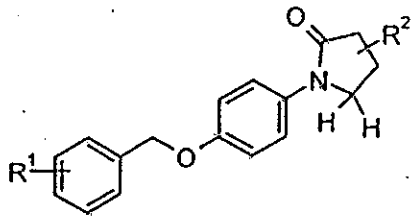
Benzyloxy derivatives as MAOB inhibitors

Disclosed herein are benzyloxy derivatives of the general formula



I

wherein

R^1 is halogen;

R^2 is $-C(O)NH_2$, $-C(NH_2)=N-OH$, $-C(O)CH_2Br$, $-C(O)N(CH_3)OCH_3$ or $-C(O)$-lower alkyl, or is a 5-membered heteroaryl group, containing 2 or 3 heteroatoms, selected from the group consisting of N, O or S, optionally substituted by lower alkyl, -NR'R" or $-C(O)R$;

R is NR'R", lower alkyl, or lower alkoxy;

R'/R" are independently hydrogen or lower alkyl;

as well as their pharmaceutically acceptable salts.

The disclosure includes individual isomers of the compounds of formula I as well as racemic and non-racemic mixtures thereof.

Compounds of formula I and their pharmaceutically acceptable salts, as individual isomers of the compounds of formula I as well as racemic and non-racemic mixtures thereof (hereinafter: Pharmaceutical Compound) have pharmacological activity and are useful as pharmaceuticals. In particular, Pharmaceutical Compounds inhibit the activity of monoamine oxidase B.

Monoamine oxidase (MAO) is a flavin-containing enzyme responsible for the oxidative deamination of endogenous monoamine neurotransmitters such as dopamine, serotonin, adrenaline, or noradrenaline, and trace amines, e.g. phenylethyl-amine, as well as a number of amine xenobiotics.The enzyme exists in two forms, MAO-A and MAO-B, encoded by different genes (A. W. Bach et al., *Proc. Natl. Acad. Sci. USA* 1988, *85*, 4934-

4938) and differing in tissue distribution, structure and substrate specificity. MAO-A has higher affinity for serotonin, octopamine, adrenaline, and noradrenaline; whereas the natural substrates for MAO-B are phenylethylamine and tyramine. Dopamine is thought to be oxidised by both isoforms. MAO-B is widely distributed in several organs including brain (A.M. Cesura and A. Pletscher, Prog. Drug Research 1992, *38*, 171-297). Brain MAO-B activity appears to increase with age. This increase has been attributed to the gliosis associated with aging (C.J. Fowler et al., *J. Neural. Transm.* 1980, *49*, 1-20). Additionally, MAO-B activity is significantly higher in the brains of patients with Alzheimer's disease (P. Dostert et al., *Biochem. Pharmacol.* 1989, *38*, 555-561) and it has been found to be highly expressed in astrocytes around senile plaques (Saura et al., *Neuroscience* 1994, 70, 755-774). In this context, since oxidative deamination of primary monoamines by MAO produces NH_3, aldehydes and H_2O_2, agents with established or potential toxicity, it is suggested that there is a rationale for the use of selective MAO-B inhibitors for the treatment of dementia and Parkinson's disease. Inhibition of MAO-B causes a reduction in the enzymatic inactivation of dopamine and thus prolongation of the availability of the neurotransmitter in dopaminergic neurons. The degeneration processes associated with age and Alzheimer's and Parkinson's diseases may also be attributed to oxidative stress due to increased MAO activity and consequent increased formation of H_2O_2 by MAO-B. Therefore, MAO-B inhibitors may act by both reducing the formation of oxygen radicals and elevating the levels of monoamines in the brain.

Given the implication of MAO-B in the neurological disorders mentioned above, there is considerable interest to obtain potent and selective inhibitors that would permit control over this enzymatic activity. The pharmacology of some known MAO-B inhibitors is for example discussed by D. Bentué-Ferrer et al. in *CNS Drugs* 1996, *6*, 217-236. Whereas a major limitation of irreversible and non-selective MAO inhibitor activity is the need to observe dietary precautions due to the risk of inducing a hypertensive crisis when dietary tyramine is ingested, as well as the potential for interactions with other medications (D. M. Gardner et al., *J. Clin. Psychiatry* 1996, *57*, 99-104), these adverse events are of less concern with reversible and selective MAO inhibitors, in particular of MAO-B. Thus, there is a need for MAO-B inhibitors with a high selectivity and without the adverse side-effects typical of irreversible MAO inhibitors with low selectivity for the enzyme.

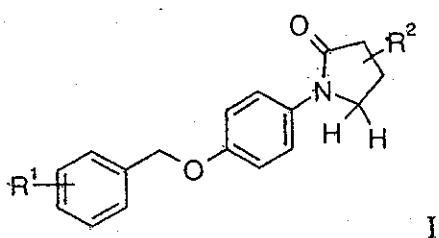
Pharmaceutical Compounds are accordingly useful as selective inhibitors of monoamine oxidase B, e.g. in the treatment or prevention of diseases and conditions in which activity of monoamine oxidase B plays a role or is implicated. Such conditions include in particular acute and/or chronic neurological disorders.

Acute and/or chronic neurological disorders include psychosis, schizophrenia, Alzheimer's disease, cognitive disorders and memory deficits like mild cognitive impairment, age-related cognitive decline, vascular dementia, Parkinsons's disease, memory impairment associated with depression or anxiety, Down's syndrome, stroke, traumatic brain injury, and attention deficit disorder. Other treatable indications are restricted brain function caused by bypass operations or transplants, poor blood supply to the brain, spinal cord injuries, head injuries, hypoxia caused by pregnancy, cardiac arrest and hypoglycaemia. Further treatable indications are acute and chronic pain, Huntington's chorea, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, eye injuries, retinopathy, idiopathic parkinsonism or parkinsonism caused by medicaments as well as conditions which lead to glutamate-deficient functions, such as e.g. muscle spasms, convulsions, migraine, urinary incontinence, nicotine addiction, psychotic episodes, opiate addiction, anxiety, vomiting, dyskinesia and depression.

In one embodiment, the acute and/or chronic neurological disorder is Alzheimer's disease. In another embodiment, the acute and/or chronic neurological disorder is mild cognitive impairment or senile dementia.

The object of the present disclosure therefore is to provide compounds which must have the advantageous properties mentioned above. It has been found that the compounds of formula I of the present disclosure and their pharmaceutically acceptable salts show the potential to be highly selective MAO-B inhibitors. Subjects further disclosed herein are medicaments based on a compound of formula I in accordance with the disclosure, a process for the manufacture of compounds of formula I and their pharmaceutically acceptable salts, as well as the use of the compounds of formula I in the control or prevention of diseases mediated by monoamine oxidase B inhibitors, and, respectively, the use for the production of corresponding medicaments.

In one aspect, there is provided compounds of the general formula



I

wherein

R^1 is halogen;

R^2 is a 5-membered heteroaryl group,
containing 2 or 3 heteroatoms, selected from the group consisting of N, O or S,
optionally substituted by R^3, wherein R^3 is lower alkyl, -NR'R" or –C(O)R;

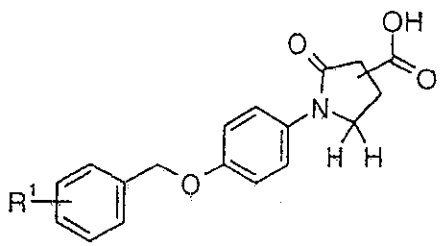
R is NR'R", lower alkyl, or lower alkoxy;

R'/R" are independently hydrogen or lower alkyl;

as well as their pharmaceutically acceptable salts.

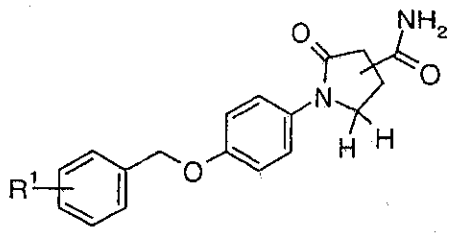
In another aspect, there is provided a process for preparation of compounds of formula I as defined above, which process comprise

a) reacting a compound of formula



II

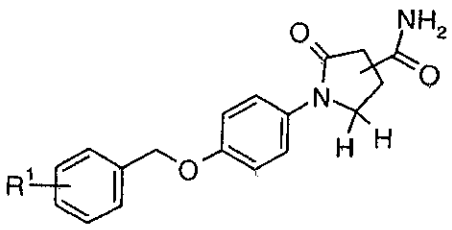
with ammonium acetate in the presence of a condensation reagent like e.g. CDI (1,1'-carbonyl-diimidazole) to a compound of formula



I-1

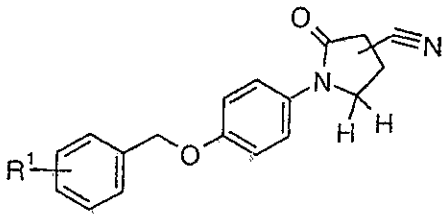
wherein the R^1 is as described above, or

b) reacting a compound of formula



I-1

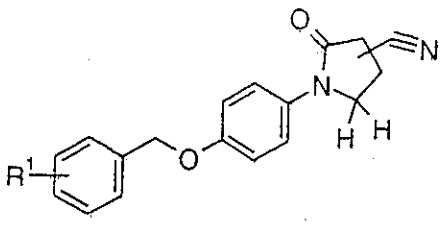
with thionyl chloride to a compound of formula



III

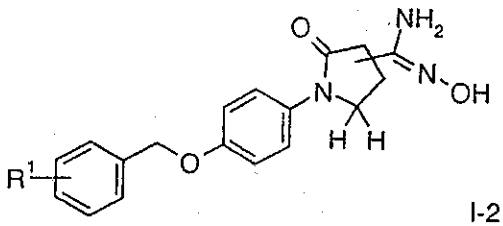
wherein the R^1 is as described above, or

c) reacting a compound of formula



III

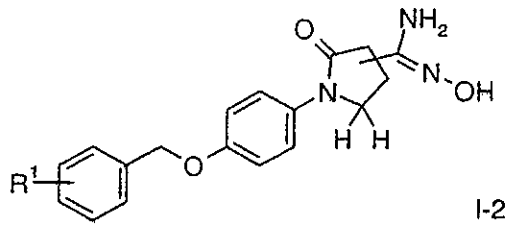
with hydroxylamine to a compound of formula



I-2

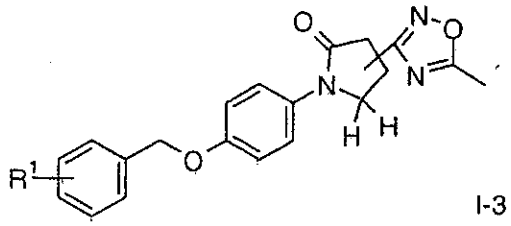
wherein the R^1 is as described above, or

d) reacting a compound of formula



I-2

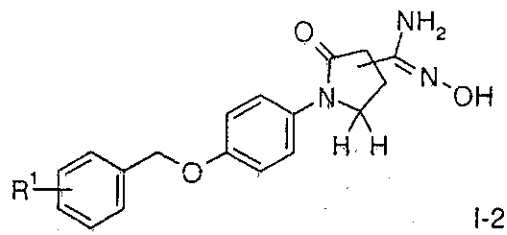
with acetyl chloride in the presence of a base to a compound of formula



I-3

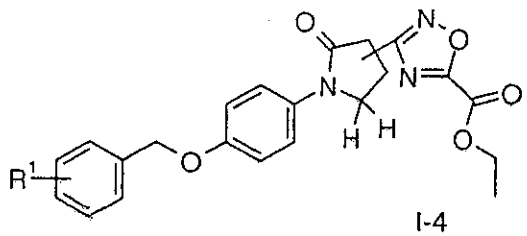
wherein the R^1 is as described above, or

e) reacting a compound of formula



I-2

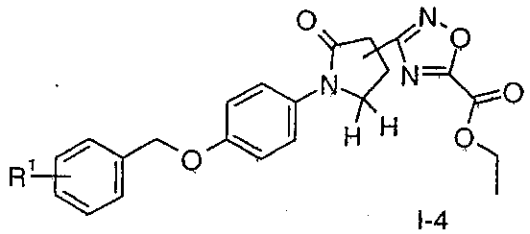
with ethyl oxalyl chloride to a compound of formula



I-4

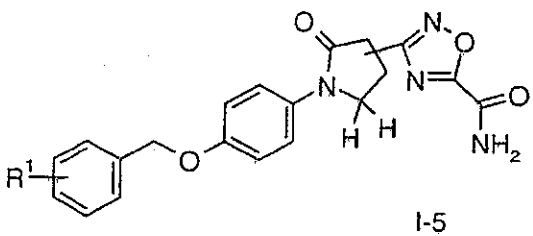
wherein the R^1 is as described above, or

f) reacting a compound of formula



I-4

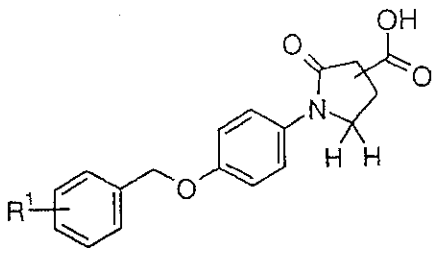
with NH_4OH to a compound of formula



I-5

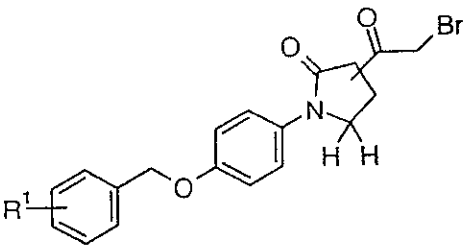
wherein the R^1 is as described above, or

g) reacting a compound of formula



II

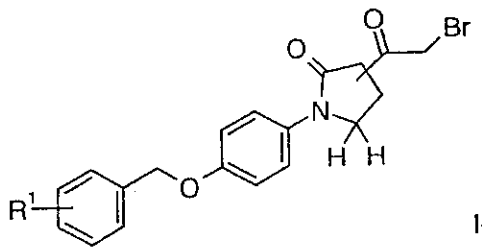
with thionyl chloride in the presence of N,N'-dimethylformamide and trimethylsilyldiazomethane and HBr to a compound of formula



I-6

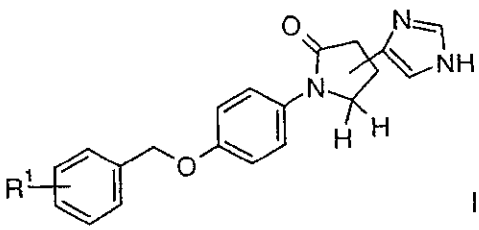
wherein the R^1 is as described above, or

h) reacting a compound of formula



I-6

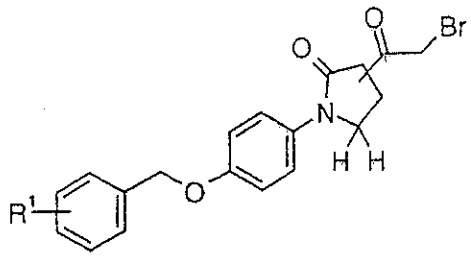
with formamide to a compound of formula



I-8

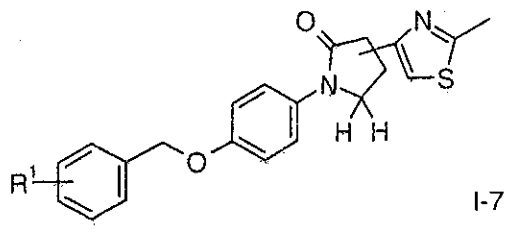
wherein the R^1 is as described above, or

i) reacting a compound of formula



I-6

with thioacetamide in THF to a compound of formula



I-7

wherein the R^1 is as described above, or

In yet another aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

In another aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients for the treatment and prevention of Alzheimer's disease and senile dementia.

In yet another aspect, there is provided a compound of formula I as defined above, as well as its pharmaceutically acceptable salts for the treatment or prevention of diseases.

In still another aspect, there is provided the use of a compound of formula I as defined above as well as its pharmaceutically acceptable salts for the manufacture of medicaments for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

The following definitions of general terms used in the present patent application apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

The term "lower alkyl" used in the present application denotes straight-chain or branched saturated hydrocarbon residues with 1 to 6 carbon atoms, preferably with 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, and the like.

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

"Lower alkoxy" means the residue -O-R, wherein R is a lower alkyl residue as defined herein. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

The term" 5-membered heteroaryl, containing 2 or 3 heteroatoms, selected from the group consisting of N, O or S" means a heteroaromatic ring system, selected from the group consisting of [1.2.4]oxadiazolyl, 1,3-thiazolyl, imidazolyl, pyrazolyl or isoxazolyl. Preferred groups are [1.2.4]oxadiazolyl, 1,3-thiazolyl or imidazolyl.

"Pharmaceutically acceptable salts" of a compound means salts that are pharmaceutically acceptable, which are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and that possess the desired pharmacological activity of the parent compound. These salts are derived from an inorganic or organic acid or base.

Such salts include:

(1) acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, hydroxynaphthoic acid, 2-hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, mandelic acid, methanesulfonic acid, muconic acid, 2-naphthalenesulfonic acid, propionic acid, salicylic acid, succinic acid, dibenzoyl-L-tartaric acid, tartaric acid, p-toluene-sulfonic acid, trimethylacetic acid, 2,2,2-trifluoroacetic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic or inorganic base. Acceptable organic bases include diethanolamine, ethanolamine, N-methylglucamine, triethanolamine, tromethamine, and the like. Acceptable inorganic bases include aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate and sodium hydroxide.

It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) of the same acid addition salt.

"Pharmaceutically acceptable" such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

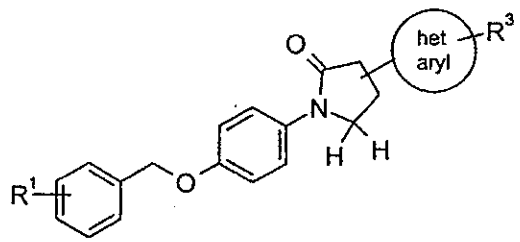
"Therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Furthermore, as used herein, a mammal in need of treatment of an acute and/or chronic neurological disorder means a mammal, e.g. a human, that is suffering from, or is at risk of suffering from, an acute and/or chronic neurological disorder.

As used herein, the terms „treat", treating" and treatment", and the like, as applied to an acute and/or chronic neurological disorder, refer to methods that slow, ameliorate, reduce or reverse such a disorder or any symptoms associated with said disorder, as currently afflicting the subject, as well as methods that prevent such a disorder or any symptoms thereof, from occurring.

Among compounds of the present invention certain compounds of formula I or pharmaceutically acceptable salts thereof, are preferred.

Preferred are further compounds of formula I, in which R^2 is a 5-membered heteroaryl group, containing 2 or 3 heteroatoms, selected from the group consisting of N, O or S, optionally substituted by R^3, which is lower alkyl, -NR'R" or –C(O)R. The following structure includes such compounds.



IA

Compounds of formula IA are, for example, the followings:
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrrolidin-2-one,
3-{(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester,
3-{(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid amide,
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(2-methyl-thiazol-4-yl)-pyrrolidin-2-one or
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(1H-imidazol-4-yl)-pyrrolidin-2-one.

Further compounds of formula I are those, in which R^2 is $-C(O)NH_2$, $-C(NH_2)=N-OH$, $-C(O)CH_2Br$, $-C(O)N(CH_3)OCH_3$ or $-C(O)$-lower alkyl, for example

(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide,

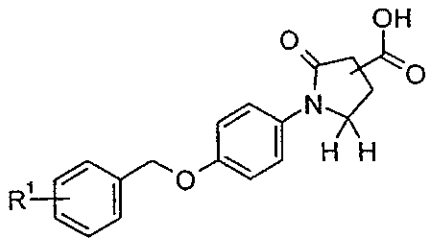
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-N-hydroxy-5-oxo-pyrrolidine-3-carboxamidine,

(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methoxy-methyl-amide or

(R)-4-acetyl-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one.

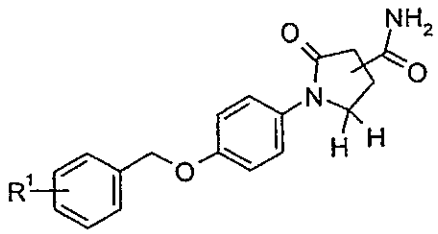
The present compounds of general formula I and their pharmaceutically acceptable salts can be manufactured by methods known in the art, for example by processes described below, which processes comprise

a) reacting a compound of formula



II

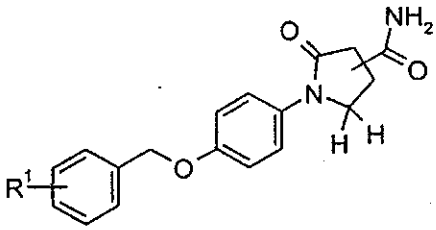
with ammonium acetate in the presence of a condensation reagent like e.g. CDI (1,1'-carbonyl-diimidazole) to a compound of formula



I-1

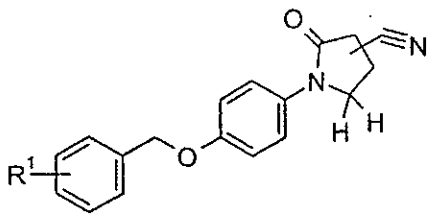
wherein the R^1 is as described above, or

b) reacting a compound of formula



I-1

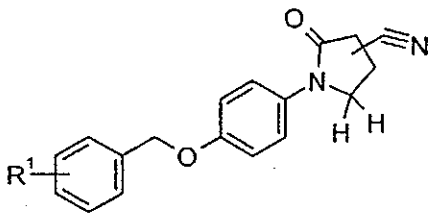
with thionyl chloride to a compound of formula



III

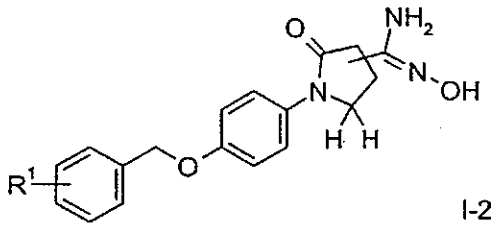
wherein the R^1 is as described above, or

c) reacting a compound of formula



III

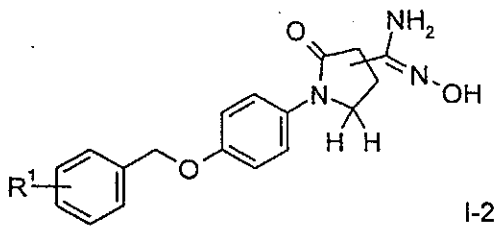
with hydroxylamine to a compound of formula



I-2

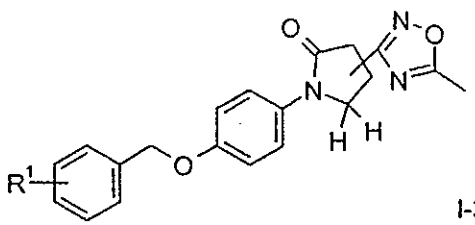
wherein the R^1 is as described above, or

d) reacting a compound of formula



I-2

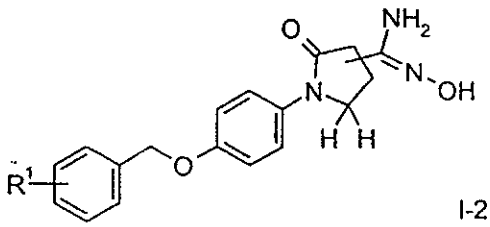
with acetyl chloride in the presence of a base to a compound of formula



I-3

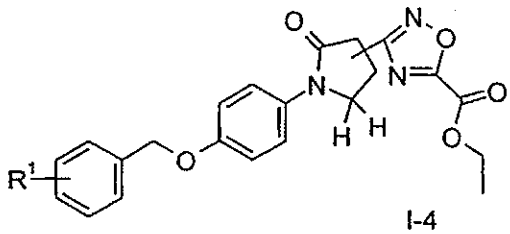
wherein the R^1 is as described above, or

e) reacting a compound of formula



I-2

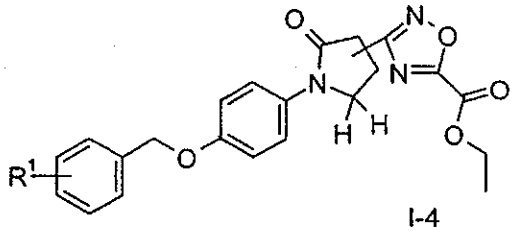
with ethyl oxalyl chloride to a compound of formula



I-4

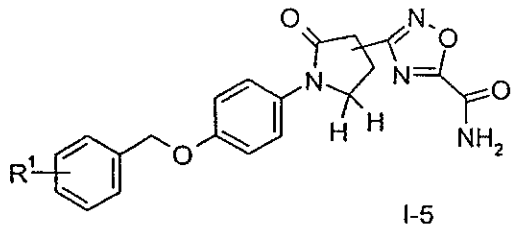
wherein the R^1 is as described above, or

f) reacting a compound of formula



I-4

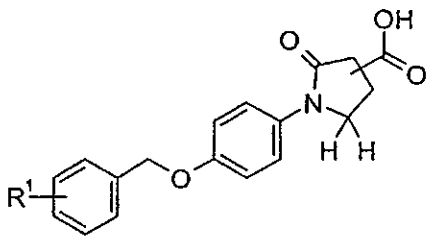
with NH_4OH to a compound of formula



I-5

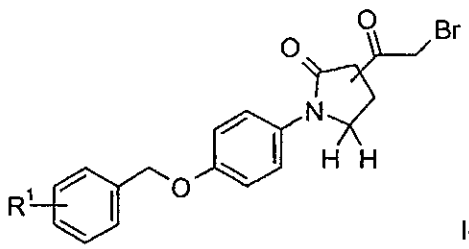
wherein the R^1 is as described above, or

g) reacting a compound of formula



II

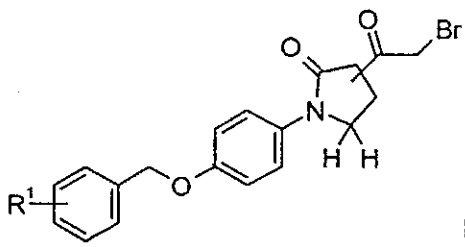
with thionyl chloride in the presence of N,N'-dimethylformamide and trimethylsilyldiazomethane and HBr to a compound of formula



I-6

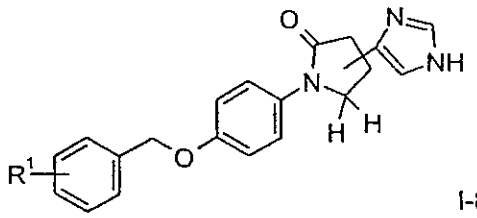
wherein the R^1 is as described above, or

h) reacting a compound of formula



I-6

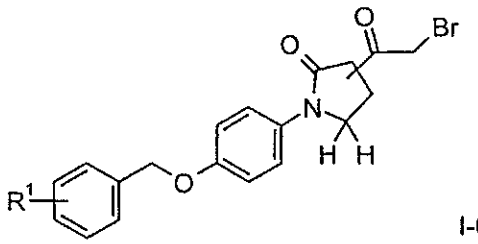
with formamide to a compound of formula



I-8

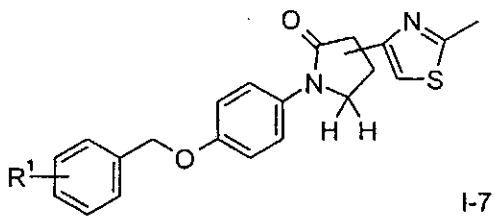
wherein the R^1 is as described above, or

i) reacting a compound of formula



I-6

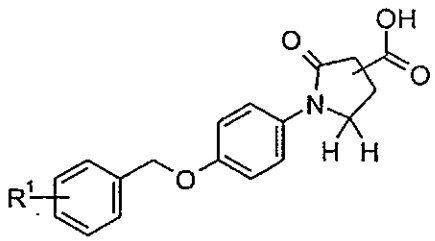
with thioacetamide in THF to a compound of formula



I-7

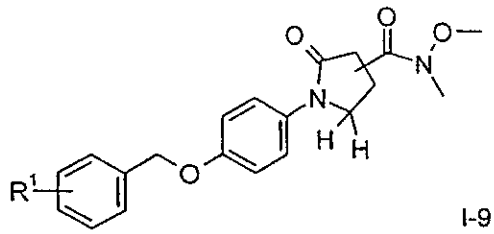
wherein the R^1 is as described above, or

j) reacting a compound of formula



II

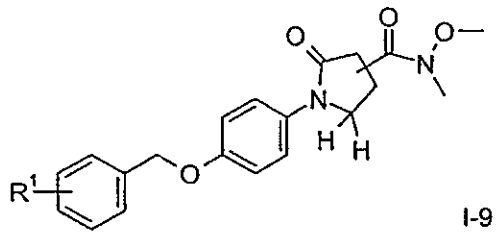
with N,O-dimethylhydroxylamine hydrochloride and CDI to a compound of formula



I-9

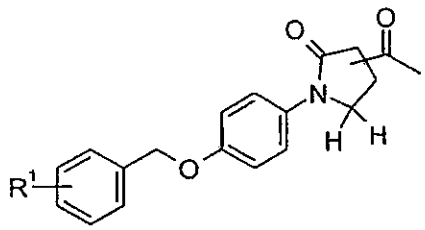
wherein the R^1 is as described above, or

k) reacting a compound of formula



I-9

with MeMgBr in THF to a compound of formula



I-10

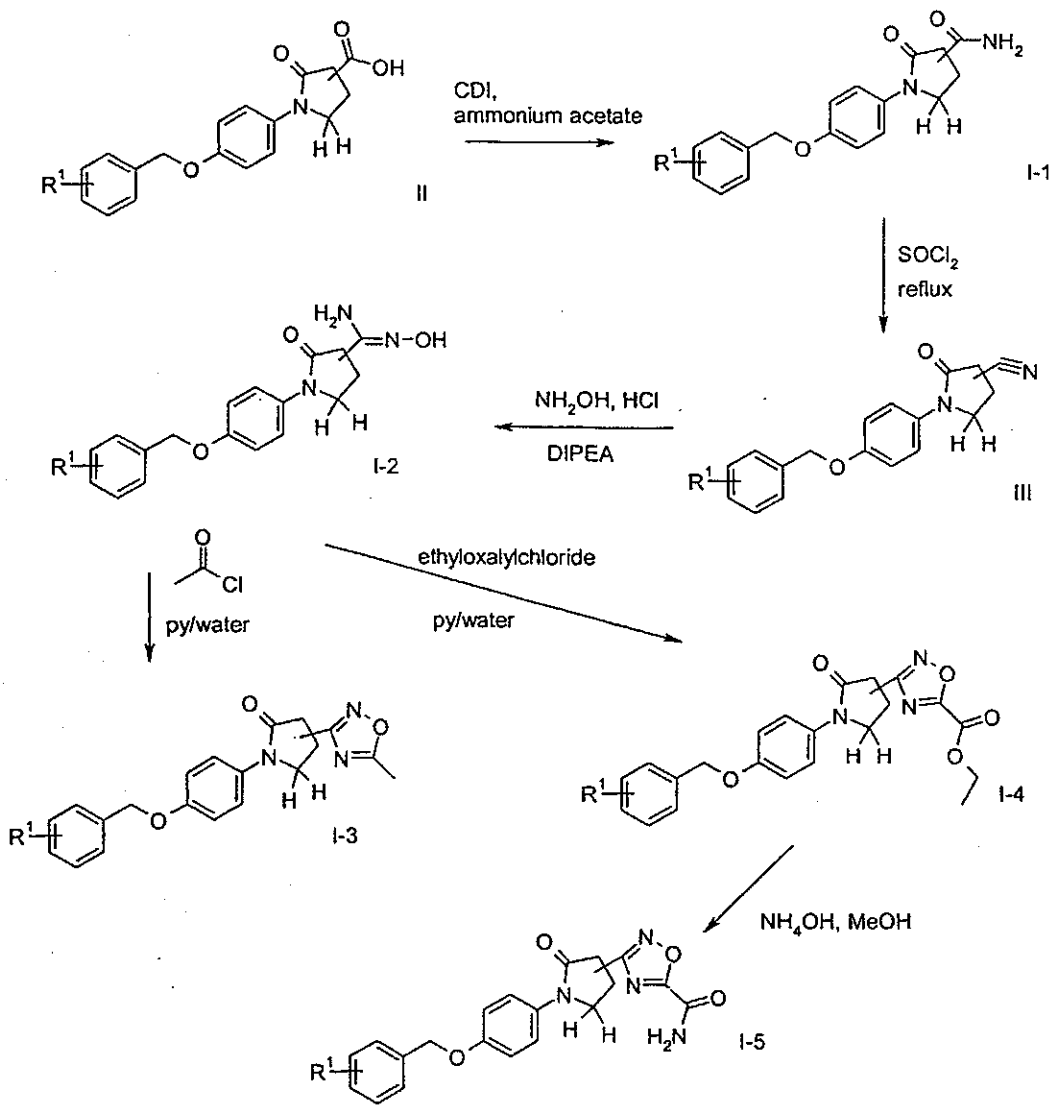
wherein the R^1 is as described above, and, if desired, converting a compound of formula I obtained into pharmaceutically active acid addition salts.

In accordance with the present invention, a possibility to prepare compounds of general formula I are shown in schemes 1 and 2.

Compounds of general formula I can be manufactured by reacting a compound of formula II with 1,1′-carbonyl-diimidazole (CDI) in N,N′-dimethylformamide (DMF) and ammonium acetate is added (scheme 1) to give the corresponding amide of formula I-1. The nitrile compound can be prepared from the amide by dehydration with a reagent like thionyl chloride preferably at 90 °C. Reaction of compound of formula III with hydroxylamine hydrochloride in the presence of a base like N,N-diisopropylethylamine gives the necessary N-hydroxy-carboxamidine of formula I-2 which reacts with acetyl chloride in the presence of a base like pyridine to give compounds of formula I-4 or with ethyl oxalyl chloride to give compounds of formula I-3. The corresponding amide of

formula I-5 could be prepared from the ester heating with ammonia in a solvent like methanol.

Scheme 1

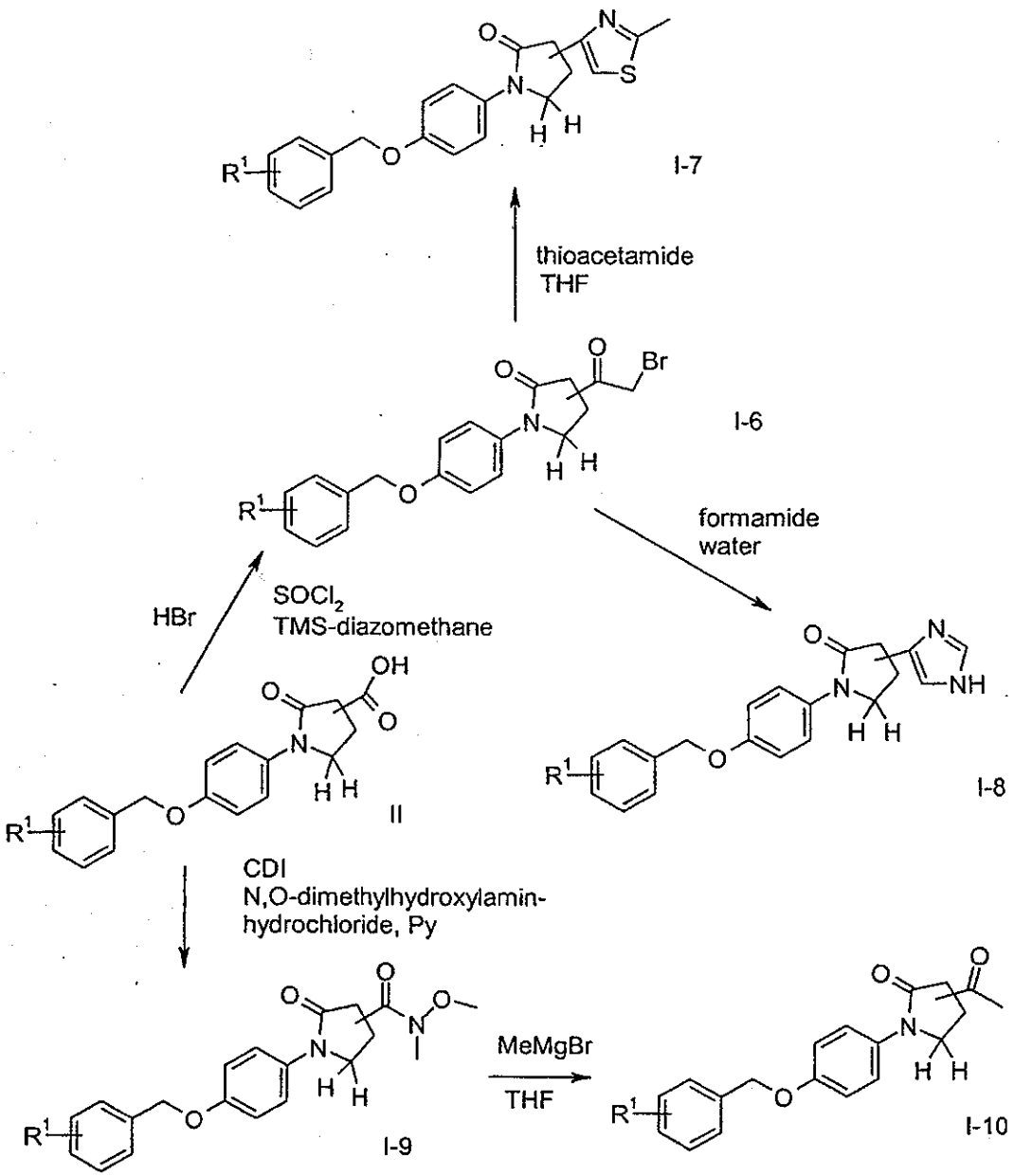


The definition of R^1 is as described above.

Other compounds of general formula I can be manufactured by reacting a compound of formula II with thionyl chloride in the presence of catalytic N,N'-dimethylformamide to give the intermediate acid chloride which reacts with trimethylsilyldiazomethane and hydrobromic acid 33% in acetic acid to give the 2-bromo acetyl compound I-6. Compounds of formula I wherein R^2 signifies imidazole (I-8) can be prepared by refluxing compounds of formula I-6 with formamide and water. Compounds of formula I wherein R^2 signifies thiazol (I-7) can be prepared by refluxing compounds of formula I-6with thioacetamide in a solvent like tetrahydrofuran.

Other compounds of formula I wherein R^2 signifies an amide, like methoxy methyl amide (I-9) can be prepared from the corresponding acid of formula II and 1,1'-carbonyl-diimidazole (CDI) in N,N'-dimethylformamide (DMF) to give an activated intermediate that reacts with the corresponding amine like the methoxy methyl amin. The methoxy methyl amide I-9 reacts with nucleophiles like alkylmagnesium bromide, e.g. methyl magnesium bromide, to give the corresponding ketone of formula I-10.

Scheme 2



The substituent R^1 has the meaning as described above.

Pharmaceutically acceptable salts of compounds of formula I can be manufactured readily according to methods known per se and taking into consideration the nature of the compound to be converted into a salt. Inorganic or organic acids such as, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid or citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like are suitable for the formation of pharmaceutically acceptable salts of basic compounds of formula I. Compounds which contain the alkali metals or alkaline earth metals, for example sodium, potassium, calcium, magnesium or the like, basic amines or basic amino acids are suitable for the formation of pharmaceutically acceptable salts of acidic compounds.

The compounds of formula I and their pharmaceutically acceptable salts are, as already mentioned above, monoamine oxidase B inhibitors and can be used for the treatment or prevention of diseases in which MAO-B inhibitors might be beneficial. These include acute and chronic neurological disorders, cognitive disorders and memory deficits. Treatable neurological disorders are for instance traumatic or chronic degenerative processes of the nervous system, such as Alzheimer's disease, other types of dementia, minimal cognitive impairment or Parkinson's disease. Other indications include psychiatric diseases such as depression, anxiety, panic attack, social phobia, schizophrenia, eating and metabolic disorders such as obesity as well as the prevention and treatment of withdrawal syndromes induced by abuse of alcohol, nicotine and other addictive drugs. Other treatable indications may be reward deficiency syndrome (G.M. Sullivan, International patent application No. WO 01/34172 A2), peripheral neuropathy caused by cancer chemotherapy (G. Bobotas, International Patent Application No. WO 97/33572 A1), or the treatment of multiple sclerosis (R.Y. Harris, International patent application No. WO 96/40095 A1) and other neuroinflammatory diseases.

The pharmacological activity of the compounds was tested using the following method:

The pharmacological activity of the Pharmaceutical compounds may be demonstrated, e.g. as follows:

The cDNA's encoding human MAO-A and MAO-B were transiently transfected into EBNA cells using the procedure described by Schlaeger and Christensen [Cytotechnology 15:1-13 (1998)]. After transfection, cells were homogenised by means of a Polytron homogenizer in 20 mM Tris HCl buffer, pH 8.0, containing 0.5 mM EGTA and 0.5 mM phenylmethanesulfonyl fluoride. Cell membranes were obtained by centrifugation at 45,000 x *g* and, after two rinsing step with 20 mM Tris HCl buffer, pH

8.0, containing 0.5 mM EGTA, membranes were eventually re-suspended in the above buffer and aliquots stored at -80°C until use.

MAO-A and MAO-B enzymatic activity was assayed in 96-well-plates using a spectrophotometric assay adapted from the method described by Zhou and Panchuk-Voloshina [Analytical Biochemistry 253:169–174 (1997)]. Briefly, membrane aliquots were incubated in 0.1 M potassium phosphate buffer, pH 7.4, for 30 min at 37°C with or without various concentrations of the compounds. After this period, the enzymatic reaction was started by the addition of the MAO substrate tyramine together with 1 U/ml horse-radish peroxidase (Roche Biochemicals) and 80 μM N-acetyl-3,7,-dihydroxyphenoxazine (Amplex Red, Molecular Probes). The samples were further incubated for 30 min at 37°C in a final volume of 200 μl and absorbance was then determined at a wavelength of 570 nm using a SpectraMax plate reader (Molecular Devices). Background (non-specific) absorbance was determined in the presence of 10 μM clorgyline for MAO-A or 10 μM L-deprenyl for MAO-B.

IC_{50} values were determined from inhibition curves obtained using nine inhibitor concentrations in duplicate, by fitting data to a four parameter logistic equation using a computer program.

The compounds of the present invention are specific MAO-B inhibitors. The IC_{50} values of compounds of formula I as measured in the assay described above are in the range of 1 μM or less, and ideally 0.1 μM or less. The below table shows exemplary IC_{50} values of compounds of formula I in one of their enantiomeric forms:

Example	human MAO-B [IC_{50} (μM)]
3	0.018
4	0.016
5	0.043
6	0.429
8	0.387
9	0.187
10	0.392
11	0.011

Pharmaceutical compounds 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. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

Pharmaceutical compounds can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, e.g., as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, e.g., 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, e.g., water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, e.g., natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Example 1

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (1.5 g, 0.005 mol) was dissolved in dry N,N-dimethylformamide under argon and cooled to 0°C. 1,1'-Carbonyl-diimidazole (1.4 g, 0.009 mol) was added to the mixture and the reaction stirred for one hour while the temperature rose from 0 °C to room temperature. Ammonium acetate (5.6 g, 0.073 mol) was added and the reaction was stirred for one hour at room temperature. Water was added dropwise to the mixture and a precipitate appeared. The solid was filtrated, washed with water and dried under vacuum to yield 1.36 g (0.0041 mol, 91 % of theory) of the title compound as a white solid.
MS (m/e)= 329.3(M+ H)$^+$.

Example 2

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carbonitrile

A mixture of (R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid amide (0.400 g, 0.001 mol) and thionyl chloride (2.3 ml, 0.032 mol) was refluxed under argon for 3 hours. The mixture was cooled to room temperature, diluted with 5 ml tetrahydrofuran, concentrated under vacuum and purified by column chromatography on silica gel using a 2:3-mixture of ethyl acetate and hexane as the eluent. The product fractions were concentrated to dryness to yield (0.106 g, 28 % of theory) of a light brown oil. MS (m/e)= 311.1 (M+ H)$^+$.

Example 3

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-N-hydroxy-5-oxo-pyrrolidine-3-carboxamidine

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carbonitrile (0.211 g, 0.001 mol) and hydroxylamine hydrochloride (0.047 g, 0.001 mol) were dissolved in ethanol (4 ml) and N,N-diisopropylethylamine (0.120 ml, 0.001 mol) was added. The reaction mixture was stirred under reflux for three hours. The reaction was cooled to room temperature, the solvent was evaporated and the residue extracted with dichloromethane and purified by column chromatography on silica gel using a 19:1 -mixture of dichloromethane and methanol as the eluent to yield (0.220 g, 94 % of theory) of a yellow oil.
MS (m/e)= 344.3(M+ H)$^+$.

Example 4

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrrolidin-2-one

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-N-hydroxy-5-oxo-pyrrolidine-3-carboxamidine (0.020 g, 0.58 mmol) was dissolved in a mixture of 0.4 ml pyridine and acetyl chloride (0.01 ml, 0.116 mmol) was slowly added at 0 °C. The mixture was then stirred at 70 °C overnight. Iced water was added and the mixture was stirred for one hour. Extraction with a saturated solution of ammonium chloride and dichloromethane gave the crude product that was purified by column cromatography on silica gel using a 19:1-mixture of dichloromethane and methanol as the eluent to obtain the title compound as a light yellow solid (0.0197 g, 92 % of theory). MS (m/e)= 368.4 $(M+H)^+$.

Example 5

3-{(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-N-hydroxy-5-oxo-pyrrolidine-3-carboxamidine (0.020 g, 0.58 mmol) was dissolved in a mixture of 0.4 ml pyridine and ethyl oxalyl chloride (0.01 ml, 0.116 mmol) was slowly added at 0 °C. The mixture was then stirred at 70 °C for half an hour. Iced water was added and the mixture was stirred for one hour. Extraction with a saturated solution of ammonium chloride and dichloromethane gave the crude product that was purified by column cromatography on silica gel using a 2:1-mixture of ethyl acetate and hexane as the eluent to obtain the title compound as a light yellow solid (0.019 g, 77 % of theory).
MS (m/e)= 426.3 $(M+H)^+$.

Example 6

3-{(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid amide

3-{(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester (0.110 g, 0.25 mmol) was dissolved in 3.5 ml of ammonia (2 M solution in methanol). The resulting mixture was stirred at 50 °C for half an hour. The mixture was cooled at 0 °C and a solid precipitated. The reaction mixture was filtrated and the solid washed with hexane and dried under vacuum. The residue was suspended in ethyl acetate and heated to reflux. Diethyl ether was added and the suspension cooled to 0

°C and filtrated to yield the title compound as a light brown solid (0.045 g, 44 % of theory). MS (m/e)= 397.4 $(M+H)^+$.

Example 7

(R)-4-(2-Bromo-acetyl)-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (0.204 g, 0.62 mmol) was dissolved in a mixture of dichloromethane (4 ml) , thionyl chloride (0.15 ml, 2.1 mmol) and a catalytic amount of N,N-dimethylformamide. The reaction mixture was stirred for half an hour at room temperature to form the intermediate acylchloride. Thereafter, the solvent was removed under reduced pressure and the residue suspended in toluene, concentrated under vacuum and dried . The resulting oil was dissolved in acetonitrile (2 ml) and trimethylsilyldiazomethane (2 M in hexane) (1.55 ml, 3.1 mmol) was added under argon. The resulting yellow solution was stirred at room temperature for half an hour until the diazoketone could be observed. After cooling of the the reaction mixture to 0 °C, hydrobromic acid (33 % in acetic acid) (0.71 ml, 4 mmol) was added dropwise. The resulting dark solution was stirred for half an hour at room temperature. Sodium bicarbonate (5 ml) was added and the mixture extracted with dichloromethane. The organic layers were dried over magnesium sulphate, filtrated and evaporated to dryness to give a residue that was purified by column cromatography on silica gel using a 1:1-mixture of ethyl acetate and hexane as the eluent to obtain the title compound as a light yellow oil (0.067 g, 67.5 % yield of theory).
MS (m/e)= 407.3$(M+H)^+$.

Example 8

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-4-(2-methyl-thiazol-4-yl)-pyrrolidin-2-one

(R)-4-(2-Bromo-acetyl)-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one (0.040 g, 0.098 mmol) was dissolved in tetrahydrofuran (1ml) and thioacetamide (0.007 g, 0.098 mmol) was added and the mixture was stirred at 40 °C for 24 hours. The tetrahydrofuran was evaporated and the residue was purified by column chromatography on silica gel using at first a 1:1-mixture then a 4:1-mixture of ethyl acetate and hexane as the eluent to yield the title compound as a light yellow solid (0.030 g, 80 % of theory).
MS (m/e)= 383.3 $(M+H)^+$.

Example 9

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-4-(1H-imidazol-4-yl)-pyrrolidin-2-one

(R)-4-(2-Bromo-acetyl)-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one (0.050 g, 0.123 mmol) was dissolved in water (0.1 ml) and formamide (0.6 ml) was added and the mixture stirred at reflux for 6 hours. 2M HCl was added and the mixture extracted with ethyl acetate. The aqueous layer was neutralized with an aqueous solution (10 %) of sodium hydroxide (pH 7-8) and extracted again with ethyl acetate to give a crude material which is subjected to chromatography on silica gel using a 19:1-mixture of dichloromethane and methanol as the eluent. There were obtained 0.011 g (25 % of theory) of the title compound as a colorless solid.
MS: m/e = 352.4 $(M+H)^+$.

Example 10

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methoxy-methyl-amide

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid (0.200 g, 0.001 mol) was dissolved in dry N,N-dimethylformamide (1 ml) under argon and the solution cooled to 0 °C. 1,1'-Carbonyl-diimidazole (0.108 g, 0.001 mol) was added to the mixture and the reaction stirred for one hour while the temperature rose from 0 °C to room temperature. After the addition of N,O-dimethylhydroxylamine hydrochloride (0.063 g, 0.001 mol) and pyridine (0.053 ml, 0.001 mmol), the reaction was stirred for two hours at room temperature. Water (10 ml) and hydrochloric acid (0.1 N) was added and the mixture extracted with ethyl acetate. The organic phase was washed with with a solution of sodium carbonate (1 M) and extracted again with ethyl acetate to yield 0.225 g (99 % of theory). The crude product obtained in this way was used in the next step without further purification. MS: m/e = 373.4$(M+H)^+$.

Example 11

(R)-4-Acetyl-1-[4-(3-fluoro-benzyloxy)-phenyl]-pyrrolidin-2-one

(R)-1-[4-(3-Fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidine-3-carboxylic acid methoxy-methyl-amide (0.050 g, 0.143 mmol) was dissolved under argon in tetrahydrofurane (1 ml) and methyl magnesium bromide (0.188 mmol, 0.063 ml) was added at 0 °C. The resulting solution was stirred at 0 °C for two hours . Water was added at 0 °C and the mixture was stirred for one hour. Extraction with ethyl acetate gave a residue which after chromatography on silica gel using a 9:1-mixture of ethyl acetate and cyclohexane as the

eluent yielded 0.040 g (91 % of theory) of the title compound as a white solid.
MS: m/e = 328.4 $(M+H)^+$.

Example A

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	100
Powdered. lactose	95
White corn starch	35
Polyvinylpyrrolidone	8
Na carboxymethylstarch	10
Magnesium stearate	2
Tablet weight	250

Example B

Tablets of the following composition are produced in a conventional manner:

	mg/Tablet
Active ingredient	200
Powdered. lactose	100
White corn starch	64
Polyvinylpyrrolidone	12
Na carboxymethylstarch	20
Magnesium stearate	4
Tablet weight	400

Example C

Capsules of the following composition are produced:

	mg/Capsule
Active ingredient	50
Crystalline. lactose	60
Microcrystalline cellulose	34
Talc	5
Magnesium stearate	1
Capsule fill weight	150

The active ingredient having a suitable particle size, the crystalline lactose and the microcrystalline cellulose are homogeneously mixed with one another, sieved and thereafter talc and magnesium stearate are admixed. The final mixture is filled into hard gelatine capsules of suitable size.

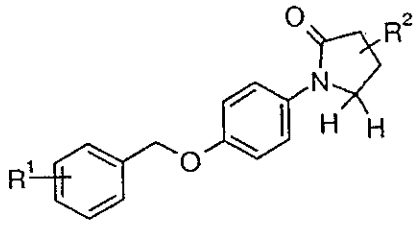
Example D

An injection solution may have the following composition and is manufactured in usual manner:

Active substance	1.0 mg
1 N HCl	20.0 µl
acetic acid	0.5 mg
NaCl	8.0 mg
phenol	10.0 mg
1 N NaOH	q.s. ad pH 5
H_2O	q.s. ad 1 ml

Claims

1. Compounds of the general formula



I

wherein

R^1 is halogen;

R^2 is a 5-membered heteroaryl group,
containing 2 or 3 heteroatoms, selected from the group consisting of N, O or S,
optionally substituted by R^3, wherein R^3 is lower alkyl, -NR'R" or –C(O)R;

R is NR'R", lower alkyl, or lower alkoxy;

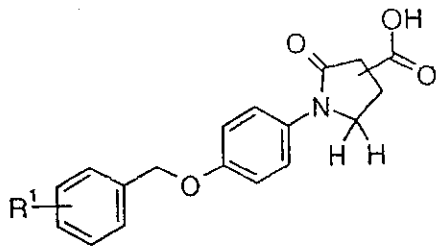
R'/R" are independently hydrogen or lower alkyl;

as well as their pharmaceutically acceptable salts.

2. Compounds of formula I according to claim 1, which compounds are
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrrolidin-2-one,
3-{(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid ethyl ester,
3-{(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-5-oxo-pyrrolidin-3-yl}-[1,2,4]oxadiazole-5-carboxylic acid amide,
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(2-methyl-thiazol-4-yl)-pyrrolidin-2-one or
(R)-1-[4-(3-fluoro-benzyloxy)-phenyl]-4-(1H-imidazol-4-yl)-pyrrolidin-2-one.

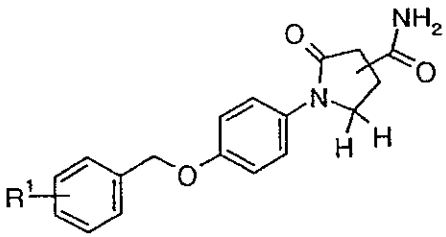
3. A process for preparation of compounds of formula I according to claim 1, which processes comprise

a) reacting a compound of formula



II

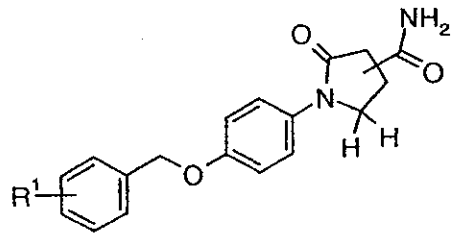
with ammonium acetate in the presence of a condensation reagent like e.g. CDI (1,1'-carbonyl-diimidazole) to a compound of formula



I-1

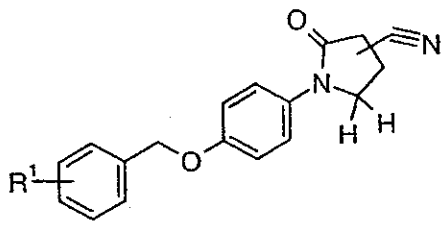
wherein the R^1 is as described above, or

b) reacting a compound of formula



I-1

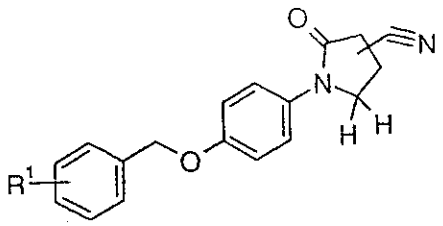
with thionyl chloride to a compound of formula



III

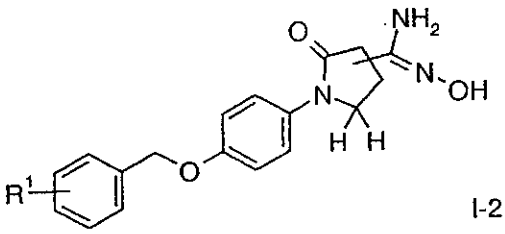
wherein the R^1 is as described above, or

c) reacting a compound of formula



III

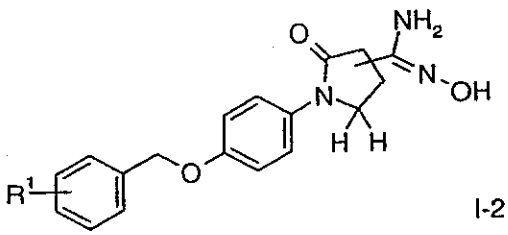
with hydroxylamine to a compound of formula



I-2

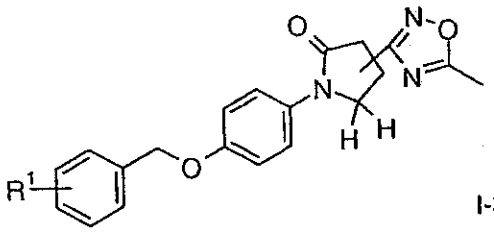
wherein the R^1 is as described above, or

d) reacting a compound of formula



I-2

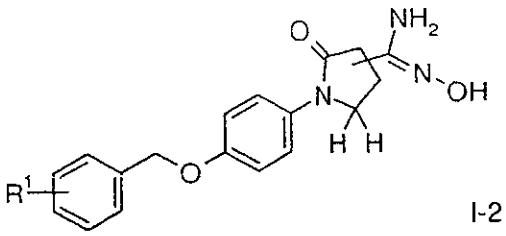
with acetyl chloride in the presence of a base to a compound of formula



I-3

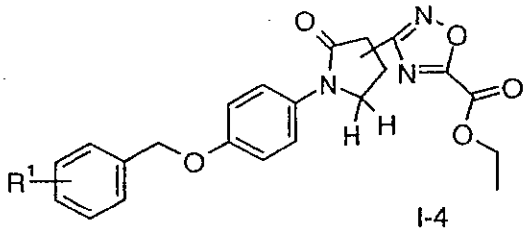
wherein the R^1 is as described above, or

e) reacting a compound of formula



I-2

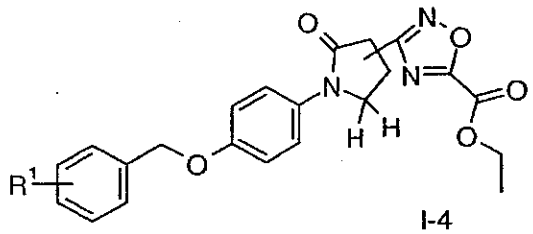
with ethyl oxalyl chloride to a compound of formula



I-4

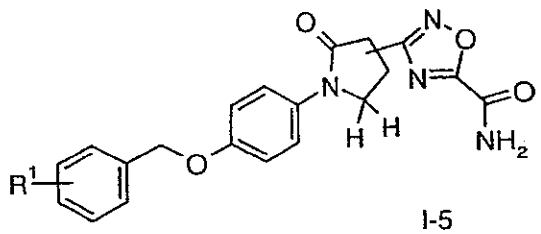
wherein the R^1 is as described above, or

f) reacting a compound of formula



I-4

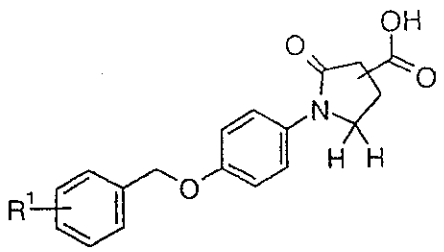
with NH_4OH to a compound of formula



I-5

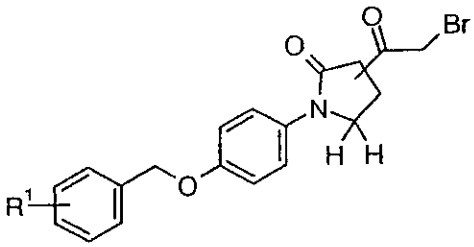
wherein the R^1 is as described above, or

g) reacting a compound of formula



II

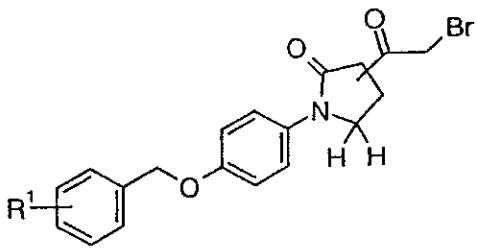
with thionyl chloride in the presence of N,N'-dimethylformamide and trimethylsilyldiazomethane and HBr to a compound of formula



I-6

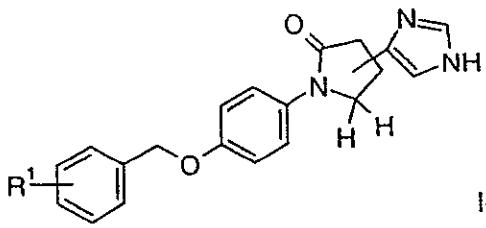
wherein the R^1 is as described above, or

h) reacting a compound of formula



I-6

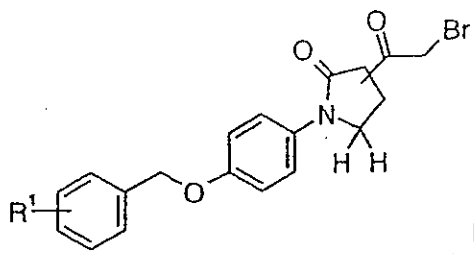
with formamide to a compound of formula



I-8

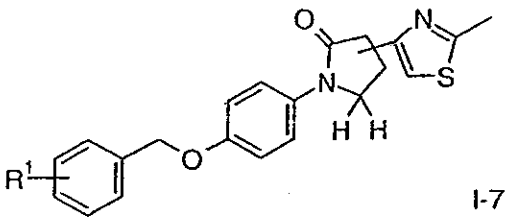
wherein the R^1 is as described above, or

i) reacting a compound of formula



I-6

with thioacetamide in THF to a compound of formula



I-7

wherein the R^1 is as described above.

4. A medicament containing one or more compounds as claimed in claim 1 or 2 and pharmaceutically acceptable excipients for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

5. A medicament containing one or more compounds as claimed in claim 1 or 2 and pharmaceutically acceptable excipients for the treatment and prevention of Alzheimer's disease and senile dementia.

6. A compound of formula I according to claim 1 or 2, as well as its pharmaceutically acceptable salts for the treatment or prevention of diseases.

7. The use of a compound of formula I according to claim 1 or 2 as well as its pharmaceutically acceptable salts for the manufacture of medicaments for the treatment and prevention of diseases which are mediated by monoamine oxidase B inhibitors.

8. The use according to claim 7, wherein the disease is Alzheimer's disease or senile dementia.