) and with the following schemes 1, 2 and 3.

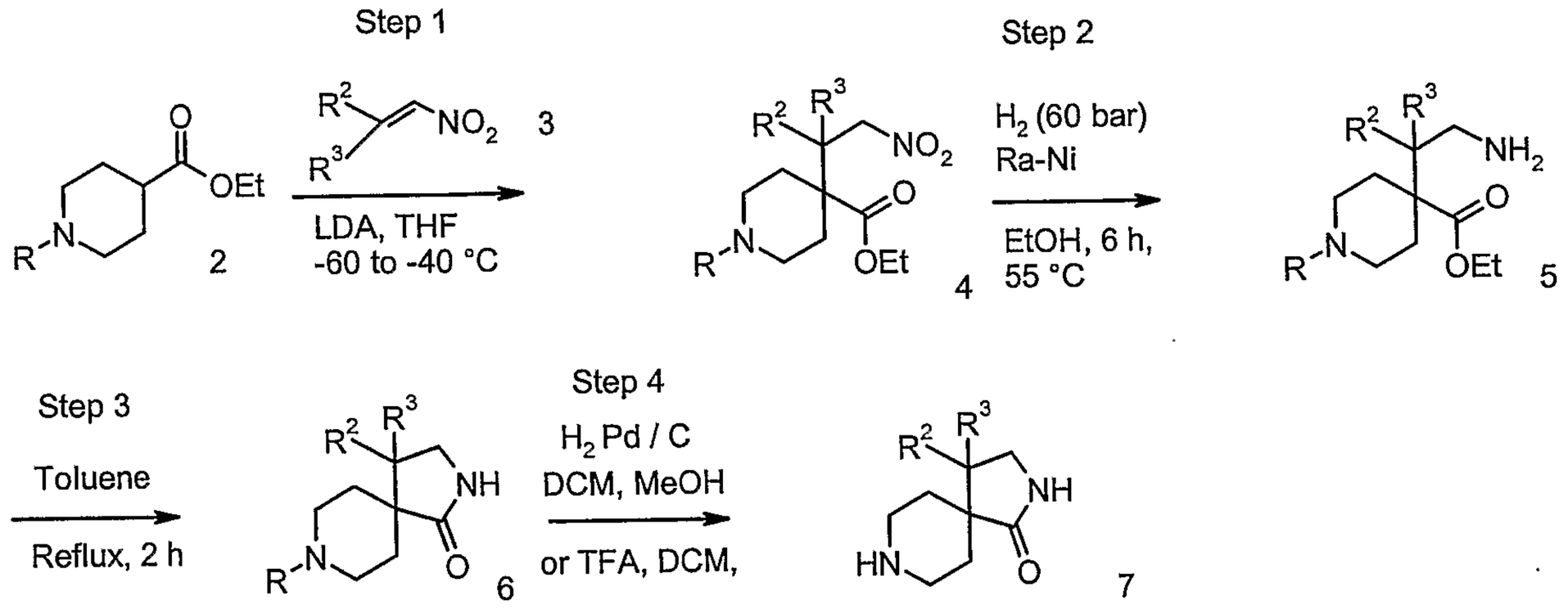
The following abbreviations have been used:

LDA = lithium diisopropylamide
TFA = trifluoroacetic acid
DCM = dichloromethane
THF = tetrahydrofuran
PMHS = polymethylhydrosiloxane
DMSO = dimethylsulfoxide

Starting from an appropriately 1-protected-piperidine-4-alkylcarboxylate 2, treatment with an appropriate base, usually LDA, followed by treatment with an appropriately substituted nitro alkene 3 results in formation of the nitro alkane 4. Reduction to the amino group facilitated by Raney-Ni and hydrogen, usually at 60 bar

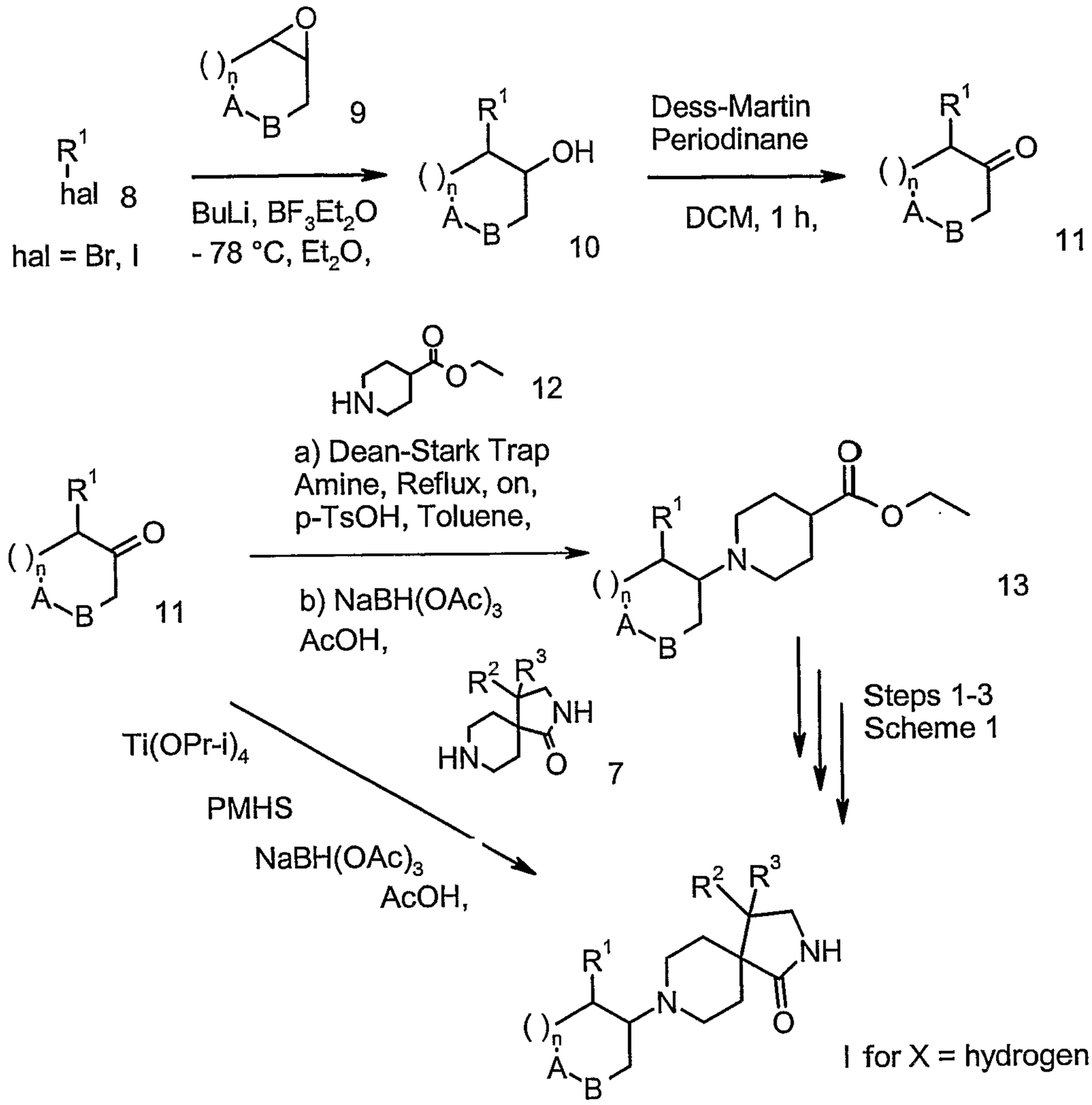
pressure and at 55 °C in EtOH as solvent results in the formation of 5. Subsequent cyclisation by heating in toluene under reflux affords the amide 6. Removal of the protecting group under standard conditions (TFA treatment in DCM for R = Boc; or hydrogenolysis with Pd/C in DCM, MeOH for R = Bn) affords the diazaspiropiperidines 7 (Scheme 1).

Scheme 1



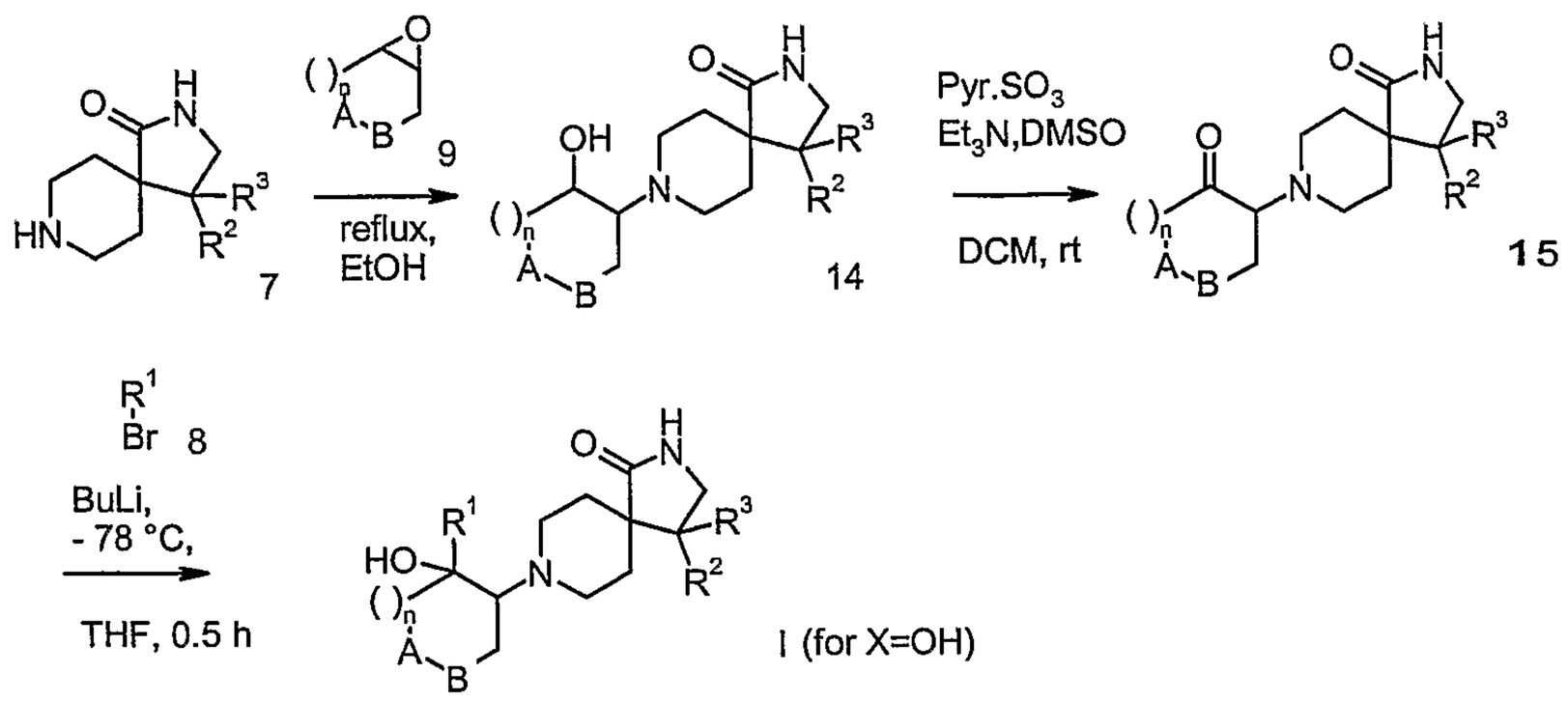
Further reaction of compounds of formula 7 with corresponding compounds of formula 11 (which can be prepared by reaction of the arylhalides of formula 8 with BuLi and subsequent reaction with an epoxide of formula 9 to give the alcohols of formula 10, which are oxidized to the corresponding ketones of formula 11 with Dess-Martin Periodinane) in the presence of $Ti(OPr\text{-}i)_4$ and $NaBH(OAc)_3$ to give compounds of formula I (Scheme 2). Alternatively, reaction of compounds of formulas 7 and 11 in the presence of $Ti(OPr\text{-}i)_4$ and $NaBH(OAc)_3$ (with or without the presence of PMHS) also gives products of formula I. An alternative strategy where overall reductive amination of the ketones of formula 11 with compounds of formula 12 in a Dean-Stark trap affords an intermediate enamine, which can be reduced in situ to the compound formula 13. Following steps 1-3 as described in Scheme 1 affords compounds of formula I.

Scheme 2



Compounds of formula I for X = OH are prepared by reacting compounds of formula 7 with an oxides of formula 9 in refluxing ethanol. The resulting β–aminoalcohol of formula 14 can then be oxidised to the ketone, preferably, with pyridine.SO_3 complex in the presence of triethylamine in DMSO to give compounds of formula 15, which are then treated with aryl lithium reagents (formed by halogen-metal exchange) to provide access to the desired products of formula I (Scheme 3).

Scheme 3



All compounds of formulas I, 4, 5, 6, 7, 11, 10, 13, 14, 15 are usually formed during the sequence of reactions into an equal mixture of (R,R,S)-, (S,S,R)-, (R,R,R)- and (S,S,S)-enantiomers (racemic forms), following the procedures described below. They may separated into chiral non-racemic enantiomers by preparative HPLC using either a Chiralpak OD or AD column (5 x 50 cm) at room temperature using an ethanol : heptane mobile phase with UV detection at 220 nM.

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 are good inhibitors of the glycine transporter I (GlyT-1).

The compounds were investigated in accordance with the test given hereinafter.

Solutions and materials

DMEM complete medium: Nutrient mixture F-12 (Gibco Life-technologies), fetal bovine serum (FBS) 5 %, (Gibco life technologies), Penicillin/Streptomycin1 % (Gibco life technologies), Hygromycin 0.6 mg/ml (Gibco life technologies), Glutamine 1 mM Gibco life technologies)

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-in™-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. IC_{50}, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [^{3}H]-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 activity as inhibitor of the glycine transporter I (GlyT-1) is dependent on its racemic or enantiomeric form.

The preferred compounds show an IC_{50} (nM) at GlyT-1 < 100.

Example No.	IC_{50} (nM) of some enantiomers
1	61
2	105
6	48
7	36, 43
10	91
11	70

15	95, 77
16	69
17	73
29	91

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, 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 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 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.

The following examples illustrate the present invention without limiting it. All temperatures are given in degree Celsius.

Preparation of Building blocks 11

rac-2-(4-Fluoro-phenyl)-cyclohexanone

rac-2-(4-Fluoro-phenyl)-cyclohexanol

a) To a solution of 1-bromo-4-fluorobenzene (12.5 mL, 114 mmol) in diethylether (250 mL) at -78 °C was added BuLi (1.6 M, 68 mL, 109 mmol) under argon. After 5 min at this temperature, cyclohexenoxide (11.0 mL, 109 mmol) was added followed by the addition of borontrifluoride-diethyletherate (13.8 mL, 109 mmol) whereby the temperature increased to approx. -50 °C. After 4 h at this temperature the reaction was quenched by the addition of ammonium chloride (saturated, 200 mL) and diluted with water (50 mL). The product was then extracted with diethylether (3 x 100 mL) and the combined organic extracts dried over sodium sulfate. Filtration and evaporation afforded the title compound
(11.9 g, 56 %) as white crystals after trituration from hexane. MS : m/e = 194.1 (M).

rac-2-(4-Fluoro-phenyl)-cyclohexanone

bi) To a solution of rac-2-(4-fluoro-phenyl)-cyclohexanol (3.8 g, 20 mmol) in DCM (320 mL) was added Dess-Martin periodinane [1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1H)-one] (10 g, 24 mmol) at room temperature and after 2 h the reaction mixture was washed with sodium hydrogen carbonate (10 %, 150 mL). The organic phase was then separated and washed with sodium thiosulfite (10 %, 150 mL) and then dried over sodium sulfate, filtered and evaporated. Purification by

chromatography through silica gel, eluting with ethyl acetate : hexane (1 : 4) afforded the title compound (3.4 g, 89 %) as white crystals. MS : m/e = 192.1 (M).

rac-2-(4-Fluoro-phenyl)-cyclohexanone

bii) Alternatively, to a solution of rac-2-(4-fluoro-phenyl)-cyclohexanol (7.5 g, 39 mmol) in dry DMSO (67 mL) was added triethylamine (27 mL, 190 mmol) under argon and the resulting mixture cooled to 0 °C and then a solution of sulfur trioxide pyridine complex (18.4 g, 116 mmol) in dry DMSO (98 mL) was added dropwise over 15 min. After 1 h, the mixture was diluted with water (200 mL) and the product extracted with DCM (2 x 100 mL). The combined organic extracts were then dried over sodium sulfate, followed by filtration and evaporation. Purification by filtration through silica gel, eluting with ethyl acetate : hexane (1 : 4) afforded the title compound (7.1 g, 95 %) as white crystals.
MS : m/e = 192.1 (M).

rac-2-*p*-Tolyl-cyclohexanone

rac-2-*p*-Tolyl-cyclohexanol

a) To a solution of p-tolylbromide (17.1 g, 100 mmol) in dry THF (100 mL) was added magnesium (2.43 g,100 mmol) and then the resulting mixture was cooled to –20 °C and (CuBr-dimethylsulfide complex (2.0 g, 10 mmol) was added and the mixture stirred at -20 °C for 10 min. Then a solution of cyclohexene oxide (10 mL, 100 mmol) in dry THF (10 mL) was added dropwise and the reaction warmed to 0 °C at which point an exothermic reaction initiates. With ice-bath cooling the temperature can be maintained below 25 °C. The reaction mixture was then stirred at 0 – 5 °C for an additional 2 h, then quenched with ammonium chloride solution (saturated, 30 mL) and the product extracted with tert-butyl methyl ether. The combined organic extracts were then washed with water, dried over sodium sulfate, filtered and evaporated. Recrystallisation from hexane afforded the title compound (9.9 g, 52 %) as white crystals. MS : m/e = 190.1 (M).

rac-2-*p*-Tolyl-cyclohexanone

b) As described for building block 11 step bi, rac-2-*p*-tolyl-cyclohexanol (4.86 g, 26 mmol) was converted to the title compound (4.68 g, 97 %) which was obtained as white crystals. MS : m/e = 188.1 (M).

rac-2-(4-Trifluoromethyl-phenyl)-cyclohexanone

rac-2-(4-Trifluoromethyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 4-bromo-benzotrifluoride (10.0 g, 44 mmol) was converted to the title compound (5.64 g, 52 %) which was obtained as a white solid. MS : m/e = 244.1 (M).

rac-2-(4-Trifluoromethyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(4-trifluoromethyl-phenyl)-cyclohexanol (5.5 g, 23 mmol) was converted to the title compound (5.26 g, 96 %) which was obtained as a white solid. MS : m/e = 242.1 (M).

rac-2-(4-Trifluoromethoxy-phenyl)-cyclohexanone

rac-2-(4-Trifluoromethoxy-phenyl)-cyclohexanol

a) As described for building block 11 step a,1-bromo-4-(trifluoromethoxy)benzene (10.3 g, 43 mmol) was converted to the title compound (6.7 g, 60 %) which was obtained as a white solid. MS : m/e = 260.1 (M).

rac-2-(4-Trifluoromethoxy-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(4-trifluoromethoxy-phenyl)-cyclohexanol (6.6 g, 25 mmol) was converted to the title compound (5.36 g, 82 %) which was obtained as a white solid. MS : m/e = 258.2 (M).

rac-2-(3-Fluoro-phenyl)-cyclohexanone

rac-2-(3-Fluoro-phenyl)-cyclohexanol

a) As described for building block 11 step a, 1-bromo-3-fluorobenzene (10.0 g, 57 mmol) was converted to the title compound (5.1 g, 46%) which was obtained as a white solid. MS : m/e = 194.1 (M).

rac-2-(3-Fluoro-phenyl)-cyclohexanone

As described for building block 11 step bi, rac-2-(3-fluoro-phenyl)-cyclohexanol (5.0 g, 26 mmol) was converted to the title compound (3.9 g, 80 %) which was obtained as a white solid. MS : m/e = 192.1 (M).

rac-2-(3-Trifluoromethyl-phenyl)-cyclohexanone

rac-2-(3-Trifluoromethyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 3-bromobenzotrifluoride (10.0 g, 44 mmol) was converted to the title compound (4.87 g, 45 %) which was obtained as a white solid. MS : m/e = 244.1 (M).

rac-2-(3-Trifluoromethyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(3-trifluoromethyl-phenyl)-cyclohexanol (4.7 g, 19 mmol) was converted to the title compound (4.34 g, 93 %) which was obtained as a light yellow oil. MS : m/e = 242.1 (M).

rac-2-(3-Fluoro-4-methyl-phenyl)-cyclohexanone

rac-2-(3-Fluoro-4-methyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 4-bromo-2-fluorotoluene (10.0 g, 53 mmol) was converted to the title compound (6.33 g, 58 %) which was obtained as a white solid. MS : m/e = 208.3 (M).

rac-2-(3-Fluoro-4-methyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(3-Fluoro-4-methyl-phenyl)-cyclohexanol (6.2 g, 30 mmol) was converted to the title compound (5.53 g, 91%) which was obtained as a white solid. MS : m/e = 206.1 (M).

rac-2-(4-Methyl-3-trifluoromethyl-phenyl)-cyclohexanone

rac-2-(4-Methyl-3-trifluoromethyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 4-methyl-3-(trifluoromethyl)bromobenzene (4.2 g, 18 mmol) was converted to the title compound (1.95 g, 43 %) which was obtained as a white solid. MS : m/e = 258.2 (M).

rac-2-(4-Methyl-3-trifluoromethyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(4-methyl-3-trifluoromethyl-phenyl)-cyclohexanol (1.91 g, 7 mmol) was converted to the title compound (1.8 g, 95 %) which was obtained as a white solid. MS : m/e = 256.1 (M).

rac-2-(4-Fluoro-3-methyl-phenyl)-cyclohexanone

rac-2-(4-Fluoro-3-methyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 5-bromo-2-fluorotoluene (10.0 g, 53 mmol) was converted to the title compound (5.47 g, 50 %) which was obtained as a white solid. MS : m/e = 208.2 (M).

rac-2-(4-Fluoro-3-methyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(4-fluoro-3-methyl-phenyl)-cyclohexanol (5.4 g, 26 mmol) was converted to the title compound (14.7 g, 88 %) which was obtained as a light yellow oil. MS : m/e = 206.1 (M).

rac-2-(4-Chloro-3-trifluoromethyl-phenyl)-cyclohexanone

rac-2-(4-Chloro-3-trifluoromethyl-phenyl)-cyclohexanol

a) As described for building block 11 step a, 5-bromo-2-chlorobenzotrifluoride (8.32 g, 30 mmol) was converted to the title compound (4.4 g, 52 %) which was obtained as a white solid. MS : m/e = 278.1 (M).

rac-2-(4-Chloro-3-trifluoromethyl-phenyl)-cyclohexanone

b) As described for building block 11 step bi, rac-2-(4-chloro-3-trifluoromethyl-phenyl)-cyclohexanol (4.3 g, 15 mmol) was converted to the title compound (4.13 g, 97 %) which was obtained as a white solid. MS : m/e = 276.1 (M).

Preparation of Building blocks 7

rac-4-Phenyl-2,8-diaza-spiro[4.5]decan-1-one

rac-1-Benzyl-4-(2-nitro-1-phenyl-ethyl)-piperidine-4-carboxylic acid ethyl ester

a) An LDA (14 mmol) solution was prepared by treating diisopropylamine (1.37 g, 14 mmol) with BuLi (1.6 M, 8.5 mL, 14 mmol) at -78 °C in dry THF (10 mL) under argon

and allowing to warm up to -20 °C. This solution was then cooled to -60 °C added to a solution of 1-benzyl-piperidine-4-ethyl carboxylate (3.05 g, 12 mmol) in THF (8 mL) at -60 °C and allowed to warm up to -40 °C over 1 h whereupon a solution of *trans*-beta-nitrostyrene (1.93 g, 13 mmol) in THF (8 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature over 1 h and then quenched with ammonium chloride (saturated, 40 mL) and the product extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were then washed with brine, dried over sodium sulfate, filtered and evaporated. Purification by chromatography on silica gel eluting with DCM : MeOH (9 : 1) afforded the title compound (4.1 g, 84 %) as a light yellow gum.

MS : m/e = 397.4 (M+H).

rac-4-(2-Amino-1-phenyl-ethyl)-1-benzyl-piperidine-4-carboxylic acid ethyl ester

b) A solution of rac-1-benzyl-4-(2-nitro-1-phenyl-ethyl)-piperidine-4-carboxylic acid ethyl ester (3.18 g, 8 mmol) in dry EtOH (240 mL) was hydrogenated in the presence of Ra-Ni (3 g) at 60 bar at 55 °C for 3 h. After cooling and decompression of the reaction vessel, the mixture was filtered over celite and the filtrate evaporated to leave the title compound (2.9 g, 99 %) as a clear oil. MS : m/e = 367.4 (M+H).

rac-8-Benzyl-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

c) A solution of rac-4-(2-amino-1-phenyl-ethyl)-1-benzyl-piperidine-4-carboxylic acid ethyl ester (2.9 g, 8 mmol) in toluene (30 mL) was heated under reflux for 4 h. After cooling to room temperature and evaporation the mixture was purified by chromatography on silica gel eluting with DCM : MeOH : NH_4OH (95 : 4.5: 0.5) to afford the title compound (1.47 g, 58 %) as a white solid. MS : m/e = 321.4 (M+H).

rac-4-Phenyl-2,8-diaza-spiro[4.5]decan-1-one

d) A suspension of rac-8-benzyl-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (28.8 g, 90 mmol) in MeOH : DCM (4 : 1, 500 mL) was hydrogenated in the presence of Pd (10% on C, 14 g, 132 mmol) at 2 bar for 48 h at room temperature. After filtration over celite, the reaction mixture was evaporated and the residue dissolved in NaOH (2 N, 200 mL). The product was extracted with DCM (3 x 150 mL) and the combined organic extracts dried over sodium sulfate. Filtration and evaporation afforded the title compound (13.1 g, 63 %) as a white solid after trituration from diethylether.

MS : m/e = 231.4 (M+H).

Scheme 1, Step 1: F-derivative from Boc protecting group

rac-4-(4-Fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one

Piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester

a) To a solution of ethyl isonipecotate (20 g, 127 mmol) in dioxane : water (1 : 1, 120 mL) was added triethylamine (12.87 g, 127 mmol) at 0 °C followed by di-tert-butyl dicarbonate (35.2 g, 161 mmol) and the resulting mixture maintained at this temperature for 2 h. The product was then extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts washed with HCl (1 N, 100 mL), brine (100 mL), dried over sodium sulfate, filtered and evaporated. Purification by Kugelrohr distillation afforded the title compound (29.0 g, 89 %) as a colourless liquid, bp 140 °C at 0.13 mbar. MS : m/e = 275.2 ($M+NH_4$).

rac-4-[1-(4-Fluoro-phenyl)-2-nitro-ethyl]-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester

b) An LDA solution was prepared by treating diisopropylamine (6.98 g, 69 mmol) with BuLi (1.6 M, 41.3 mL, 66 mmol) at -78 °C in dry THF (45 mL) under argon and allowing to warm up to -20 °C. This solution was then cooled to -60 °C added to a solution of piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (15.44 g, 60 mmol) in dry THF (45 mL) at -60 °C and allowed to warm up to -40 °C over 1 h whereupon a solution of 4-fluoro-*trans*-beta-nitrostyrene (10.02 g, 60 mmol) in dry THF (40 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature over 1 h and then quenched with ammonium chloride (saturated, 250 mL) and the product extracted with diethylether (3 x 100 mL). The combined organic extracts were then washed with brine, dried over sodium sulfate, filtered and evaporated to afford the title compound (26.7 g, 99 %) as a light yellow gum. MS : m/e = 442.4 ($M+NH_4$).

rac-4-(2-Amino-1-phenyl-ethyl)-1-tert-butyl-piperidine-1,4-dicarboxylic acid ethyl ester

c) A solution of rac-4-[1-(4-fluoro-phenyl)-2-nitro-ethyl]-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (26.6 g, 60 mmol) in dry EtOH (600 mL) was hydrogenated in the presence of Ra-Ni (25 g) at 50 bar at 50 °C for 20 h. After cooling and decompression of the reaction vessel, the mixture was filtered over celite and the

filtrate evaporated to leave the title compound (23.4 g, 99 %) as a clear oil which was used directly in the next step.

rac-4-(4-Fluoro-phenyl)-1-oxo-2,8-diaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester

d) A solution of 4-(2-amino-1-phenyl-ethyl)-1-tert-butyl-piperidine-1,4-dicarboxylic acid ethyl ester (23.4 g, 60 mmol) in toluene (200 mL) was heated under reflux for 18 h. After cooling to room temperature, evaporation afforded the title compound (17.17 g, 83 %) as a white solid after trituration from hot pentane. MS : m/e = 349.3 (M+H).

rac-4-(4-Fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one

e) A solution of 4-(4-fluoro-phenyl)-1-oxo-2,8-diaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester (46.0 g, 132 mmol) in DCM (260 mL) containing TFA (150 mL, 1.32 mol) was stirred vigorously at 0 °C for 15 min. The reaction mixture was then poured into NaOH (3 N, 200 mL) and the product extracted with DCM (3 x 100 mL). The combined organic extracts were then washed with water (100 mL) and brine (100 mL) and then dried over sodium sulfate. Filtration and evaporation afforded the title compound
(22.14 g, 68 %) as a white solid after trituration from ethyl acetate. MS : m/e = 249.2 (M+H).

Example 1

cis-rac-4-Phenyl-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-(2-Phenyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

a) A solution of ethyl isonipecotate (3.7 g, 24 mmol), 2-phenylcyclohexanone (5.0 g, 29 mmol) in toluene (50 mL) containing *para*-toluenesulfonic acid (446 mg, 2 mmol) was heated under reflux with a Dean-Stark trap for 13 h. After cooling to room temperature the mixture was evaporated to leave approximately 15 mL of solution and then diluted with 1,2-dichloroethane (120 mL) and then acetic acid (0.95 mL) was added followed by the portionwise addition of sodium triacetoxyborohydride (7.3 g, 33 mmol). After 3.5 h the mixture was quenched with NaOH (3 N, 50 mL), diluted with water (50 mL) and the organic layer separated. The organic layer was then dried and evaporated to leave a residue which was purified by silica gel chromatography eluting with heptane : ethyl

acetate (9 : 1) to (4 : 1) to (3 : 2) to afford the title compound as a light yellow oil (5.5 g, 75 %). MS : m/e = 316.2 (M+H).

cis-rac 4-(2-Nitro-1-phenyl-ethyl)-1-(2-phenyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

b) As described for building block 7 step a, 1-(2-phenyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (1.0 g, 3 mmol) was converted to the title compound (1.1 g, 73 %) which was obtained as an off-white solid. MS : m/e = 465.4 (M+H).

cis-rac-4-Phenyl-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

c) As described for building block 7 step b, 4-(2-nitro-1-phenyl-ethyl)-1-(2-phenyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (1.0 g, 2 mmol) was converted to the amino compound (810 mg, 87 %) which was obtained as a light yellow oil and used directly in the next step. MS : m/e = 435.4 (M+H).

d) As described for example building block 7 step c, the amino compound (810 mg, 2 mmol) was converted to the title compound (607 mg, 93 %) which was obtained as a white solid. MS : m/e = 389.4 (M+H).

Example 2

Cis-rac-4-Phenyl-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

A mixture of rac-2-*p*-tolyl-cyclohexanone (410 mg, 2 mmol), rac-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (502 mg, 2 mmol) and titanium(IV) isopropoxide (810 uL, 3 mmol) were stirred at rt for 3 h. The mixture was then diluted with THF (5 mL) and then a solution of polymethylhydroxysiloxane (261 mg, 4 mmol) in THF (5 mL) was added and the resulting solution stirred at rt overnight. To this solution $Na(CN)BH_3$ (245 mg) was added and the resulting mixture stirred at rt for 3 h. Then NaOH (3M, 10 mL) was added and the mixture stirred for 1 h. The resulting precipitate was then filtered off over celite and the filtrate was washed with brine, dried and evaporated to leave a light yellow foam. Purification by chromatography on silica gel eluting with DCM : MeOH :NH_4OH (25%) (98 : 2 : 0.1 to 95 : 4.5 : 0.5) afforded the title compound (250 mg, 29 %) which was obtained as a white solid. MS : m/e = 403.6 (M+H).

Example 3

cis-rac-4-(4-Fluoro-phenyl)-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-(2-p-Tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1a, rac-2-*p*-tolyl-cyclohexanone (4.2 g, 22 mmol) was converted to the title compound (3.7 g, 48 %) which was obtained as a light yellow oil. MS : m/e = 330.4 (M+H).

cis-rac-4-[1-(4-Fluoro-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

b) As described for example 1b, cis-rac-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (700 mg, 2 mmol) was converted to the title compound (880 mg, 83 %) which was obtained as a yellow gum. MS : m/e = 497.3 (M+H).

cis-rac 4-(4-Fluoro-phenyl)-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

c) As described for example 1c, cis-rac-4-[1-(4-fluoro-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (880 mg, 2 mmol) was converted to the amino compound (670 mg, 81 %) which was obtained as a yellow gum and used directly in the next step. MS : m/e = 467.3 (M+H).

d) As described for example 1d, the amino compound (665 mg, 1 mmol) was converted to the title compound (130 mg, 22 %) which was obtained as a light yellow solid. MS : m/e = 421.2 (M+H).

Example 4

cis-rac-4-(3,4-Dichloro-phenyl)-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-4-[1-(3,4-Dichloro-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1b, rac-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (700 mg, 2 mmol) was converted to the title compound (772 mg, 66 %) which was obtained as a yellow solid. MS : m/e = 547.2 (M).

b) As described for example 1c, cis-rac-4-[1-(3,4-dichloro-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (772 mg, 1 mmol) was converted to the title compound (43 mg, 6 %) which was obtained as a yellow gum. MS : m/e = 471.3 (M).

Example 5

cis-rac-4-(4-Methoxy-phenyl)-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-4-[1-(4-Methoxy-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1b, rac-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (700 mg, 2 mmol) was converted to the title compound (620 mg, 57 %) which was obtained as a yellow gum. MS : m/e = 509.4 (M+H).

cis-rac-4-(4-Methoxy-phenyl)-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

b) As described for example 1c, cis-rac-4-[1-(4-methoxy-phenyl)-2-nitro-ethyl]-1-(2-p-tolyl-cyclohexyl)-piperidine-4-carboxylic acid ethyl ester (620 mg, 1 mmol) was converted to the title compound (410 mg, 70 %) which was obtained as a yellow gum. MS : m/e = 433.5 (M+H).

Example 6

cis-rac-8-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

As described for example 2, rac-2-(4-fluoro-phenyl)-cyclohexanone (417 mg, 2 mmol) was converted to the title compound (150 mg, 17 %) (using 4-phenyl-2,8-diaza-spiro[4.5]decan-1-one instead of 4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one) which was obtained as a white solid. MS : m/e = 407.5 (M+H).

Alternatively

cis-rac-8-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-(2-nitro-1-phenyl-ethyl)-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1b, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (800 mg, 2.4 mmol) was converted to the title compound (677 mg, 59 %) which was obtained as a light yellow gum. MS : m/e = 483.3 (M).

cis-rac-8-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

b) As described for example 1c, 1-[2-(4-fluoro-phenyl)-cyclohexyl]-4-(2-nitro-1-phenyl-ethyl)-piperidine-4-carboxylic acid ethyl ester (627 mg, 1.3 mmol) was converted to the

amino compound (497 mg, 85 %) which was obtained as a light yellow oil and used directly in the next step. MS : m/e = 453.6 (M).

c) As described for example 1d, the amino compound (497 mg, 1.1 mmol) was converted to the title compound (197 mg, 4 4%) which was obtained as an off-white solid. MS : m/e = 407.3 (M+H).

Example 7

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-[2-(4-Fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1a, rac-2-(4-fluoro-phenyl)-cyclohexanone (7.0 g, 36 mmol) was converted to the title compound (4.5 g, 38 %) which was obtained as a light yellow oil. MS : m/e = 334.3 (M+H).

cis-rac-1-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-[1-(4-fluoro-phenyl)-2-nitro-ethyl]-piperidine-4-carboxylic acid ethyl ester

b) As described for example 1b, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (1.0 g, 3 mmol) (using 4-fluoro-*trans*-beta-nitrostyrene instead of *trans*-beta-nitrostyrene) was converted to the title compound (1.2 g, 77 %) which was obtained as a white solid. MS : m/e = 501.4 (M+H).

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

c) As described for example 1c, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-4-[1-(4-fluoro-phenyl)-2-nitro-ethyl]-piperidine-4-carboxylic acid ethyl ester (1.1 g, 2 mmol) was converted to the amino compound (1.0 g, 99 %) which was obtained as a light yellow oil and used directly in the next step. MS : m/e = 471.3 (M+H).

d) As described for example 1d, the amino compound (1.05 g, 2 mmol) was converted to the title compound (670 mg, 71 %) which was obtained as a white solid. MS : m/e = 425.2 (M+H).

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

e) Alternatively a mixture of rac-2-(4-fluoro-phenyl)-cyclohexanone (775 mg, 3 mmol), rac-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one (500 mg, 3 mmol) and titanium(IV) isopropoxide (887 uL, 3 mmol) were stirred at 60 °C overnight. The resulting solution was then cooled to room temperature and $Na(CN)BH_3$ (245 mg, 4 mmol) was added and the resulting mixture stirred at 50 °C for 3 h. Then NaOH (6M, 15 mL) was added and the mixture stirred for 1 h. The resulting mixture was then filtered off over celite and the filtrate was washed with brine, dried and evaporated to leave a light yellow foam. Purification by chromatography on silica gel eluting with DCM : MeOH : NH_4OH (25 %) (98 : 2 : 0.1 to 95 : 4.5 : 0.5) afforded the title compound (212 mg, 20%) which was obtained as a white solid. MS : m/e = 425.2 (M+H).

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

f) Alternatively as described for example 2, rac-2-(4-fluoro-phenyl)-cyclohexanone (500 mg, 3 mmol) was converted to the title compound (219 mg, 20 %) which was obtained as a white solid. MS : m/e = 425.2 (M+H).

Example 8

cis-rac-4-(3,4-Dichloro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-4-[1-(3,4-Dichloro-phenyl)-2-nitro-ethyl]-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1b, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (800 mg, 2.4 mmol) (using 3,4-dichloro-omega-nitrostyrene instead of *trans*-beta-nitrostyrene) was converted to the title compound (779 mg, 59 %) which was obtained as a light yellow foam. MS : m/e = 551.3 (M).

cis-rac-4-(3,4-Dichloro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

b) As described for example 1c, cis-rac-4-[1-(3,4-dichloro-phenyl)-2-nitro-ethyl]-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (729 mg, 1.3 mmol) was converted to the amino compound (646 mg, 93 %) which was obtained as a light yellow oil and used directly in the next step.

c) As described for example 1d, the amino compound (646 mg, 1.2 mmol) was converted to the title compound (270 mg, 46 %) which was obtained as an off-white solid. MS : m/e = 475.2 (M).

Example 9

cis-rac-8-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-(4-methoxy-phenyl)-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-[2-(4-Fluoro-phenyl)-cyclohexyl]-4-[1-(4-methoxy-phenyl)-2-nitro-ethyl]-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1b, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (800 mg, 2.4 mmol) (using 4-methoxy-beta-nitrostyrene instead of *trans*-beta-nitrostyrene) was converted to the title compound (642 mg, 52 %) which was obtained as a light yellow foam. MS : m/e = 513.4 (M+H).

cis-rac-4-(3,4-Dichloro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

b) As described for example 1c, cis-rac-1-[2-(4-fluoro-phenyl)-cyclohexyl]-4-[1-(4-methoxy-phenyl)-2-nitro-ethyl]-piperidine-4-carboxylic acid ethyl ester (601 mg, 1.2 mmol) was converted to the amino compound (523 mg, 92 %) which was obtained as a light yellow oil and used directly in the next step. MS : m/e = 483.5 (M+H).

c) As described for example 1d, the amino compound (523 mg, 1.1 mmol) was converted to the title compound (216 mg, 46 %) which was obtained as a white foam.
MS : m/e = 437.3 (M+H).

Example 10

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

cis-rac-1-[2-(4-Trifluoromethyl-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester

a) As described for example 1a, rac-2-(4-trifluoromethyl-phenyl)-cyclohexanone (5.0 g, 21 mmol) was converted to the title compound (2.7 g, 34 %) which was obtained as a light yellow oil. MS : m/e = 384.2 (M+H).

cis-rac-4-[1-(4–Fluoro-phenyl)-2-nitro-ethyl]-1-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester

b) As described for example 1b, 1-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (1.0 g, 3 mmol) was converted to the title compound (610 mg, 43 %) which was obtained as a light yellow oil. MS : m/e = 551.3 (M+H).

cis-rac-4-(4-Fluoro-phenyl)-8-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

c) As described for example 1c, 4-[1-(4-fluoro-phenyl)-2-nitro-ethyl]-1-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-piperidine-4-carboxylic acid ethyl ester (610 mg, 1 mmol) was converted to the amino compound (345 mg, 60 %) which was obtained as a light yellow oil and used directly in the next step. MS : m/e = 521.4 (M+H).

d) As described for example 1d, the amino compound (345 mg, 1 mmol) was converted to the title compound (268 mg, 85 %) which was obtained as a white solid.
MS : m/e = 475.4 (M+H).

Preparation of Building blocks 15

rac-8-(2-Oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

rac-8-(2-Hydroxy-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

a) A suspension of rac-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (13.10 g, 56.9 mmol) and 7-oxa-bicyclo[4.1.0]heptane (5.58 g, 56.9 mmol) in ethanol (250 mL) was heated under reflux for 3 days. After cooling to room temperature the mixture was filtered and the filtrate evaporated to afford the title compound (18.14 g, 97 %) which was obtained as off-white solid. MS : m/e = 329.3 (M+H).

rac-8-(2-Oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

b) As described for building block 11 step bi, 8-(2-hydroxy-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (18.10 g, 55.0 mmol) was converted to the title compound (15.26 g, 76 %) which was obtained as a light yellow solid after trituration from hot diethylether. MS : m/e = 327.2 (M+H).

rac-4-(4-Fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

rac-4-(4-Fluoro-phenyl)-8-(2-hydroxy-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

a) As described for building block 15 step a,1, rac-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one (8.45 g, 34.0 mmol) was converted to the title compound (11.63 g, 99 %) which was obtained as an off-white solid. MS : m/e = 347.0 (M+H).

rac-4-(4-Fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

b) As described for building block 15 step b, 4-(4-fluoro-phenyl)-8-(2-hydroxy-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (2.06 g, 6.0 mmol) was converted to the title compound (1.26 g, 59 %) which was obtained as a light yellow solid after purification by chromatography on silica gel eluting with DCM : MeOH (95 : 5 to 85 : 15). MS : m/e = 345.2 (M+H).

Example 11

8-[2-(4-Fluoro-phenyl)-2-hydroxy-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

To a solution of 1-bromo-4-fluorobenzene (1.4 g, 8 mmol) in dry THF (5 mL) under argon at – 78 °C was added BuLi (1.6 M in hexanes, 5 mL, 8 mmol) and the mixture maintained at this temperature for 1 h. To this solution was added a solution of 8-(2-oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (687 mg, 2 mmol) in dry THF (15 mL) and the reaction mixture allowed to warm up to – 20 °C after 2 h before ammonium chloride (saturated, 20 mL) was added. The resulting mixture was then evaporated and water (20 mL) added. The product was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts washed with brine (10 mL), dried over sodium sulfate, filtered and evaporated to leave a light brown solid. Purification by chromatography on silica gel eluting with DCM : MeOH - NH_4OH (0.5 %) (95 : 5 to 4 : 1) afforded the title compound (380 mg, 45 %) which was obtained as a white solid. MS : m/e = 423.5 (M+H).

Example 12

8-[2-(3-Fluoro-phenyl)-2-hydroxy-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 8-(2-oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (500 mg, 1.53 mmol) was converted to the title compound (348 mg, 50 %) (using 3-bromo-fluorobenzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 423.4 (M+H).

Example 13

8-[2-Hydroxy-2-(4-methoxy-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 8-(2-oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (500 mg, 1.53 mmol) was converted to the title compound (88 mg, 15 %) (using 4-bromoanisole instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 435.6 (M+H).

Example 14

8-[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 8-(2-oxo-cyclohexyl)-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one (500 mg, 1.53 mmol) was converted to the title compound (411 mg, 69 %) (using 3-bromoanisole instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 435.4 (M+H).

Example 15

4-(4-Fluoro-phenyl)-8-[2-(3-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (195 mg, 76 %) (using 1-bromo-3-fluorobenzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid.

Example 16

4-(4-Fluoro-phenyl)-8-[2-(2-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (178 mg, 70 %) (using 2-bromofluorobenzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 441.2 (M+H).

Example 17

8-[2-(3-Chloro-phenyl)-2-hydroxy-cyclohexyl]-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (205 mg, 77 %) (using 1-bromo-3-chlorobenzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 457.3 (M).

Example 18

4-{2-[4-(4-Fluoro-phenyl)-1-oxo-2,8-diaza-spiro[4.5]dec-8-yl]-1-hydroxy-cyclohexyl}-benzonitrile

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (118 mg, 45 %) (using 4-bromobenzonitrile instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 448.2 (M+H).

Example 19

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(4-trifluoromethyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (271 mg, 95 %) (using 4-bromobenzotrifluoride instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 491.2 (M+H).

Example 20

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(4-methanesulfonyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (16 mg, 6 %) (using 4-bromophenylmethyl sulfone instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 501.5 (M+H).

Example 21

4-(4-Fluoro-phenyl)-8-(2-hydroxy-2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (178 mg, 70 %) (using 4-bromotoluene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 437.4 (M+H).

Example 22

4-(4-Fluoro-phenyl)-8-(2-hydroxy-2-m-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (229 mg, 90 %) (using 3-bromotoluene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 437.3 (M+H).

Example 23

4-(4-Fluoro-phenyl)-8-(2-hydroxy-2-o-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (158 mg, 62 %) (using 2-bromotoluene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 437.4 (M+H).

Example 24

8-[2-(4-tert-Butyl-phenyl)-2-hydroxy-cyclohexyl]-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (192 mg, 69 %) (using 1-bromo-4-tert-butylbenzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 479.6 (M+H).

Example 25

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(2-trifluoromethoxy-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (216 mg, 0.63 mmol) was converted to the title compound (209 mg, 66 %) (using 1-bromo-2-(trifluoromethoxy)benzene instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 507.3 (M+H).

Example 26

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(4-imidazol-1-yl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (344 mg, 1.0 mmol) was converted to the title compound (231 mg, 47 %) (using 1-(4-bromophenyl)imidazole instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 489.3 (M+H).

Example 27

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(4-methoxy-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (517 mg, 1.5 mmol) was converted to the title compound (568 mg, 84 %) (using 4-bromoanisole instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 453.3 (M+H).

Example 28

4-(4-Fluoro-phenyl)-8-[2-hydroxy-2-(3-methoxy-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one

As described for example 11, 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (200 mg, 1 mmol) was converted to the title compound (199 mg, 76 %) (using 3-bromoanisole instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 453.3 (M+H).

Example 29

4-(4-Fluoro-phenyl)-8-*trans*-(4-hydroxy-4-phenyl-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one

4-(4-Fluoro-phenyl)-8-*trans*-(4-hydroxy-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one

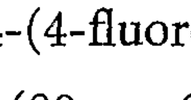
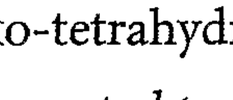
a) As described for example 12a, (R)- 4-(4-fluoro-phenyl)-8-(2-oxo-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one (100 mg, 0.4 mmol) was converted to the title compound (57 mg, 41 %) (using 3,5-epoxytetrahydrofuran instead of oxa-bicyclo[4.1.0]heptane) which was obtained as a white solid after purification by chromatography on silica gel eluting with DCM : MeOH (9 : 1). MS : m/e = 349.2 (M+H).

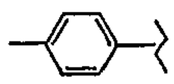
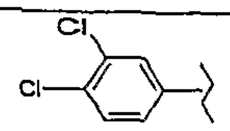
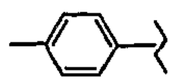
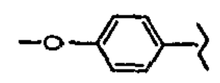
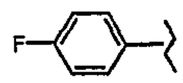
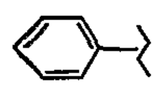
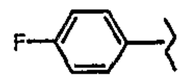
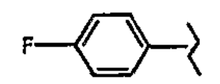
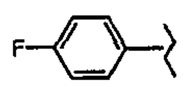
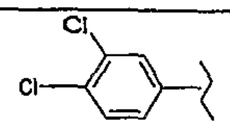
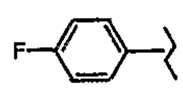
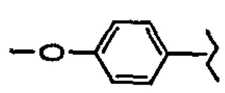
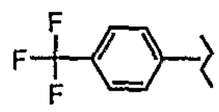
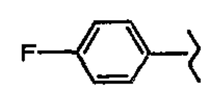
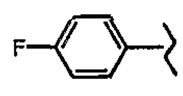
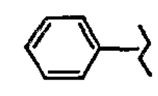
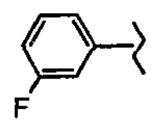
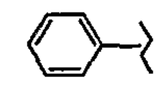
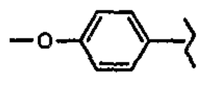
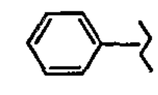
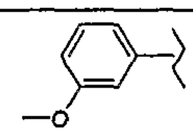
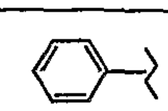
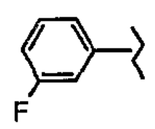
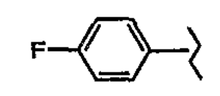
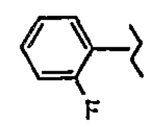
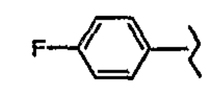
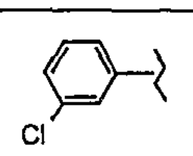
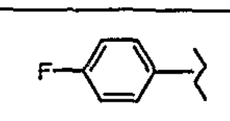
4-(4-Fluoro-phenyl)-8-(4-oxo-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one

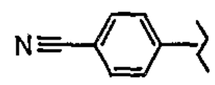
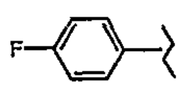
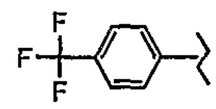
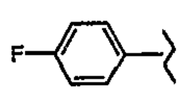
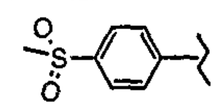
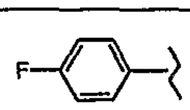
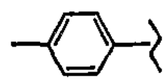
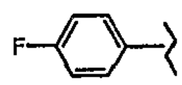
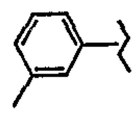
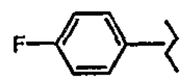
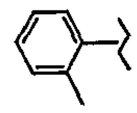
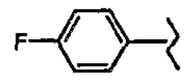
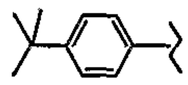
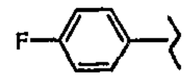
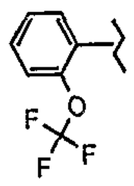
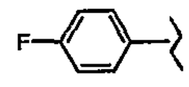
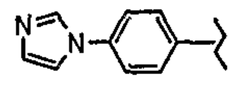
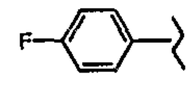
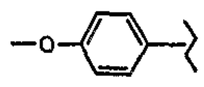
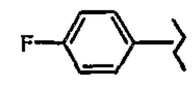
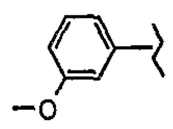
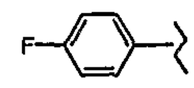
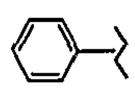
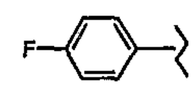
b) As described for building block 11 step bi) 4-(4-fluoro-phenyl)-8-*trans*-(4-hydroxy-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one (128 mg, 0.37 mmol) was converted to the title compound (100 mg, 79 %) which was obtained as a white solid after purification by chromatography on silica gel eluting with DCM : MeOH (9 : 1). MS : m/e = 347.4 (M+H).

4-(4-Fluoro-phenyl)-8-*trans*-(4-hydroxy-4-phenyl-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one

c) As described for example 11, 4-(4-fluoro-phenyl)-8-(4-oxo-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one (90 mg, 0.26 mmol) was converted to the title compound (65 mg, 59 %) (using phenyllithium instead of 1-bromo-4-fluorobenzene) which was obtained as a white solid. MS : m/e = 425.4 (M+H).

n	X	A-B	R^1	R^3	R^2	Example
1	H	CH_2CH_2		H		1
1	H	CH_2CH_2		H		2
1	H	CH_2CH_2		H		3

1	H	CH_2CH_2		H		4
1	H	CH_2CH_2		H		5
1	H	CH_2CH_2		H		6
1	H	CH_2CH_2		H		7
1	H	CH_2CH_2		H		8
1	H	CH_2CH_2		H		9
1	H	CH_2CH_2		H		10
1	OH	CH_2CH_2		H		11
1	OH	CH_2CH_2		H		12
1	OH	CH_2CH_2		H		13
1	OH	CH_2CH_2		H		14
1	OH	CH_2CH_2		H		15
1	OH	CH_2CH_2		H		16
1	OH	CH_2CH_2		H		17

1	OH	CH_2CH_2		H		18
1	OH	CH_2CH_2		H		19
1	OH	CH_2CH_2		H		20
1	OH	CH_2CH_2		H		21
1	OH	CH_2CH_2		H		22
1	OH	CH_2CH_2		H		23
1	OH	CH_2CH_2		H		24
1	OH	CH_2CH_2		H		25
1	OH	CH_2CH_2				26
1	OH	CH_2CH_2		H		27
1	OH	CH_2CH_2		H		28
1	OH	CH_2O		H		29

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
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
	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

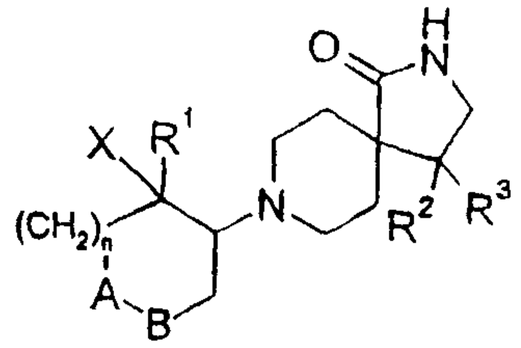
Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

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. Compounds of the general formula



I

wherein

A-B is $-CH_2-CH_2-$, $-CH_2-O-$ or $-O-CH_2-$;

X is hydrogen or hydroxy;

R^1 is aryl, unsubstituted or substituted by one or two of halogen, C_{1-7} alkyl, cyano, CF_3, $-OCF_3$, C_{1-7} alkoxy, $-SO_2-C_{1-7}$ alkyl or by heteroaryl,

R^2 is aryl, unsubstituted or substituted by one or two of halogen, C_{1-7} alkyl, CF_3 or C_{1-7} alkoxy;

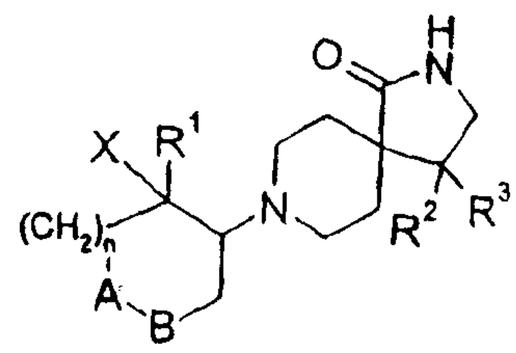
R^3 is hydrogen or C_{1-7} alkyl;

n is 0, 1 or 2;

wherein aryl denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature and heteroaryl denotes a cyclic aromatic hydrocarbon radical, containing one, two or three heteroatoms, the heteroatoms being oxygen, sulphur or nitrogen;

or their pharmaceutically active salts.

2. Compounds of formula I according to claim 1



I

wherein

A-B is $-CH_2-CH_2-$ or $-CH_2-O-$;

X is hydrogen or hydroxy;

R^1 is phenyl, unsubstituted or substituted by one or two of halogen, C_{1-7} alkyl, cyano, CF_3, $-OCF_3$, C_{1-7} alkoxy, $-SO_2-C_{1-7}$ alkyl or by heteroaryl,

R^2 is phenyl, unsubstituted or substituted by one or two of halogen or C_{1-7} alkoxy;

R^3 is hydrogen;

n is 1;

wherein aryl denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature and heteroaryl denotes a cyclic aromatic hydrocarbon radical, containing one, two or three heteroatoms, the heteroatoms being oxygen, sulphur or nitrogen;
or their pharmaceutically active salts.

3. Compounds of formula I according to claim 2, wherein A-B is $-CH_2-CH_2-$.

4. Compounds of formula I according to claim 3, wherein R^1 is phenyl, optionally substituted by one or two of C_{1-7} alkyl, halogen or CF_3, and wherein R^2 is phenyl, optionally substituted by one or two halogen.

5. Compounds of formula I according to claim 4, wherein the compounds are
cis-rac-4-phenyl-8-(2-phenyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one,
cis-rac4-phenyl-8-(2-p-tolyl-cyclohexyl)-2,8-diaza-spiro[4.5]decan-1-one,
cis-rac-8-[2-(4-fluoro-phenyl)-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one,
cis-rac-4-(4-fluoro-phenyl)-8-[2-(4-fluoro-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,
cis-rac-4-(4-fluoro-phenyl)-8-[2-(4-trifluoromethyl-phenyl)-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,
8-[2-(4-fluoro-phenyl)-2-hydroxy-cyclohexyl]-4-phenyl-2,8-diaza-spiro[4.5]decan-1-one,
4-(4-fluoro-phenyl)-8-[2-(3-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-spiro[4.5]decan-1-one,
4-(4-fluoro-phenyl)-8-[2-(2-fluoro-phenyl)-2-hydroxy-cyclohexyl]-2,8-diaza-

spiro[4.5]decan-1-one,

8-[2-(3-chloro-phenyl)-2-hydroxy-cyclohexyl]-4-(4-fluoro-phenyl)-2,8-diaza-spiro[4.5]decan-1-one or

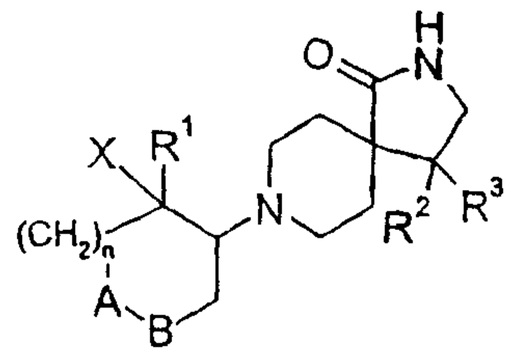
4-(4-fluoro-phenyl)-8-*trans*-(4-hydroxy-4-phenyl-tetrahydro-pyran-3-yl)-2,8-diaza-spiro[4.5]decan-1-one.

6. Compounds of formula I according to claim 1, wherein X is hydrogen.

7. Compounds of formula I according to claim 1, wherein X is hydroxy.

8. Compounds of formula I according to claim 2, wherein A-B is $-CH_2-O-$.

9. A process for preparation of compounds of formula I or their pharmaceutically acceptable salts,



I

wherein

A-B is $-CH_2-CH_2-$, $-CH_2-O-$ or $-O-CH_2-$;

X is hydrogen or hydroxy;

R^1 is aryl, unsubstituted or substituted by one or two of halogen, C_{1-7} alkyl, cyano, CF_3, $-OCF_3$, C_{1-7} alkoxy, $-SO_2-C_{1-7}$ alkyl or by heteroaryl,

R^2 is aryl, unsubstituted or substituted by one or two of halogen, C_{1-7} alkyl, CF_3 or C_{1-7} alkoxy;

R^3 is hydrogen or C_{1-7} alkyl;

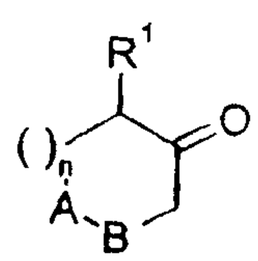
n is 0, 1 or 2;

wherein aryl denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature and heteroaryl

denotes a cyclic aromatic hydrocarbon radical, containing one, two or three heteroatoms, the heteroatoms being oxygen, sulphur or nitrogen;

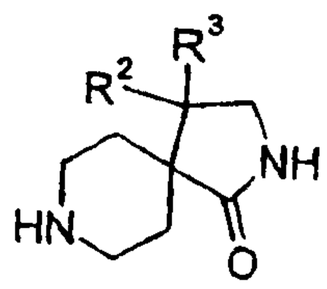
which process comprises

a) reacting a compound of formula



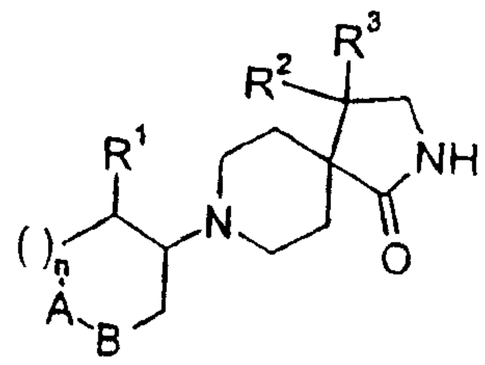
11

with a compound of formula



7

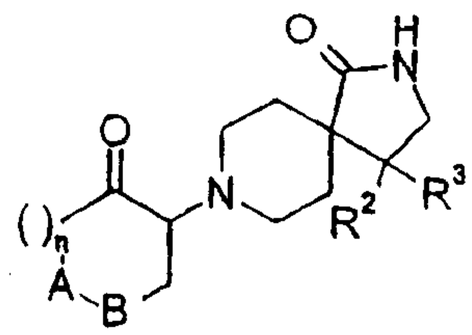
to obtain a compound of formula



I where X = hydrogen

wherein the substituents are as defined above, or

b) reacting a compound of formula

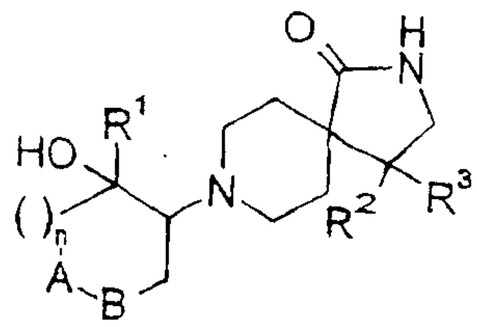


15

with a compound of formula

R^1Br 8

to obtain a compound of formula



I where X = hydroxy

wherein the substituents are as defined above.

10. The process of claim 9, additionally comprising the step of separating the obtained racemic forms into corresponding enantiomers.

11. The process of claim 9 or claim 10, additionally comprising the step of converting the compounds obtained into pharmaceutically acceptable acid addition salts.

12. A compound according to claim 1, whenever prepared by a process as claimed in any one of claims 9 to 11.

13. A medicament containing one or more compounds as claimed in claim 1 and a pharmaceutically acceptable excipient.

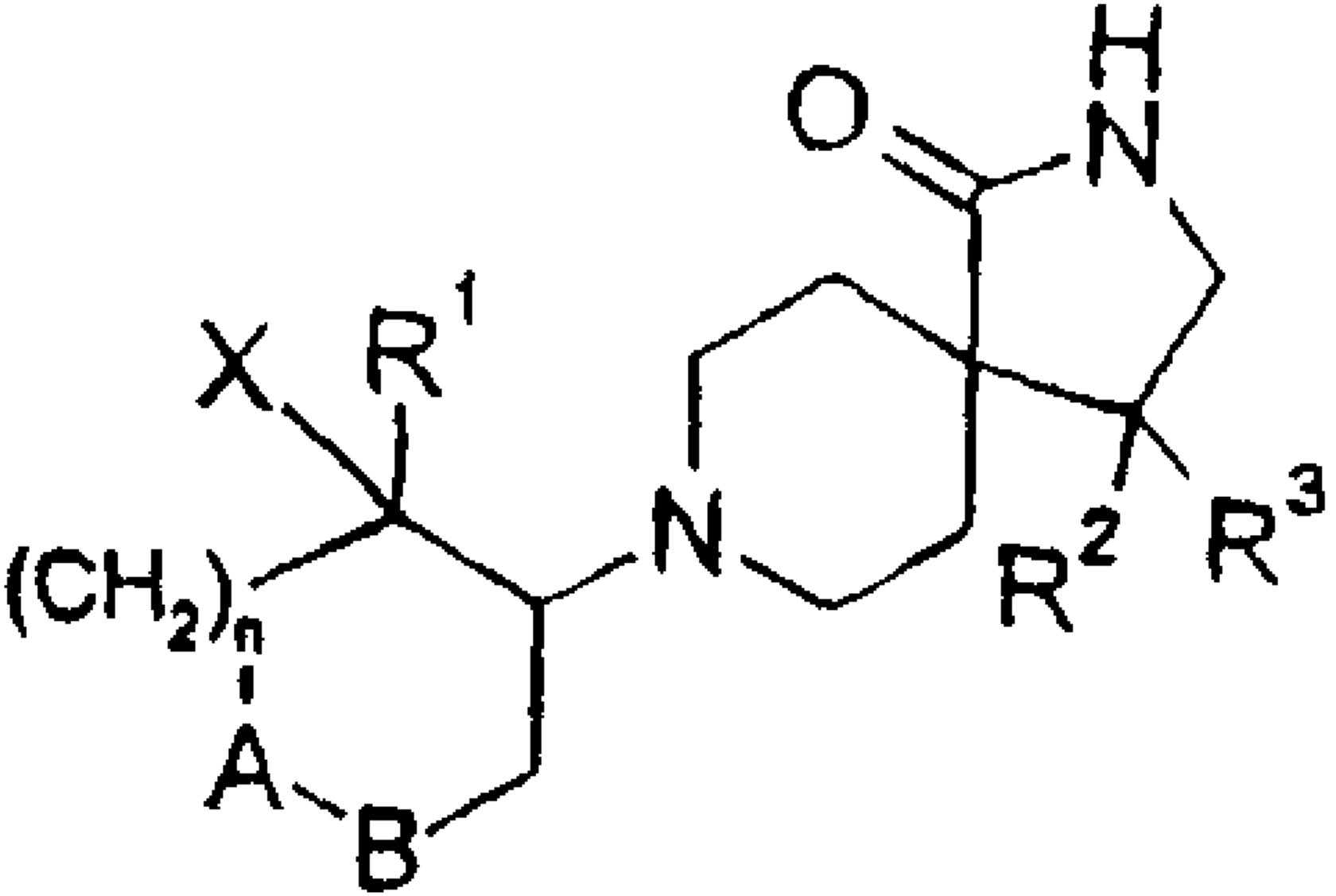
14. A medicament according to claim 13 for the treatment of an illness based on the glycine uptake inhibitor.

15. A medicament according to claim 13 or 14, wherein the illness is psychosis, pain, disfunction in memory and learning, schizophrenia, dementia, attention deficit disorder or Alzheimer's disease.

16. Use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of psychosis, pain, neurodegenerative disfunction in memory or learning, schizophrenia, dementia, attention deficit disorder or Alzheimer's disease.

17. Use of a compound as claimed in claim 1 for treatment of psychosis, pain, neurodegenerative disfunction in memory or learning, schizophrenia, dementia, attention deficit disorder or Alzheimer's disease.

18. A commercial package containing the compound as claimed in claim 1, along with instructions for use in the treatment of psychosis, pain, neurodegenerative disfunction in memory or learning, schizophrenia, dementia, attention deficit disorder or Alzheimer's disease.



I