[Giardina, Williams; CNS Drug Reviews, 7, 305 (2001)]. An alternative approach involves the 'masking' of the two hydroxyl groups in the catechol as the corresponding methylene-di-oxy (MDO) acetal, as the acetal derived from other aldehydes than formaldehyde, or as the ketal derived from various ketones. This prodrug principle has been reported for the Aporphines more than 20 years ago [Baldessarini, Ram, Neumeyer; Neurorophar macology, 21(10), 953 (1982)]. Of these potential prodrugs to Apomorphine and related compounds, only that derived from N-*n*-propyl Apomorphine (NPA) and formaldehyde showed significant efficacy in animal models of PD. Over the following ~25 years, these findings have not lead to a PD drug based on the MDO-masked Apoporphines or related compounds.

Despite the long-standing interest in the field, there is evidently still an unmet need as regards developing efficient, well-tolerated and orally active drugs for the treatment of PD. A mixed D1-like/D2-like agonist giving continuous dopaminergic stimulation may fulfill such unmet needs.

Summary of the Invention

The present ~~invention~~ disclosure relates to novel catecholamine derivatives, which the inventors have found may offer suitable alternatives to current marketed treatments of neurodegenerative diseases such as PD and Huntington's disease and to the treatment of other indications discussed herein, such as eg. dyskinetic disorders, cognitive impairment and restless legs syndrome (RLS), and to compounds that are *in vivo* metabolizable prodrugs hereof.

Cognitive impairment can be experienced in several patients groups, e.g. schizophrenic, depressive or psychotic patients and patients with attention deficit hyperactivity disorder (ADHD), Parkinson's disease, mild cognitive impairment (MCI), dementia, anxiety, age associated memory impairment, Alzheimer's Disease or post-traumatic stress disorder and patients taking benzodiazepines or tricyclic antidepressants and in a range of neurodegenerative diseases in addition to Parkinson's Disease and Alzheimer's Disease. The phrase "cognitive impairment" refers to the difficulties with attention, learning, memory and executive function (relevant reactions to external stimuli). These can include: deficits in attention, disorganized thinking, slow thinking, difficulty in understanding, poor

concentration, impairment of problem solving, poor memory, difficulty in expressing thoughts and/or difficulty in integrating thoughts, feelings and behaviour and extinction of irrelevant thoughts as well as attention and vigilance, verbal learning and memory, visual learning and memory, speed of processing and social cognition.

The objective of the present disclosure ~~invention~~ is to provide novel compounds, which are both potent dopamine D1-like and D2-like agonists, and which may be used in the treatment of neurological and psychiatric diseases

A further objective of the present disclosure ~~invention~~ is to provide novel compounds for oral administration in the treatment of PD and other diseases or disorders, which responds favourably to an increased dopaminergic turnover.

PET (positron emission tomography) analysis is an important tool in the diagnosis of PD. Some of the compounds of the present disclosure ~~invention~~ have potential applications as PET ligands for imaging studies of the DA-receptors or as intermediates for the preparation of such ligands, which may, for example, be applied in receptor localization studies as well as for the determination of receptor occupancy determination for compounds with affinities for the DA receptors. A further objective is therefore to provide radiolabeled compounds of the present disclosure~~invention~~, which are considered to be valuable PET ligands.

Further objectives of the disclosure ~~invention~~ will become apparent upon reading the present specification.

In one aspect, there is provided a compound, (6aR,10aR)-7-*n*-propyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a]anthracene, characterized in that it is the substantially pure (6aR,10aR)-enantiomer, wherein the (6aR,10aR)-enantiomeric excess is at least 60%, or a pharmaceutically acceptable acid addition salt thereof.

In another aspect, there is provided a compound as defined herein for use as a medicament.

In yet another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined herein and one or more pharmaceutically acceptable carriers, diluents and excipients.

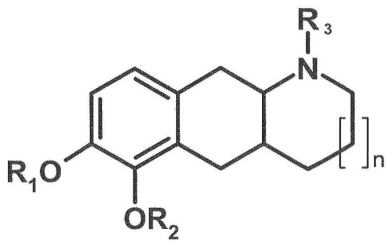
In a further aspect, there is provided a use of a compound as defined herein or a pharmaceutically acceptable acid addition salt thereof in the preparation of a medicament for the treatment of neurodegenerative disorders in a mammal.

In another aspect, there is provided a use of a compound as defined herein or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of psychoses, impotence, renal failure, heart failure, hypertension, cognitive impairment, restless legs syndrome (RLS), periodic limb movement disorder (PLMD), movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor in a mammal.

In another aspect, there is provided a use of a compound as defined herein or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of depression, bipolar disorder and anxiety in a mammal.

In another aspect, there is provided a use of a compound as defined herein or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of cognitive impairment associated with a disorder or disease selected from schizophrenia, Parkinson's Disease, dementia, anxiety disorder, age associated memory impairment, depression, Alzheimer's Disease, attention deficit hyperactivity disorder (ADHD) or post-traumatic stress disorder (PTSD) in a mammal.

Accordingly, in one ~~aspect~~ embodiment the present disclosure ~~invention~~ relates to compounds of formula **I:**



I

- wherein n = 0, 1

- R_1 and R_2 are independently selected from hydrogen, C_{1-6} alkanoyl, phenylacetyl or benzoyl, or wherein R_1 and R_2 are fused and form a methylene (CH_2) group, a carbonyl (C=O) group, or an oxalyl (O=C-C=O) group
- R_3 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, *cyclo*-propyl, *cyclo*-butyl, allyl, propargyl, hydroxyethyl, 3-fluoropropyl and 2-fluoroethyl

and addition salts thereof with pharmaceutically acceptable acids, provided that the compound is not one of the following racemates:

- Racemic-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
- Racemic-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
- Racemic-1-ethyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
- Racemic-1-*n*-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

The C_{1-6} alkanoyl group means a straight-chain or branched-chain alkanoyl group containing from 1 to six carbon atoms, examples of which include a formyl group, an acetyl group, a pivaloyl group, and the like.

In a particular embodiment, the present disclosure ~~invention~~ relates to compounds of formula I in the form of a substantially pure single enantiomer or a single diastereomer.

In another particular embodiment, the present disclosure ~~invention~~ relates to compounds of formula I in the form of a mixture of enantiomers, a mixture of diastereomers, or a substantially pure polymorph.

In a particular embodiment, the present disclosure ~~invention~~ relates to compounds of Formula I which have *trans*-fused ring systems. In another embodiment the present disclosure ~~invention~~ relates to compounds of Formula I, which have *cis*-fused ring systems.

In an embodiment the present disclosure ~~invention~~ relates to compounds of Formula I, for which n = 0. In another embodiment the present disclosure ~~invention~~ relates to compounds of Formula I, for which n = 1.

In separate embodiments of the present disclosure~~invention~~, the compound is selected from one of the specific compounds disclosed in the Experimental Section.

In a particular embodiment, the present disclosure ~~invention~~ relates to compounds of Formula I wherein R_3 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, allyl, and propargyl. In another embodiment, the present disclosure ~~invention~~ relates to compounds of Formula I wherein R_3 is selected from the group consisting of *cyclo*-propyl, *cyclo*-butyl, and hydroxyethyl.

In a specific embodiment, the present disclosure ~~invention~~ relates to compounds of Formula I wherein n=1, and which are further characterized by being the substantially pure (4aR,10aR)-enantiomer.

The present disclosure ~~invention~~ furthermore relates to compounds of Formula I wherein R_1 and R_2 are both hydrogen and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl.

The present disclosure ~~invention~~ also relates to compounds of Formula I wherein R_1 and R_2 are fused and form a methylene (CH_2) group, and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl, such as methyl and n-propyl.

In separate embodiments of the present disclosure~~invention~~, the compound is selected from one of the following specific compounds:

trans-1-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]indole-5,6-diol

cis-1-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]indole-5,6-diol

trans-1-*n*-propyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]indole-5,6-diol

cis-1-*n*-propyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]indole-5,6-diol

(4aR,10aR)-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aS,10aS)-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aS,10aS)-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-ethyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aS,10aS)-1-ethyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-*n*-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aS,10aS)-1-*n*-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-(2-hydroxyethyl)-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-allyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol

(4aR,10aR)-1-prop-2-ynyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
(4aR,10aR)-1-*cyclo*-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
(4aR,10aR)-1-*cyclo*-butyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol
(6aR,10aR)-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a]anthracene
(6aR,10aR)-7-methyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-azacyclopenta[a] anthracene
(6aR,10aR)-7-ethyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a] anthracene
(6aR,10aR)-7-*n*-propyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a] anthracene
Acetic acid (4aR,10aR)-7-acetoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g] quinolin-6-yl ester
Acetic acid (4aS,10aS)-7-acetoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[g] quinolin-6-yl ester
2,2-Dimethylpropionic acid (4aR,10aR)-7-(2,2-dimethyl-propionyloxy)-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-6-yl ester
Acetic acid (4aS,10aS)-6-acetoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g] quinolin-7-yl ester
Acetic acid (4aS,10aS)-6-acetoxy-1-ethyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g] quinolin-7-yl ester
2,2-Dimethylpropionic acid (4aR,10aR)-7-(2,2-dimethyl-propionyloxy)-1-*n*-propyl-1,2,3,4,4a,5, 10,10a-octahydro-benzo[g]quinolin-6-yl ester

or a pharmaceutically acceptable acid addition salt thereof

In another ~~aspect~~ embodiment the present disclosure ~~invention~~ relates to radiolabeled compounds of Formula I and the use thereof in various biological assays such as PET-studies, *in vivo* binding studies and *in vitro* assays.

In a further ~~aspect~~ embodiment the present disclosure ~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt hereof, as a medicament.

The compound of Formula I, either as the free base, or as a pharmaceutically acceptable acid addition salt, or as a pharmaceutical composition, may be administered in any suitable way e.g. orally, buccally, sublingually, non-orally or parenterally, and the compound may be

presented in any suitable form for such administration, e.g. orally in the form of tablets, capsules, powders, syrups, solutions or dispersions, non-orally in the form of eg. transdermal patches or parenterally in the form of dispersions or solutions for injection. In one embodiment, the compound of Formula I is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

The compounds of Formula I form pharmaceutically acceptable acid addition salts with a wide variety of organic and inorganic acids. Such salts are also part of this disclosure~~invention~~.

A pharmaceutically acceptable acid addition salt of the compound of Formula I is formed from a pharmaceutically acceptable acid as is well known in the art. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66,2-19 (1977) and are known to the skilled person. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydriodic, nitric, sulphuric, phosphoric, hypophosphoric, metaphosphoric, pyrophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include the chloride, bromide, iodide, nitrate, acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, isobutyrate, phenylbutyrate, α-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-l,4-dicarboxylate, caprate, caprylate, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, oxalate, phthalate, teraphthalate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, benzenesulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, naphthalene-1,5-sulfonate, p-toluenesulfonate, xylenesulfonate, tartrate, and the like.

Methods for the preparation of solid pharmaceutical preparations are also well known in the art. Tablets may thus be prepared by mixing the active ingredient with ordinary adjuvants, fillers and diluents and subsequently compressing the mixture in a convenient tabletting

machine. Examples of adjuvants, fillers and diluents comprise microcrystalline cellulose, corn starch, potato starch, lactose, mannitol, sorbitol talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

In particular, the tablet formulations according to the ~~invention~~ present disclosure may be prepared by direct compression of a compound of Formula I in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of a compound of Formula I, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Solutions of a compound of Formula I for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, solubilising agents, etc. Alternatively the active ingredient, eg. as the free base may be dissolved in a digestible or non-digestible oil, mixtures hereof or similar, to prepare an intramuscular depot formulation capable of releasing the active ingredient over a prolonged period of time.

Pharmaceutical formulations of the compound of Formula I to be used in transdermal applications, such as transdermal patches, may optionally contain permeation activators to facilitate the passage of the active ingredient through the skin.

In another ~~aspect~~embodiment, the present disclosure ~~invention~~ relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, and one or more pharmaceutically acceptable carriers, diluents and excipients.

In a specific embodiment of the present disclosure ~~invention~~ there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, wherein R_1 and R_2 are both hydrogen

and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl for non-oral administration, such as transdermal, nasal, buccal, intramuscular or subcutaneous administration.

In a further embodiment~~aspect~~ the present disclosure ~~invention~~ provides the use of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of neurodegenerative disorders such as Parkinson's disease and Huntington's disease.

In a further ~~aspect~~ embodiment the present disclosure ~~invention~~ provides the use of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of psychoses, impotence, renal failure, heart failure or hypertension.

In another embodiment ~~aspect~~ the present disclosure ~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of cognitive impairment in a mammal.

In a still further embodiment~~aspect~~ the present disclosure ~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of restless legs syndrome (RLS) or periodic limb movement disorder (PLMD).

In a different embodiment~~aspect~~ the present disclosure ~~invention~~ provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor in a mammal.

In a further embodiment~~aspect~~ the present disclosure ~~invention~~ provides the use of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof for the treatment of neurodegenerative disorders such as Parkinson's disease and Huntington's disease.

In a further embodimentaspect the present disclosure invention provides the use of a compound of Formula I or a pharmaceutically acceptable acid addition salt thereof for the treatment of psychoses, impotence, renal failure, heart failure or hypertension.

In another embodimentaspect the present disclosure invention provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of cognitive impairment in a mammal.

In a still further embodimentaspect the present disclosure invention provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of restless legs syndrome (RLS) or periodic limb movement disorder (PLMD).

In a different embodimentaspect the present disclosure invention provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor in a mammal.

In separate embodimentaspects the present disclosure invention provides the use of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of medicaments, which are intended for oral administration, or for non-oral administration.

The present disclosure invention also provides a method of treating a mammal suffering from a neurodegenerative disorder such as Parkinson's disease and Huntington's disease comprising administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof.

In another embodimentaspect the present disclosure invention also provides a method of treating a mammal suffering from psychoses, impotence, renal failure, heart failure or hypertension, comprising administering to the mammal a therapeutically effective amount of a compound of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof.

In a further embodiment~~aspect~~ the present disclosure ~~invention~~ provides a method of treating a mammal suffering from a cognitive impairment, comprising administering to the mammal an effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof.

The present disclosure ~~invention~~ also relates to a method of treating a mammal suffering from restless legs syndrome (RLS) or periodic limb movement disorder (PLMD), comprising administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable addition salt thereof.

The present disclosure ~~invention~~ also relates in a separate ~~aspect~~ embodiment to a method of treating a mammal suffering from movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor comprising administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable acid addition salt thereof.

In a specific embodiment of the present disclosure ~~invention~~ the mammal is a human subject The therapeutically effective amount of a compound of Formula I, calculated as the daily dose of the compound of Formula (I) above as the free base, is suitably between 0.01 and 125 mg/day, more suitable between 0.05 and 100 mg/day, e.g. preferably between 0.1 and 50 mg/day.

In a specific embodiment the daily dose of the compound of Formula I is between 1 and 10 mg/day.

In another embodiment the daily dose of the compound of Formula I is less than about 1 mg/day.

In a separate embodiment the daily dose of the compound of Formula I is about 0.1 mg/day.

In a further embodiment the present disclosure ~~invention~~ provides an oral formulation comprising from 0.001 mg to 125 mg of a compound of Formula I.

In a further embodiment the present disclosure ~~invention~~ provides an oral formulation comprising from 0.001 mg to 0.1 mg of a compound of Formula I.

In a further embodiment the present disclosure ~~invention~~ provides an oral formulation comprising from 0.01 mg to 1 mg of a compound of Formula I.

In a further embodiment the present disclosure ~~invention~~ provides an oral formulation comprising from 0.1 mg to 10 mg of a compound of Formula I.

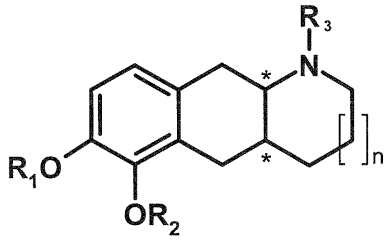
Figures

Figure 1: Dose-response curve for the concentration-dependent stimulation of intracellular Ca^{2+} release by dopamine in hD5-transfected CHO-Ga16 cells.

Figure 2: Crystal structure of example **2d2**. The absolute configuration was determined by the anomalous scattering of the 'heavy' bromine atom.

Detailed Description of the Invention

The compounds of the present invention contain two chiral centers (denoted with * in the below formula)



I

The compounds of the invention therefore can exist in two different diastereomeric forms, the *cis*- and *trans*-isomers, which forms both fall under the scope of the present invention.

What is claimed:

1. A compound, (6aR,10aR)-7-*n*-propyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a]anthracene, characterized in that it is the substantially pure (6aR,10aR)-enantiomer, wherein the (6aR,10aR)-enantiomeric excess is at least 60%, or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as defined in claim 1 for use as a medicament.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and one or more pharmaceutically acceptable carriers, diluents and excipients.

4. Use of a compound of claim 1 or a pharmaceutically acceptable acid addition salt thereof in the preparation of a medicament for the treatment of neurodegenerative disorders in a mammal.

5. The use according to claim 4 for the treatment of Parkinson's disease or Huntington's disease in a mammal.

6. Use of a compound according to claim 1 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of psychoses, impotence, renal failure, heart failure, hypertension, cognitive impairment, restless legs syndrome (RLS), periodic limb movement disorder (PLMD), movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor in a mammal.

7. Use of a compound of claim 1 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of depression, bipolar disorder and anxiety in a mammal.

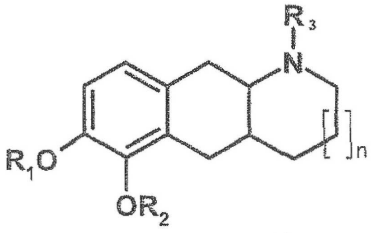
8. Use of a compound of claim 1 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for the treatment of cognitive impairment associated with a disorder or disease selected from schizophrenia, Parkinson's Disease, dementia, anxiety

disorder, age associated memory impairment, depression, Alzheimer's Disease, attention deficit hyperactivity disorder (ADHD) or post-traumatic stress disorder (PTSD) in a mammal.

9. The use according to anyone of claims 4-8 in which the mammal is a human subject.

What is claimed:

1. A compound having the structure I



I

- wherein n = 0, 1
- wherein R_1 and R_2 are fused and form a methylene (CH_2) group, a carbonyl (C=O) group, or an oxalyl (O=C-C=O) group
- R_3 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, *cyclo*-propyl, *cyclo*-butyl, allyl, propargyl, hydroxyethyl, 3-fluoropropyl and 2-fluoroethyl

, and pharmaceutically acceptable acid addition salts thereof.

2. The compound according to Claim 1 wherein R_3 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, allyl, and propargyl, such as methyl and n-propyl.

3. The compound according to any one of the preceding claims wherein R_3 is selected from the group consisting of *cyclo*-propyl, *cyclo*-butyl, and hydroxyethyl.

4. The compound according to any one of the preceding claims wherein n = 0.

5. The compound according to any one of claims 1-3 wherein n = 1.

6. The compound according to any one of the preceding claims further characterized by being the substantially pure *trans*-diastereoisomer.

7. The compound according to any one of the preceding claims wherein R_1 and R_2 are fused and form a methylene (CH_2) group.

8. The compound according to claim 1 wherein n=1, further characterized by being the substantially pure (6aR,10aR)-enantiomer.

9. The compound of claim 1, wherein the compound is selected from:

- (6aR,10aR)-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a]anthracene
- (6aR,10aR)-7-methyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-azacyclopenta[a] anthracene
- (6aR,10aR)-7-ethyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a] anthracene
- (6aR,10aR)-7-*n*-propyl-6,6a,7,8,9,10,10a,11-octahydro-1,3-dioxa-7-aza-cyclopenta[a] anthracene

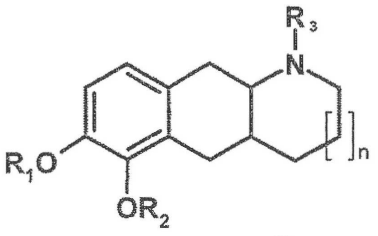
, or a pharmaceutically acceptable acid addition salt thereof.

10. The compound according to Claim 8 wherein R_1 and R_2 are fused and form a methylene (CH_2) group, and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl, such as methyl and n-propyl.

11. The compound according to Claim 6 wherein n=0, R_1 and R_2 are fused and form a methylene (CH_2) group, and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl.

12. The use of a compound as defined in any one of the preceding claims as a medicament.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I and one or more pharmaceutically acceptable carriers, diluents and excipients, the compound of formula I having the following structure:



I

- wherein n = 0, 1
- wherein R_1 and R_2 are fused and form a methylene (CH_2) group, a carbonyl (C=O) group, or an oxalyl (O=C-C=O) group
- R_3 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, *cyclo*-propyl, *cyclo*-butyl, allyl, propargyl and hydroxyethyl,

, and pharmaceutically acceptable acid addition salts thereof.

14. A pharmaceutical composition according to claim 13, wherein R_1 and R_2 are fused and form a methylene (CH_2) group, and R_3 is selected from the group consisting of hydrogen, methyl, ethyl and *n*-propyl, for non-oral administration.

15. A pharmaceutical composition according to claim 14 for transdermal, nasal, buccal, intramuscular, parenteral, or subcutaneous administration.

16. A pharmaceutical composition according to any one of claims 13-15, wherein the compound of formula I is a substantially pure diastereoisomer or a substantially pure enantiomer.

17. The use of a compound of any one of claims 1 to 11 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of neurodegenerative disorders in a mammal.

18. The use of a compound according to claim 17 for the preparation of a medicament for the treatment of Parkinson's disease or Huntington's disease in a mammal.

19. The use of a compound of any one of claims 1 to 11 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of psychoses, impotence, renal failure, heart failure, or hypertension in a mammal.

20. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of cognitive impairment in a mammal.

21. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of restless legs syndrome (RLS) or periodic limb movement disorder (PLMD) in a mammal.

22. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor in a mammal.

23. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of dyskinesias in a mammal.

24. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of depression, bipolar disorder and anxiety in a mammal.

25. The use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament for the treatment of cognitive impairment associated with a disorder or disease selected from schizophrenia, Parkinson's Disease, dementia such as AIDS dementia, anxiety disorder, age associated memory impairment, depression, including major depression, in particular in elderly, Alzheimer's Disease, attention deficit hyperactivity disorder (ADHD) or post-traumatic stress disorder (PTSD) in a mammal.

26. The use according to anyone of claims 17-25 in which the mammal is a human subject.

27. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof for the treatment of neurodegenerative disorders in a mammal.

28. A compound according to claim 27 for the treatment of Parkinson's disease or Huntington's disease in a mammal.

29. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof for the treatment of psychoses, impotence, renal failure, heart failure, or hypertension in a mammal.

30. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of cognitive impairment in a mammal.

31. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of restless legs syndrome (RLS) or periodic limb movement disorder (PLMD) in a mammal.

32. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of movement disorders, poverty of movement, dyskinetic disorders, gait disorders, or intention tremor in a mammal.

33. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of dyskinesias in a mammal.

34. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of depression, bipolar disorder and anxiety in a mammal.

35. A compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, for the treatment of cognitive impairment associated with a disorder or disease selected from schizophrenia, Parkinson's Disease, dementia such as AIDS

dementia, anxiety disorder, age associated memory impairment, depression, including major depression, in particular in elderly, Alzheimer's Disease, attention deficit hyperactivity disorder (ADHD) or post-traumatic stress disorder (PTSD) in a mammal.

36. The compound for treatment according to Claim 27-35 in which the mammal is a human subject.

37. A method of treating a mammal suffering from a neurodegenerative disorder such as Parkinson's disease or Huntington's disease comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

38. A method of treating a mammal suffering from psychoses, impotence, renal failure, heart failure or hypertension, comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

39. A method of treating a mammal suffering from cognitive impairment, comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

40. A method of treating a mammal suffering from restless legs syndrome (RLS) or periodic limb movement disorder (PLMD), comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable addition salt thereof.

41. A method of treating a mammal suffering from movement disorders, poverty of movement, dyskinetic disorders, gait disorders or intention tremor comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

42. A method of treating a mammal suffering from dyskinesias comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

43. A method of treating a mammal suffering from depression, such as major depresion, bipolar disorder or anxiety comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

44. A method of treating a mammal suffering from cognitive impairment associated with a disorder or disease selected from schizophrenia, Parkinson's Disease, dementia such as AIDS dementia, anxiety disorder, age associated memory impairment, depression, including major depression, in particular in elderly, Alzheimer's Disease, attention deficit hyperactivity disorder (ADHD) or post-traumatic stress disorder (PTSD), comprising administering to said mammal a therapeutically effective amount of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof.

45. The method according to Claim 37-44 in which the mammal is a human subject.