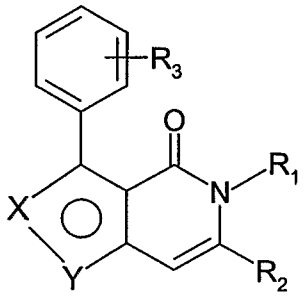
Isoxazolopyridinones

The present invention relates to novel isoxazolopyridinone derivatives, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

The invention provides compounds of formula I



I

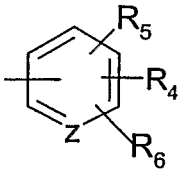
wherein

either X is O and Y is N

or X is N and Y is O,

R_1 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-4}alkyl or di-C_{1-4}alkylamino-C_{1-4}alkyl,

R_2 is C_{1-4}alkyl, C_{3-7}cycloalkyl, benzo [1,3]dioxol-5-yl, benzo[1,2,5]oxadiazol-5-yl, benzo[1,2,5]thiadiazol-5-yl or a group of formula (a)



(a)

wherein Z is CH or N, R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, hydroxy, trifluoromethyl, di-C_{1-4}alkylamino, C_{1-4}alkylamino, di-C_{1-4}alkylamino-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkoxy, C_{1-4}alkylamino-C_{1-4}alkoxy, di-C_{1-4}alkylamino-C_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkoxy-C_{1-4}alkyl, di-(C_{1-4}alkoxy-C_{1-4}alkyl)amino, di-(C_{1-4}alkoxy-C_{1-4}alkyl)amino-C_{1-4}alkyl, phenyl, phenoxy, benzyloxy C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, CHO, carboxy, C_{1-4}alkoxycarbonyl, morpholinomethyl, 4-C_{1-4}alkyl-piperazinylmethyl, piperazinylmethyl, tetrazol-1-ylmethyl, 1-pyrrolylmethyl, 3-(di-C_{1-4}-alkylamino)-2-hydroxy-propoxy-C_{1-4}alkyl, 3-(di-C_{1-4}-alkylamino)-2-hydroxy-propoxy, 3-C_{1-4}-alkylamino-2-hydroxy-propoxy-C_{1-4}alkyl, 3-C_{1-4}-alkylamino-2-hydroxy-propoxy, 2-hydroxy-3-imidazol-1-yl-

propoxy-C_{1-4}alkyl, 2-hydroxy-3-imidazol-1-yl-propoxy, 2-hydroxy-3-morpholin-4-yl-propoxy, 2-hydroxy-3-morpholin-4-yl-propoxy-C_{1-4}alkyl, and R_5 and R_6, independently, are hydrogen, halogen, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy, and

R_3 is hydrogen, halogen, C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkoxy, C_{1-4}alkylamino-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkoxy or C_{1-4}alkoxy,

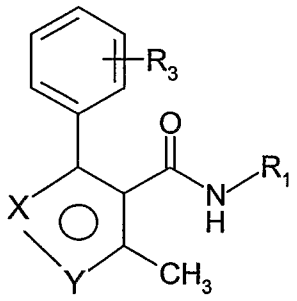
in free base or pharmaceutically acceptable acid addition salt form,

for use in the treatment of Parkinson's disease.

Any alkyl or alkoxy group as defined above preferably has one or two carbon atoms and more preferably is methyl or methoxy.

Halogen denotes fluorine, chlorine or bromine.

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the step of reacting a compound of formula II



II

wherein R_1 and R_3 are as defined above, with a compound of formula III

$$R_7 - R_2 \qquad \text{III}$$

wherein R_2 is as defined above and R_7 is CHO, CN, CO-Hal, wherein Hal is halogen, $CON(CH_3)$-OCH_3 or morpholinocarbonyl.

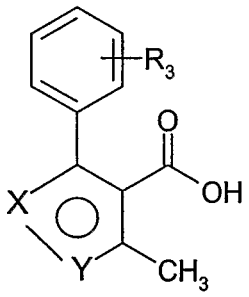
The reaction can be effected according to known methods, for example as described in Example 1b).

Compounds of formula I wherein R_2 is a group of formula (a) wherein R_4 is di-C_{1-4}alkylaminomethyl, C_{1-4}alkoxymethyl, di-C_{1-4}alkylamino-C_{2-4}alkoxymethyl, C_{1-4}alkoxy C_{2-4}alkoxymethyl, morpholinomethyl, piperazinylmethyl, 4-C_{1-4}alkylpiperazinylmethyl, tetrazol-1-ylmethyl or 1-pyrrolylmethyl, can also be produced from the corresponding compounds wherein R_4 is methyl, by bromination followed by nucleophilic substitution, according to conventional procedures, e.g. as described in Example 29.

Working up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

The starting compounds of formula II may be produced from carboxylic acids of formula IV



IV

wherein X, Y and R_3 are as defined above, according to known procedures, e.g. as described in Example 1a).

The starting materials of formulae III and IV are known or may be produced in analogous manner to known procedures.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties where tested in vitro using Nurr1 expressing cell cultures and in vivo, and are therefore useful as pharmaceuticals.

The nuclear receptor Nurr1 is known to be causally involved in the functional differentiation of midbrain dopaminergic neurones both during development and in adult animals. The defects of dopaminergic neurones observed in the ventral midbrain of Nurr1 knockout

animals resemble the pattern of neuronal degeneration in Parkinson's disease, in which the primary motor defects are caused by the degeneration of the substantia nigra dopaminergic system (Zetterström et al., 1997; Castillo et al., 1998 and Saucedo-Cardenas et al., 1998). Nurr1 activators are therefore suggested for preventing or delaying the onset of Parkinsonian symptoms.

The affinity of the agents of the invention to the Nurr1 receptor can be determined in vitro in binding studies:

Two-dimensional ^{1}H-^{15}N correlated spectra (HSQC) are recorded of uniformly ^{15}N-labeled ligand binding domain (LBD) of Nurr1 expressed in E. Coli. The spectra provide a fingerprint of the protein structure and changes in the exact positions of some of the cross peaks in the 2-d spectrum upon titration of a compound indicate ligand binding.

In this assay, changes in chemical shift are observed in some peaks at concentrations of 300 µM of the agent of the invention, using 50 µM uniformly ^{15}N-labeled Nurr1 LBD.

The activity of the agents of the invention at the Nurr1 receptor can be determined in vitro in cellular assays:

Induction of the biological activity of the Nurr1 receptor by the agents of the invention can be measured by the transactivation of a Nurr1 responsive reporter gene in a midbrain dopaminergic cell line. The assay is based on the transcription promoting effect of Nurr1. The reporter gene can be activated both by Nurr1 monomers and Nurr1/RXR heterodimers. RXR is a frequent heterodimerisation partner of nuclear receptors and it has been shown that Nurr1 can form heterodimers with RXR (Zetterström RH et al. Mol. Endocrinol. 1996; 10:1656-1666).

In this assay the agents of the invention significantly increase the reporter gene activity dose dependently at EC_{50}s of about 1 to about 1000nM.

In vivo, the agents of the invention significantly increase midbrain dopamine levels at doses of 5 to 30 mg/kg p.o. in the following assay:

OF1 mice are treated with the test compound for five days and sacrificed 5 hours after the last compound application. Dopamine levels are measured in substantia nigra and striatal tissue punches. 10 animals are treated in each group.

The agents of the invention are therefore useful in the treatment of Parkinson's disease.

For the above-mentioned indication, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 500, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agents of the invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The agents of the invention may alternatively be administered e.g. topically in the form of a cream, gel or the like, or by inhalation, e.g. in dry powder form.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of an agent of the invention. The composition may be buffered to a pH in the range of e.g. from 3.5 to 9.5, by a suitable buffer.

The agents of the invention can be administered either alone or in combination with other pharmaceutical agents effective in the treatment of Parkinson's disease.

Thus, the agents of the invention can be used for the treatment of Parkinson's disease in combination with, for example, dopamine precursors (e.g. different levodopa preparations), dopamine agonists (e.g. Bromocriptine, Pramipexole), catechol-O-methyltransferase inhibitors (e.g. Entacapone, Tolcapone), monoamine oxidase B inhibitors (e.g. Selegiline), NMDA antagonists (e.g. Amantadine) and anticholinergics (e.g. Biperiden, Orphenedrine).

In accordance with the foregoing, the present invention also provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of Parkinson's disease.

The preferred agents of the invention include 6-(4-dimethylaminomethyl-phenyl)-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one and 6-[4-(2-methoxy-ethoxymethyl)-phenyl]-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one, in free base or pharmaceutically acceptable acid addition salt form.

In the above-mentioned in vitro cellular assay, these compounds increase the reporter gene activity with EC_{50}s of 70 and 40nM respectively. In the above-mentioned in vivo test, they increase the dopamine levels by about 20-30% on administration of 5, 10 and 30 mg/kg p.o.

In still a further aspect, the invention provides compounds of formula I wherein X, Y, R_1, R_2 and R_3 are as defined above, provided that

i) when X is N, Y is O, R_2 is unsubstituted phenyl and R_3 is hydrogen, then R_1 is different from hydrogen, and

ii) when X is N, Y is O, R_2 is a group of formula (a) wherein either Z is N and R_4 is hydrogen, or Z is CH and R_4 is hydrogen, methyl, methoxy, halogen, trifluoromethyl, p-bromomethyl, p-benzyloxy, dimethylaminomethyl, methylaminomethyl, 4-C_{1-4}alkylpiperazinomethyl, piperidinomethyl or morpholinomethyl and R_3 is hydrogen, chlorine, fluorine, methyl, trifluoromethyl or C_{1-4}alkoxy, then R_1 is different from methyl,

hereinafter referred to as novel compounds of formula I.

The present invention furthermore provides a pharmaceutical composition comprising a novel compound of formula I in free base or pharmaceutically acceptable acid addition salt form, in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of the compound.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners according to the invention, can be prepared in a manner known per se and are thus suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

In particular, a therapeutically effective amount of each of the combination partners may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as fixed combination.

Accordingly the invention also provides a combination comprising a therapeutically effective amount of a novel compound of formula I in free base or pharmaceutically acceptable acid addition salt form and a second drug substance, said second drug substance being for example for use in Parkinson's disease.

Moreover the present invention provides the use of a novel compound of formula I in free base or pharmaceutically acceptable acid addition salt form, as pharmaceutical for the treatment of Parkinson's disease.

In still a further aspect the present invention provides a method for the treatment of Parkinson's disease in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a novel compound of formula I in free base or pharmaceutically acceptable acid addition salt form.

The following examples illustrate the invention.

Example 1:

5-Methyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one:

a) 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid methylamide:

To a suspension of 50.0 g (0.25 mol) of 5-methyl-3-phenyl-isoxazole-4-carboxylic acid in 1.2 l of 1,2-dichloroethane (DCE) is added 1.9 ml dimethyl formamide (DMF) and 21.4 ml (0.3 mol, 1.2 eq.) of thionyl chloride. The mixture is stirred for 2h at reflux until a clear, yellow solution is formed. The solution is cooled to room temperature and then slowly added to a 8M solution of methylamine in ethanol (146 ml) at 5 °C. The suspension is poured onto methylene chloride, washed with sat. $NaHCO_3$-solution, dried over Na_2SO_4 and concentrated. This yields 52.3 g (99%) of the title compound as light brown solid, which is used for further reaction without purification. Mass spectrum: m/z $(M+H)^+$: 217.1

b) 5-Methyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one

In a 500 ml flask, 10.0 g (46.3 mmol) of 5-methyl-3-phenyl-isoxazole-4-carboxylic acid methylamide is suspended in 150 ml of tetrahydrofuran (THF) under argon. At –70 °C a solution of butyl lithium (63 ml, 1.6M in hexane, 101 mmol, 2.2 eq.) is slowly added. After 1h at this temperature, the solution is warmed to –10 °C and a solution of 11.9 g (55.5 mmol, 1.2 eq.) of 4-(4-methyl-piperazin-1-ylmethyl)-benzonitrile in 80 ml of THF is slowly added. Under warming to room temperature, the red solution is stirred for another hour, then quenched with 2 ml of water and concentrated. The yellow residue is then taken up in 75 ml of dioxane and kept at 5 °C. Then, 230 ml of a 4M solution of HCl in dioxane is carefully added and the suspension stirred for 20h at room temperature. Then, the solvent is removed and the residue dissolved in ethyl acetate and carefully neutralised with sat. $NaHCO_3$-solution. The phases are separated and the organic phases washed with brine, dried over Na_2SO_4 and concentrated. Chromatographic purification (CH_2Cl_2/MeOH 95:5 to 90:10) yields 7.9 g (41%) of 5-methyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one as a white solid. Mass spectrum: m/z $(M+H)^+$: 415.0

According to the procedure described for Example 1, using the appropriate nitrile or Weinreb Amide, the following compounds are prepared:

Example 2:

6-Benzo[1,3]dioxol-5-yl-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzo[1,3]dioxole-5-carbonitrile in 56% as a light yellow solid. Mass spectrum: m/z $(M+H)^+$: 347.2

Example 3:

6-Biphenyl-4-yl-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using biphenyl-4-carbonitrile in 11% as a white foam. Mass spectrum: m/z $(M+H)^+$: 379.1

Example 4:

5-Methyl-3-phenyl-6-pyridin-4-yl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using isonicotinonitrile in 59% as a pink solid. Mass spectrum: m/z $(M+H)^+$: 304.1

Example 5:

6-(4-Diethylamino-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-diethylamino-benzonitrile in 11% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 374.1

Example 6:

5-Methyl-6-(4-phenoxy-phenyl)-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-phenoxy-benzonitrile in 44% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 395.0

Example 7:

6-[4-(2-Methoxy-ethoxymethyl)-phenyl]-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using N-Methoxy-4-(2-methoxy-ethoxymethyl)-N-methyl-benzamide in 58% as a white solid. Mass spectrum: m/z $(M+H)^+$: 391.2

Example 8:

5-Methyl-3-phenyl-6-(4-tetrazol-1-ylmethyl-phenyl)-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-tetrazol-1-ylmethyl-benzonitrile and after additional RP18-purification in 6% as a white solid. Mass spectrum: m/z $(M-N_2+H)^+$: 357.1

Example 9:

5-Methyl-3-phenyl-6-*p*-tolyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-methyl-benzonitrile in 56% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 317.1

Example 9a:

6-(3,4-Dimethoxy-phenyl)-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using 3,4-dimethoxy-benzonitrile in 11% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 363.1

Example 9b:

6-(3,5-Dimethoxy-phenyl)-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using 3,5-dimethoxy-benzonitrile in 25% as a yellow resin. Mass spectrum: m/z $(M+H)^+$: 363.1

According to the procedure described for Example 1, using acetylchloride instead of the nitrile, the following compound is prepared:

Example 10:

5,6-Dimethyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: Mass spectrum: m/z $(M+H)^+$: 241.2

According to the procedure described for example 1, using the appropriate nitrile or Weinreb Amide, 5-methyl-3-phenyl-isoxazole-4-carboxylic acid amide and 3.3 eq. of butyl lithium, the following compounds are prepared:

Example 11:

6-(4-Dimethylaminomethyl-phenyl)-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-dimethylaminomethyl-benzonitrile in 25% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 346.2

Example 12:

6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 4-(4-methyl-piperazin-1-ylmethyl)-benzonitrile in 13% as a solid. Mass spectrum: m/z $(M+H)^+$: 401.1

Example 13:

6-[4-(2-Methoxy-ethoxymethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using N-Methoxy-4-(2-methoxy-ethoxymethyl)-N-methyl-benzamide in 70% as a white solid. Mass spectrum: m/z $(M+H)^+$: 377.1

According to the procedure described for example 1, using the appropriate nitrile and 5-methyl-3-phenyl-isoxazole-4-carboxylic acid ethylamide, the following compounds are prepared:

Example 14:

5-Ethyl-6-(3-methoxy-phenyl)-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 3-methoxy-benzonitrile in 28% as a solid. Mass spectrum: m/z $(M+H)^+$: 347.2

Example 15:

6-Benzo[1,3]dioxol-5-yl-5-ethyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzo[1,3]dioxole-5-carbonitrile in 10% as a solid. Mass spectrum: m/z $(M+H)^+$: 361.2

According to the procedure described for example 1, using the appropriate nitrile and 5-methyl-3-phenyl-isoxazole-4-carboxylic acid propylamide, the following compound is prepared:

Example 16:

3,6-Diphenyl-5-propyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzonitrile in 49% as a solid. Mass spectrum: m/z $(M+H)^+$: 331.2

According to the procedure described for example 1, using the appropriate nitrile and 5-methyl-3-phenyl-isoxazole-4-carboxylic acid cyclopropylamide, the following compounds are prepared:

Example 17:

5-Cyclopropyl-3,6-diphenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzonitrile in 17% as a solid. Mass spectrum: m/z $(M+H)^+$: 329.2

Example 18:

6-Benzo[1,3]dioxol-5-yl-5-cyclopropyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzo[1,3]dioxole-5-carbonitrile in 12% as a solid. Mass spectrum: m/z $(M+H)^+$: 373.2

Example 19:

5-Methyl-3,6-diphenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one:

a) 3-Methyl-5-phenyl-isoxazole-4-carboxylic acid methylamide:

To a suspension of 6.0 g (29.6 mmol) of 3-methyl-5-phenyl-isoxazole-4-carboxylic acid in 150 ml DCE is added 0.3 ml of DMF and 2.6 ml (35.5 mmol, 1.2 eq.) of thionyl chloride. The mixture is stirred for 2h at reflux until a brown solution is formed. The solution is cooled to room temperature and then slowly added to a 8M solution of methylamine in ethanol (18 ml) at 5 °C. The suspension is poured onto methylene chloride, washed with sat. $NaHCO_3$-solution, dried over Na_2SO_4 and concentrated. This yields 6.7 g (quant.) of the title compound as brown solid, which is used for further reactions without purification. Mass spectrum: m/z $(M+H)^+$: 217.2

b) 5-Methyl-3,6-diphenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one:

159 mg (0.73 mmol) of 3-methyl-5-phenyl-isoxazole-4-carboxylic acid methylamide is suspended in 4 ml of THF under argon. At –5 °C a solution of butyl lithium (1.0 ml, 1.6M in hexane, 1.6 mmol, 2.2 eq.) is slowly added. After 1h at this temperature, the solution is warmed to 0 °C and 0.92 ml (0.88 mmol, 1.2 eq.) of benzonitrile is slowly added. Under warming to room temperature, the red solution is stirred for another 2h, then quenched with 0.1 ml of water and concentrated. The residue is then taken up in 4 ml of a 4M solution of HCl in dioxane and the suspension stirred for 16h at room temperature. Then, the solvent is removed and the residue dissolved in ethyl acetate and carefully neutralised with sat. $NaHCO_3$-solution. The phases are separated and the organic phases washed with brine, dried over Na_2SO_4 and concentrated. Chromatographic purification (hexane/ethyl acetate 90:10) yields 108 mg (48%) of 5-

methyl-3,6-diphenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one as a white solid. Mass spectrum: m/z $(M+H)^+$: 303.2

According to the procedure described for example 19, using the appropriate nitrile, the following compounds are prepared:

Example 20:

6-(4-Chloro-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one: This compound is obtained using 4-chloro-benzonitrile in 54% as a solid. Mass spectrum: m/z $(M+H)^+$: 337.2, 339.3

Example 21:

5-Methyl-6-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one: This compound is obtained using 4-(4-methyl-piperazin-1-ylmethyl)-benzonitrile in 8% as a solid. Mass spectrum: m/z $(M+H)^+$: 415.3

According to the procedure described for example 19, using the appropriate nitrile, 3-methyl-5-phenyl-isoxazole-4-carboxylic acid amide and 3.3 eq. of butyl lithium, the following compounds are prepared:

Example 22:

6-(4-Dimethylaminomethyl-phenyl)-3-phenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one: This compound is obtained using 4-dimethylaminomethyl-benzonitrile in 9% as a brown solid. Mass spectrum: m/z $(M+H)^+$: 346.2

Example 23:

6-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-3-phenyl-5*H*-isoxazolo[4,3-*c*]pyridin-4-one: This compound is obtained using 4-(4-Methyl-piperazin-1-ylmethyl)-benzonitrile in 9% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 401.2

Example 24:

6-(2,4-Dimethoxy-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: To a solution of 216 mg (1.0 mmol) of 5-methyl-3-phenyl-isoxazole-4-carboxylic acid methylamide in 5 ml of THF are slowly added 1.4 ml of butyl lithium (1.6M in hexane, 2.2

mmol, 2.2 eq.) at –40 °C. The orange suspension is stirred under warming to room temperature for 1h. Then, at 0 °C 300 mg (1.2 mmol, 1.2 eq.) of 2,4-dimethoxy-benzaldehyde is added and the mixture stirred for another hour under warming to room temperature. The mixture is quenched with 0.1 ml of water and the solvents are removed under reduced pressure. The residue is taken up in CH_2Cl_2, washed with sat. $NaHCO_3$-solution, dried over Na_2SO_4 and concentrated. Purification by flash chromatography yields 278 mg of a white foam.
This intermediate is dissolved in 5 ml of acetone, treated with 0.55 ml of Jones' reagent (1.1 mmol) and stirred at room temperature for 24h. The mixture is taken up in CH_2Cl_2 and the phases are separated, the aqueous phases is extracted 2 times with CH_2Cl_2, the combined organic phases washed with brine and dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue is then purified over silica gel (hexane/ethyl acetate 8:2 to 1:1) to yield 154 mg (43%) of the title compound as white solid. Mass spectrum: m/z $(M+H)^+$: 363.1

According to the procedure described for example 24, using the appropriate isoxazoles and aldehydes, the following compounds are prepared:

Example 25:
6-Cyclohexyl-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 5-methyl-3-phenyl-isoxazole-4-carboxylic acid methylamide and cyclohexanecarbaldehyde in 40% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 309.0

Example 25a:
6-(2,4-Dimethoxy-phenyl)-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using 5-methyl-3-phenyl-isoxazole-4-carboxylic acid methylamide and 2,4-dimethoxy-benzaldehyde in 42% as a white solid. Mass spectrum: m/z $(M+H)^+$: 363.1

Example 26:
4-(5-Methyl-4-oxo-3-phenyl-4,5-dihydro-isoxazolo[4,3-*c*]pyridin-6-yl)-benzoic acid methyl ester: This compound is obtained using 3-methyl-5-phenyl-isoxazole-4-carboxylic acid methylamide and 4-formyl-benzoic acid methyl ester in 15% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 361.2

Example 27:

6-Benzo[1,3]dioxol-5-yl-3-(2-chloro-phenyl)-5-methyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 3-(2-chloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid methylamide and benzo[1,3]dioxole-5-carbaldehyde in 35% as a beige solid. Mass spectrum: m/z $(M+H)^+$: 380.9, 382.9

Example 28:

6-Cyclohexyl-5-ethyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using 5-methyl-3-phenyl-isoxazole-4-carboxylic acid ethylamide and cyclohexanecarbaldehyde in 20% as a solid. Mass spectrum: m/z $(M+H)^+$: 323.3

Example 29:

5-Methyl-3-phenyl-6-(4-pyrrol-1-ylmethyl-phenyl)-5*H*-isoxazolo[4,5-*c*]pyridin-4-one:

a) 6-(4-Bromomethyl-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: At room temperature, 640 mg (2.0 mmol) of 5-methyl-3-phenyl-6-*p*-tolyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one is dissolved in 40 ml of CCl_4. After addition of 34 mg (0.2 mmol, 0.1 eq.) of azoisobutyronitrile, the reaction is heated to reflux and stirred for 16h. After cooling to room temperature, the suspension is taken up in CH_2Cl_2 and washed with 0.1M $NaHSO_3$-solution and sat. $NaHCO_3$-solution, dried over Na_2SO_4 and the solvent removed *in vacuo* to yield 1.1 g (crude, quant.) of a foam, which is used for further reaction without purification. Mass spectrum: m/z $(M+H)^+$: 394.9, 396.9

b) 5-Methyl-3-phenyl-6-(4-pyrrol-1-ylmethyl-phenyl)-5*H*-isoxazolo[4,5-*c*]pyridin-4-one:

To a solution of 198 mg (0.5 mmol) of 6-(4-bromomethyl-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one in 2.5 ml of DMF is added 326 mg (1.0 mmol, 2.0 eq.) of caesium carbonate and 0.05 ml (0,6 mmol, 1.2 eq.) of pyrrole. After stirring 16h at room temperature the solvent is removed *in vacuo* and the residue taken up in CH_2Cl_2. The organic phase is washed with $NaHCO_3$-solution, dried over Na_2SO_4 and concentrated. Flash chromatography yields 34 mg (18%) of the desired compound as a white solid. Mass spectrum: m/z $(M+H)^+$: 382.1

According to the procedure described for example 29, replacing pyrrole by the appropriate nucleophile, the following examples are prepared:

Example 30:

6-(4-Benzyloxymethyl-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using benzyl alcohol in 18% as a white solid. Mass spectrum: m/z $(M+H)^+$: 423.0

Example 31:

6-(4-Methoxymethyl-phenyl)-5-methyl-3-phenyl-5*H*-isoxazolo[4,5-*c*]pyridin-4-one: This compound is obtained using methanol in 27% as a white solid. Mass spectrum: m/z $(M+H)^+$: 347.3

Example 32:

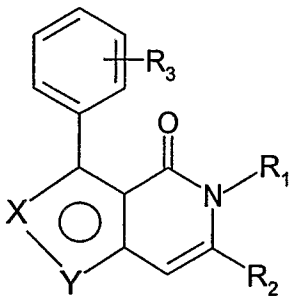
6-[4-(2-Hydroxy-ethoxymethyl)-phenyl]-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using 2-amino-ethanol in 20% as a white solid. Mass spectrum: m/z $(M+H)^+$: 404.1

Example 33:

6-[4-(2-Hydroxy-ethoxymethyl)-phenyl]-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one: This compound is obtained using ethane-1,2-diol and potassium hydroxide as base in 35% as a clear oil. Mass spectrum: m/z $(M+H)^+$: 377.1

CLAIMS

1. The use of a compound of formula I



I

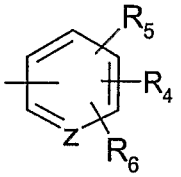
wherein

either X is O and Y is N

or X is N and Y is O,

R_1 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-4}alkyl or di C_{1-4}alkylamino-C_{1-4}alkyl,

R_2 is C_{1-4}alkyl, C_{3-7}cycloalkyl, benzo [1,3]dioxol-5-yl, benzo[1,2,5]oxadiazol-5-yl, benzo[1,2,5]thiadiazol-5-yl or a group of formula (a)



(a)

wherein Z is CH or N, R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen, hydroxy, trifluoromethyl, di-C_{1-4}alkylamino, C_{1-4}alkylamino, di-C_{1-4}alkylamino-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkoxy, C_{1-4}alkylamino-C_{1-4}alkoxy, di-C_{1-4}alkylamino-C_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkoxy-C_{1-4}alkyl, di-(C_{1-4}alkoxy-C_{1-4}alkyl)amino, di-(C_{1-4}alkoxy-C_{1-4}alkyl)amino-C_{1-4}alkyl, phenyl, phenoxy, benzyloxy C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkoxy-C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, CHO, carboxy, C_{1-4}alkoxycarbonyl, morpholinomethyl, 4-C_{1-4}alkyl-piperazinylmethyl, piperazinylmethyl, tetrazol-1-ylmethyl, 1-pyrrolylmethyl, 3-(di-C_{1-4}-alkylamino)-2-hydroxy-propoxy-C_{1-4}alkyl, 3-(di-C_{1-4}-alkylamino)-2-hydroxy- propoxy, 3-C_{1-4}-alkylamino-2-hydroxy-propoxy-C_{1-4}alkyl, 3-C_{1-4}-alkylamino-2-hydroxy-propoxy, 2-hydroxy-3-imidazol-1-yl-propoxy-C_{1-4}alkyl, 2-hydroxy-3-imidazol-1-yl-propoxy, 2-hydroxy-3-morpholin-4-yl-propoxy, 2-hydroxy-3-morpholin-4-yl-propoxy-C_{1-4}alkyl, and R_5 and R_6, independently, are hydrogen, halogen, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy, and

R_3 is hydrogen, halogen, C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkyl, di-C_{1-4}alkylamino-C_{1-4}alkoxy, C_{1-4}alkylamino-C_{1-4}alkyl, C_{1-4}alkylamino-C_{1-4}alkoxy or C_{1-4}alkoxy,

in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of Parkinson's disease.

2. A compound of formula I wherein X, Y, R_1, R_2 and R_3 are as defined in claim 1 provided that,

i) when X is N, Y is O, R_2 is unsubstituted phenyl and R_3 is hydrogen, then R_1 is different from hydrogen, and

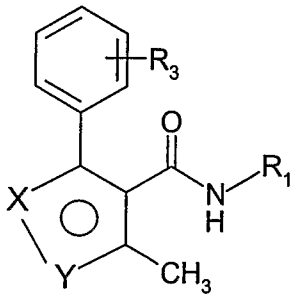
ii) when X is N, Y is O, R_2 is a group of formula (a) wherein either Z is N and R_4 is hydrogen, or Z is CH and R_4 is hydrogen, methyl, methoxy, halogen, trifluoromethyl, p-bromomethyl, p-benzyloxy, dimethylaminomethyl, methylaminomethyl, 4-C_{1-4}alkylpiperazinomethyl, piperidinomethyl or morpholinomethyl and R_3 is hydrogen, chlorine, fluorine, methyl, trifluoromethyl or C_{1-4}alkoxy, then R_1 is different from methyl,

in free base or acid addition salt form.

3. 6-(4-Dimethylaminomethyl-phenyl)-3-phenyl-5H-isoxazolo[4,5-c]pyridine-4-one in free base or acid addition salt form.

4. 6-[4-(2-Methoxy-ethoxymethyl)-phenyl]-5-methyl-3-phenyl-5H-isoxazolo[4,5-c]pyridin-4-one in free base or acid addition salt form.

5. A process for the preparation of a compound of formula I as defined in claim 2 or a salt thereof, comprising the step of reacting a compound of formula II



II

wherein R_1 and R_3 are as defined in claim 2, with a compound of formula III

R_7-R_2 III

wherein R_2 is as defined in claim 2 and R_7 is CHO, CN, CO-Hal, wherein Hal is halogen, $CON(CH_3)$-OCH_3 or morpholinocarbonyl, and recovering the resulting compound in free base or acid addition salt form.

6. A compound of claim 2 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

7. A pharmaceutical composition comprising a compound of claim 2 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

8. A combination comprising a therapeutically effective amount of a compound of claim 2 in free base of pharmaceutically acceptable acid addition salt form, and a second drug substance, for simultaneous or sequential administration.

9. The use of a compound of claim 2 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of Parkinson's disease.

10. A method for the treatment of Parkinson's disease in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 2 in free base or pharmaceutically acceptable acid addition salt form.