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(73) Patenthaver: Imphar Aktiengesellschaft, Fontanestrasse 84 - 90, 15366 Neuenhagen bei Berlin, Tyskland

(72) Opfinder: Ailken, Rudolf-Giesbert, Sjödalavägen 85, S-23335 Sjödala Gard, Sverige

(74) Fuldmægtig i Danmark: RWS Group, Europa House, Chiltem Park, Chiltem Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien

(54) Benævnelse: Deutererede catecholamininderivater og medikamenter, der omfatter disse forbindelser

(56) Fremdragne publikationer:
WO-A-2004/056306
DE-A1- 10 261 807
Edwards, Rizk: "Conversion of 3,4-dihydroxyphenylalanine and deuterated 3,4-dihydroxyphenylalanine to alcoholic metabolites of catecholamines in rat brain" JOURNAL OF NEUROCHEMISTRY, vol. 36, 1981, pages 1641-1647, XP009086843
Dewar, Dyck, Durden, Boulton: "Changes in brain catecholamine levels following DL-dopa are not potentiated by deuterium substitution" PROG. NEURO-PHYSIOPHARMACOL. & BIOL. PSYCHIAT., vol. 9, 1985, pages 675-680, XP000443264
[0001] The invention concerns the use of deuterated catecholamine derivatives as medicaments as well as pharmaceuticals containing these compounds.

[0002] Known representatives of catecholamines, such as L-dopa (levodopa) as well as their carboxylic acid esters, are utilized, among other things, for the treatment of Parkinson’s disease and restless leg syndrome. Such a pharmaceutical which contains levodopa is, for example, Dopaflex®. L-dopa acts on the dopamine concentration in neurons of the brain. Unlike dopamine itself, it can pass through the blood-brain barrier and is converted to dopamine in the brain.

[0003] In addition, levodopa is administered in combination with active additives in pharmaceuticals. Combinations of levodopa are used with peripheral decarboxylase inhibitors, with inhibitors of the enzyme catechol-O-methyltransferase (COMT), with inhibitors of the enzyme monoamine oxidase (MAO) and with dopamine β-hydroxylase inhibitors.

[0004] In this connection, the decarboxylase inhibitors used are, for example: D.L-serine 2-(2,3,4-trihydroxybenzyl) hydrazide (benserazide), (+)-L-α-hydrazino-3,4-dihydroxy-o-methylnorcamphimic acid (carbidopa), L-serine-2-(2,3,4-trihydroxybenzyl) hydrazide, glycine-2-(2,3,4-trihydroxybenzyl) hydrazide and L-tyrosine-2-(2,3,4-trihydroxybenzyl) hydrazide. Examples of combination preparations of levodopa and decarboxylase inhibitors include, among others: Madopar® (levodopa and benserazide hydrochloride) as well as Nacomet® (levodopa and carbidopa).

[0005] Examples of COMT inhibitors are entacapone (Comtan®) and cabergoline and frequently used MAO inhibitors are seleqoline hydrochloride, moclobemide and tranylcypromine.

[0006] Calcium 5-butyl picolinate and calcium 5-pentyl picolinate are described as inhibitors for dopamine-β-hydroxylase (DE 2,049,115).

[0007] WO-A 2004/058724 discloses deuterated catecholamine having two deuterium atoms in the β-position. These compounds exhibit improved pharmacokinetic and/or pharmacodynamic properties with respect to undeuterated compounds and as compared to L-DOPA.

[0008] An object of the present invention is to use deuterated catecholamine derivatives, which have improved pharmacokinetic and/or pharmacodynamic properties when compared to compounds already known, as well as to prepare catecholamine derivatives, which can be utilized for the prophylaxis of psychoses including schizophrenia, and which can be used for producing pharmaceuticals for the prophylaxis of psychoses.

[0009] It has been surprisingly found that the deuterated catecholamine derivatives according to the invention have substantially better pharmacokinetic and/or pharmacodynamic properties than the undeuterated compounds and the β,β-di-deuterated compounds known in the art and that they can also be utilized for the prophylaxis of psychoses and can be used for producing pharmaceuticals for the prophylaxis of psychoses.

[0010] According to the invention, the object is thus solved by using compounds of general formula I:

\[
\begin{align*}
\text{Formula I} \\
\text{wherein} \\
R^1 \text{ is } H, \\
R^2 \text{ indicates D,}
\end{align*}
\]
R^3 is H,

R^4 indicates H,

R^5 is H, and

one of R^6 is H and the other R^6 is D,

as well as their physiologically acceptable salts and their stereoisomers, enantiomers or diastereomers in optically pure form as a medicament.

[0011] Preferred are deuterated catecholamine derivatives according to formula 1, namely L/R-2-amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid, and L/S-2-amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid.

[0012] An embodiment of the invention is the use of the deuterated catecholamine derivatives as well as physiologically acceptable salts thereof for the treatment of dopamine deficiency diseases or diseases which are based on disrupted tyrosine transport or disrupted tyrosine decarboxylase, such as Parkinson's disease, restless leg syndrome, dystonia, for the inhibition of prolactin secretion, for the stimulation of the release of growth hormone, for the treatment of neurological symptoms of chronic manganese intoxications, of amyotrophic lateral sclerosis and of multiple system atrophy.

[0013] Preferred is the use of deuterated catecholamine derivatives as well as physiologically acceptable salts thereof, in combination with an enzyme inhibitor or several enzyme inhibitors, for the treatment of dopamine deficiency diseases or diseases which are based on disrupted tyrosine transport or disrupted tyrosine decarboxylase, such as Parkinson's disease, restless leg syndrome, dystonia, for the inhibition of prolactin secretion, for stimulating the release of growth hormone, for the treatment of neurological symptoms of chronic manganese intoxications, of amyotrophic lateral sclerosis and of multiple system atrophy.

[0014] It is advantageous if the enzyme inhibitor or the enzyme inhibitors involve decarboxylase inhibitors and/or catechol-O-methyltransferase inhibitors and/or monoamine oxidase inhibitors and/or β-hydroxylase inhibitors.

[0015] It is particularly advantageous if the decarboxylase inhibitor is selected from the group consisting of the following: D,L-serine 2-(2,3,4-trihydroxybenzyl) hydrazide (benserazide), (L)-L-α-hydrazino-3,4-dihydroxy-α-methylhydroxynamic acid (carbidopa), L-serine 2-(2,3,4-trihydroxybenzyl) hydrazide, glycine 2-(2,3,4-trihydroxybenzyl) hydrazide and L-tyrosine 2-(2,3,4-trihydroxybenzyl) hydrazide as well as physiologically acceptable salts thereof.

[0016] In particular, it is also advantageous if the catechol-O-methyltransferase inhibitor is selected from entacapone and cabergoline as well as physiologically acceptable salts thereof.

[0017] It is also preferred if the monoamine oxidase inhibitor is selected from the group consisting of selegiline, moclobemide and tranylcypromine, as well as physiologically acceptable salts thereof.

[0018] In addition, it is particularly preferred if the β-hydroxylase inhibitor is selected from calcium 5-butyl picolinate and calcium 5-pentyl picolinate as well as physiologically acceptable salts thereof.

[0019] Another subject of the invention is the use of the deuterated catecholamines according to the invention as well as physiologically acceptable salts thereof for the production of pharmaceuticals for the treatment of dopamine deficiency diseases or diseases which are based on disrupted tyrosine transport or disrupted tyrosine decarboxylase, such as Parkinson's disease, restless leg syndrome, dystonia, for the inhibition of prolactin secretion, for stimulating the release of growth hormone, for the treatment of neurological symptoms of chronic manganese intoxications, of amyotrophic lateral sclerosis and of multiple system atrophy.

[0020] Another subject of the present invention is a pharmaceutical composition which contains the deuterated catecholamines according to the invention as well as their physiologically acceptable salts for the treatment of dopamine deficiency diseases or diseases which are based on disrupted tyrosine transport or disrupted tyrosine decarboxylase, such as Parkinson's disease, restless leg syndrome, dystonia, for the inhibition of prolactin secretion, for stimulating the release of growth hormone, for the treatment of neurological symptoms of chronic manganese intoxications, of amyotrophic lateral sclerosis and of multiple system atrophy, in addition to pharmaceutically acceptable adjuvants and additives.

[0021] Particularly advantageous is a pharmaceutical composition which contains the deuterated catecholamines according to
the invention as well as physiologically acceptable salts thereof for the treatment of Parkinson’s disease, restless leg syndrome, dystonia, for the inhibition of prolactin secretion, for stimulating of the release of growth hormone, for the treatment of neurological symptoms of chronic manganese intoxications, of amyotrophic lateral sclerosis and of multiple system atrophy, as well as one or more enzyme inhibitors, in addition to pharmaceutically acceptable adjuvants and additives.

[0022] A pharmaceutical composition is particularly preferred in which the enzyme inhibitor or the enzyme inhibitors involve decarboxylase inhibitors and/or catechol-O-methyltransferase inhibitors and/or monoamine oxidase inhibitors and/or \( \beta \)-hydroxylase inhibitors.

[0023] Additionally preferred is a pharmaceutical composition in which the decarboxylase inhibitor is selected from the group consisting of D,L-serine 2-(2,3,4-trihydroxybenzyl) hydrazide (benzerazide), 2-(3,4-dihydroxy-alpha-methylhydrocinnamic acid (carbidopa), L-serine 2-(2,3,4-trihydroxybenzyl) hydrazide, glycine 2-(2,3,4-trihydroxybenzyl) hydrazide and L-tyrosine 2-(2,3,4-trihydroxybenzyl) hydrazide as well as physiologically acceptable salts thereof.

[0024] Particularly advantageous is a pharmaceutical composition in which the catechol-O-methyltransferase inhibitor is selected from entacapone and cabergoline as well as their physiologically acceptable salts.

[0025] Additionally advantageous is a pharmaceutical composition in which the monoamine oxidase inhibitor is selected from the group consisting of selegiline, moclobemide and tranylcypromine as well as physiologically acceptable salts thereof.

[0026] In addition, a pharmaceutical composition is preferred in which the \( \beta \)-hydroxylase inhibitor is selected from calcium 5-butyl picolinate and calcium 5-pentyl picolinate as well as physiologically acceptable salts thereof.

[0027] The production of the compounds used according to the invention is known to one skilled in the art. Analogous production methods are used as described, for example, in DE-A 102 61 807.

[0028] For the production of the physiologically acceptable salts of the deuterated catecholamine derivatives used according to the invention, the usual physiologically acceptable inorganic and organic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, malic acid, citric acid, salicylic acid, adipic acid and benzoic acid can be used. Additional acids that can be used are described, for example, in Fortschritte der Arzneimittelforschung, Vol. 10, pp. 224-225, Birkhauser Publishers, Basel and Stuttgart, 1968, and Journal of Pharmaceutical Sciences, Vol. 66, pp. 1-5 (1977).

[0029] The acid addition salts are usually obtained in a way known in and of itself by mixing the free base or solutions thereof with the corresponding acid or solutions thereof in an organic solvent, for example, a lower alcohol, such as methanol, ethanol, n-propanol or isopropanol or a lower ketone such as acetone, methyl ethyl ketone or methyl isobutyl ketone or an ether such as diethyl ether, tetrahydrofuran or dioxane. For better crystal precipitation, mixtures of the named solvents can also be used. In addition, physiologically acceptable aqueous solutions of acid addition salts of the compounds used according to the invention can be produced therefrom in an aqueous acid solution.

[0030] The acid addition salts of the compounds according to the invention can be converted to the free base in a way known in and of itself, e.g., with alkalis or ion exchangers. Additional salts can be obtained from the free base by reaction with inorganic or organic acids, particularly those which are suitable for the formation of salts that can be employed therapeutically. These or also other salts of the new compound, such as, e.g., the pircate, may also serve for purification of the free base by converting the free base into a salt, separating this salt, and again releasing the base from the salt.

[0031] The subject of the present invention is also pharmaceuticals for oral, buccal, sublingual, nasal, rectal, subcutaneous, intravenous or intramuscular application as well as for inhalation, which, in addition to the usual vehicle and dilution agents, also contain a compound of general formula I or the acid addition salt thereof as an active ingredient.

[0032] The pharmaceuticals of the invention are produced, in the known way and with suitable dosage, with the usual solid or liquid vehicle substances or dilution agents and the usually used pharmaceutical-technical adjuvants corresponding to the desired type of application. The preferred preparations consist of a form of administration which is suitable for oral application. Such forms of administration include, for example, tablets, sucking tablets, film tablets, dragees, capsules, pills, powders, solutions, aerosols or suspensions or slow-release forms.

[0033] Of course, parenteral preparations such as injection solutions are also considered. In addition, suppositories, for example, have also been named as preparations. Corresponding tablets can be obtained, for example, by mixing the active
substance with known adjuvants, for example, inert dilution agents such as dextrose, sugar, sorbitol, mannitol, polyvinylpyrrolidone, bursting agents such as corn starch or alginic acid, binders such as starches or gelatins, lubricants such as magnesium stearate or talc and/or agents for achieving a slow-release effect such as carboxypolymethylene, carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also consist of several layers.

[0034] Dragées can also be produced correspondingly, for controlled or delayed release forms of preparation, by coating the cores produced analogously to the tablets with agents commonly used in dragée coatings, for example, polyvinylpyrrolidone or shellac, gum arabic, talc, titanium dioxide or sugar. The dragée envelope may also consist of several layers, wherein the adjuvants mentioned above in the case of tablets can be used.

[0035] Solutions or suspensions containing the active substance used according to the invention may additionally contain agents that improve taste, such as saccharin, cyclamate or sugar, as well as, e.g., taste enhancers such as vanilla or orange extract. They may also contain suspension adjuvants such as sodium carboxymethylcellulose or preservatives such as p-hydroxybenzoate. Capsules containing active substances can be produced, for example, by mixing the active substance with an inert vehicle such as lactose or sorbitol and encapsulating this mixture in gelatin capsules. Suitable suppositories can be produced, for example, by mixing with vehicle agents provided therefore, such as neutral fats or polyethylene glycol or derivatives thereof.


[0037] As known from WO-A 2004/055724, L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid is a selectively deuterated L-DOPA derivative with better pharmacokinetic and pharmacodynamic properties when compared to L-DOPA. Administration of L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid to male Wistar rats increased dopamine in the striatum significantly more compared to non-deuterated L-DOPA.

[0038] It has been surprisingly found that L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid increased dopamine in the striatum significantly more than L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid, although the compound has less deuterium at the beta position of the side chain of its molecule (Example 2 and Table 1).

[0039] Furthermore, whereas L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid reduces the striatal output of norepinephrine compared to L-DOPA, L-2-Amino-2,3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid does not block the formation of norepinephrine.

[0040] Therefore, L-2-Amino-2,3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid has two advantages, it provides more dopamine and enough norepinephrine which has been shown to play an important role in compensating for the loss in dopaminergic function (Archer and Fredriksson, 2006, Neural Transm., 113(9): 1119-29; Cathala et al. 2002, Neuroscience, 115(4): 1059-65; Tong et al. 2006, Arch Neurol, 63(12): 1724-8).

[0041] The highly soluble L-DOPA methyl ester has been shown to function as a prodrug of L-DOPA. In animal experiments, L-DOPA methyl ester given orally or intraperitoneally was equivalent on a molar basis to L-DOPA. However, therapeutic equivalence was not maintained with continuous intravenous infusion in Patients with Parkinson's disease exhibiting severe on-off phenomena. The optimal infusion rate for L-DOPA methyl ester was 2.7 times that required for L-DOPA ( Stocchi et al. 1992, Movement Disorders, 7: 249-256). Surprisingly, L-2-Amino-2,3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid methyl ester is therapeutically equivalent to L-2-Amino-2,3,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid during continuous intravenous infusion.

[0042] The following examples are given to explain the present invention.

Example 1

L-2-Amino-2,3(S)-dideutero-3-(3,4-dihydroxyphenyl) propionic acid
[0043] 2.5 g of N-acetyl-3-methoxy-4-acetoxy cinnamic acid are dissolved in 30 mL methanol containing 0.027 g sodium hydroxide and placed into an autoclave. The oxygen is replaced by nitrogen before the reactor is filled with deuterium gas. At the same time 0.5 g of Monsanto catalyst are prepared in 2.5 mL toluene by treating with deuterium gas. After addition of the catalyst to the autoclave, the "hydrogenation" is started at 60°C and 4-5 bar. After 4 hours, the excess of deuterium gas is removed and the solvent is distilled off. The sodium salt of the deuterated product is isolated and recrystallized.

Yield: 2.4 g (94%)

0.9 g of the sodium salt are dissolved in 2.5 mL of hydrobromic acid (23%) and heated to reflux at about 105-110°C. Afterwards, the reaction mixture is cooled to 25-30°C and the pH is adjusted to 3 by addition of concentrated sodium hydroxide solution to start the precipitation of L-2-Amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid. The precipitate is washed with cold water and recrystallized in hot water under protective gas. After recrystallization, 0.51 g of the product are isolated.

Yield: 85.1%

Melting point: 286-299°C

C₈H₇NO₄D₂: calc. C 54.27 %; H 4.55 %; N 7.03 %; O 32.13 %; D 2.02 % found C 54.15 %; H 6.50 %; N 7.08 %

[1H-NMR (400 MHz, d6-DMSO): 6.59 (d, 1H); 6.54 (s, 1H); 6.48 (d, 1H); 2.74 (m, 1H)

Example 2

Striatal dopamine output measured by microdialysis

[0044] The striatal output of dopamine was measured in Male Wistar rats following intraperitoneal administration of 50 mg/kg L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA), L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid (WOA 2004/056724, Example 6) and L-2-Amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (Example 1), respectively. Male wistar rats (BK Universal, Sollentuna, Sweden) weighing about 300 g at the time of experiment were anaesthetized with a cocktail containing fentanyl citrate (0.39 mg/kg) and sufentanil (12.5 mg/kg, Hypnorm®, Janssen-Cilag) and midazolam (6.25 mg/kg, Dormicum®, Roche) diluted in distilled water (1:1:2; 5 ml/kg i.p.) and mounted in a stereotaxic frame. Dialysis probes were implanted in the dorsolateral striatum (AP +0.6; ML +3.0; DV -6.2 relative to bregma and the dural surface according to the atlas of Paxinos and Watson (1998)). Dialysis occurs through a semipermeable membrane (Filmal AN69, Hospal Industrie, France) with an active surface length of 3.5 mm. Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. The rats received 30 min before administration of test items 10 mg/kg Carbicapa, (i.p.). The dialysis probe was perfused with a physiological perfusion solution (Apoteksbolaget, Sweden) at a rate of 2.5ml/min set by a microinfusion pump (Harvard Apparatus, Holliston, MA). Dialysate was collected over 15 min intervals and automatically injected into a high performance liquid chromatography (HPLC) system. On-line quantification of dopamine in the dialysate was accomplished by electrochemical detection (ESA, Chelmsford, MA). The location of microdialysis probes was verified in slices of formalin-fixed tissue stained with neutral red. The baseline corrected concentrations (fmol/min) were plotted over the time.

[0045] Comparison of AUC₀₄ (area under the curve) values revealed that the increase of dopamine in the striatum following administration of 50 mg/kg L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid was about twice as high compared to L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid (L-DOPA) as displayed in Table 1. The increase of striatal dopamine following administration of 50 mg/kg L-2-Amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (Example 1) was even threefold higher than that measured after administration of L-DOPA.

<table>
<thead>
<tr>
<th>Baseline corrected dopamine output in the striatum</th>
<th>AUC₀₄ [fmol/min*min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-2-Amino-3-(3,4-dihydroxyphenyl) propionic acid</td>
<td>228</td>
</tr>
<tr>
<td>L-2-Amino-2,3,3-trideutero-3-(3,4-dihydroxyphenyl) propionic acid</td>
<td>533</td>
</tr>
<tr>
<td>L-2-Amino-2,3-dideutero-3-(3,4-dihydroxyphenyl) propionic acid (Ex. 1)</td>
<td>685</td>
</tr>
</tbody>
</table>

REFERENCES CITED IN THE DESCRIPTION
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**Patent documents cited in the description**

- DE20494115 [0006]
- WO2004056724A [0007] [0037] [0044]
- DE19261907A [0027]

**Non-patent literature cited in the description**

- Fortschritte der ArzneimittelforchungBirkhauser Publishers19660000vol. 10, 224-225 [0028]
- LIST et al.Arzneiformenlehre [Instructions for Drug FormsVerlagges19850000 [0036]
- SUCKER et al.Pharmaceutische Technologie [Pharmaceutical TechnologyThieme 19900000 [0036]
- VOIGTPharmaceutische Technologie [Pharmaceutical TechnologyUllstein Mosby19950000 [0036]
Patentkrav

1. L-2-amino-2,3-dideutero-3-(3,4-dihydroxyphenyl)-propionsyre og stereoisomerer, enantiomerer eller diastereomerer i optisk ren form samt fysiologisk acceptable salte deraf til anvendelse som et medikament.

2. L-2-amino-2,3-dideutero-3-(3,4-dihydroxyphenyl)-propionsyre og stereoisomerer, enantiomerer eller diastereomerer i optisk ren form samt fysiologisk acceptable salte deraf til anvendelse til behandling af Parkinsons sygdom, restless legs-syndrom, dystoni, til hæmning af prolactinsekretion, til stimulering af frigørelse af væksthormon, til behandling af neurologiske symptomer på kroniske mangangiftninger, på amyotrofisk lateral sklerose og af multipel system atrofi.

3. Forbindelse til anvendelse ifølge krav 2 i kombination med en enzymhæmmer eller adskillige enzymhæmmere, der er udvalgt fra gruppen, der består af D,L-serin-2-(2,3,4-trihydroxybenzyl)-hydrazid (benzerazid), (-)-L-α-hydrazino-3,4-dihydroxy-α-methylhydrokanelsyre (carbidopa), L-serin-2(2,3,4-trihydroxybenzyl)-hydrazid, glycine-2-(2,3,4-trihydroxybenzyl)-hydrazid og L-tyrosin-2-(2,3,4-trihydroxybenzyl)-hydrazid, entacapon, cabergolin, selegilin, moclobemid, tranylcypromin, calcium-5-butilpicolinat og calcium-5-pentylpicolinat samt fysiologisk acceptable salte deraf.

4. Farmaceutisk sammensætning, der omfatter L-2-amino-2,3-dideutero-3-(3,4-dihydroxyphenyl)-propionsyre og stereoisomerer, enantiomerer eller diastereomerer i optisk ren form samt fysiologisk acceptable salte deraf foruden farmaceutisk acceptable adjuvanser og additiver.

5. Farmaceutisk sammensætning ifølge krav 4, der yderligere omfatter en enzymhæmmer eller adskillige enzymhæmmere, der er udvalgt fra gruppen, der består af D,L-serin-2-(2,3,4-
trihydroxybenzyl)-hydrazid (benserazid), (-)-L-α-hydrazino-3,4-dihydroxy-α-methylhydrokanelisyre (carbidopa), L-serin-2-(2,3,4-trihydroxybenzyl)-hydrazid, glycine2-(2,3,4-trihydroxybenzyl)-hydrazid og L-tyrosin-2-(2,3,4-trihydroxybenzyl)-hydrazid, entacapon, cabergolin, selegilin, moclobemid, tranylcypromin, calcium-5-butylpicolinat og calcium-5-pentylpicolinat samt fysiologisk acceptable salte deraf.