

Figure 2: PK profiles in Wistar rats obtained after oral dosing according to Example 4.

Profiles are based on mean plasma concentrations from 3 subjects for each compound.

X-axis: time (hours); Y-axis: plasma concentration of Compound (I) (pg/mL) obtained after dosing of the following compounds : ● : compound (Ia) ▲ : compound (Ib); ◆ : compound (Id-ia); X: compound (Id-ib); ▲ : compound (Id-ia); + : compound (Id-iib), X: compound (Id-iab) and ◆ : compound (Id-iib).

Figures 3 and 4: Locomotor activity time-course (Figure 3) and total distance travelled

(Figure 4) following treatment with vehicle (H₂O, p.o.), or compound (Id-ia) (10, 30, 100 or 300 µg/kg, p.o.) and compared to standard-of-care (SoC) treatments: apomorphine (APO, 3 mg/kg, s.c.), pramipexole (PPX, 0.3 mg/kg, s.c.). Animals were dosed at t=60 minutes after a 60-min. habituation period in test chambers, and activity was monitored for 350 minutes thereafter. Data was evaluated by use of a Kruskal-Wallis test with Dunn's Multiple Comparisons test, resulting in an overall P-value of <0.0001.

Figure 3: X-axis: time (min); Y-axis: Distance travelled (cm) ± SEM/5-minute-bins

Figure 4: Y-axis: Total distance travelled (cm) ± SEM. Significance levels for post-hoc comparisons (relative to the vehicle group) are indicated: *<0.05, **<0.01, ***<0.001, ****<0.0001.

Figures 5 and 6: Relationships between plasma concentrations of compound (Id-ia) and compound (I) and hyperactivity induced by compound (Id-ia) (100 µg/kg, p.o.) (Figure 5) and the corresponding relationship between plasma apomorphine concentrations and hyperactivity induced by apomorphine (3 mg/kg, s.c.) (Figure 6).

X-axis time (min); Y-axis left: Distance travelled (cm) ± SEM/5-minute-bins; Y-axis right (figure 5): plasma concentration of compound (I) (pg/mL); Y axis right (figure 6): plasma concentration of apomorphine (ng/mL).

□: Distance travelled (cm) ● plasmaconcentration.

Figure 7: conversion of compounds (Id-ia), (Id-ib), (Id-ia), (Id-iib) and (Id-iab) to compound (I) in rat (7a) and human (7b) hepatocytes.

X-axis time (min); Y-axis: concentration of compound (I) (pg/mL).

E39. The compound or pharmaceutically acceptable salt thereof according to any of embodiments 1-23, for use in the treatment according to any of embodiments 34-38, wherein said compound is comprised in an oral pharmaceutical composition such as a tablet or a capsule for oral administration.

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E40. A method for the treatment of a neurodegenerative disease or disorder such as Parkinson's Disease, Huntington's disease, Restless leg syndrome or Alzheimer's disease; or a neuropsychiatric disease or disorder such as schizophrenia, attention deficit hyperactivity disorder or drug addiction; which method comprises the administration of a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof according to any of embodiments 1-23, to a patient in need thereof.

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E41. The method according to embodiment 40, wherein said neurodegenerative disease or disorder is Parkinson's Disease.

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E42. The method according to any of embodiments 40-41, wherein said compound or pharmaceutically acceptable salt thereof according to any of embodiments 1-23, is used in combination with another agent which is useful in the treatment of a neurodegenerative disease or disorder such as Parkinson's disease.

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E43. The method according to any of embodiments 40-41, wherein said compound or pharmaceutically acceptable salt thereof according to any of embodiments 1-23, is used in combination with a compound selected from the group consisting of L-DOPA, a MAO-B inhibitor such as selegiline or rasagiline, a COMT inhibitor such as entacapone or tolcapone, an adenosine 2a antagonist such as istradefylline, an antiglutamatergic agent such as amantadine or memantine, an acetylcholinesterase inhibitor such as rivastigmine, donepezil or galantamine, an antipsychotic agent such as quetiapine, clozapine, risperidone, pimavanserin, olanzapine, haloperidol, aripiprazole or brexpiprazole; or in combination with an antibody targeting alpha-synuclein, Tau or A-beta protein.

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The present invention includes all modifications and equivalents of the subject-matter recited in the claims appended hereto, as permitted by applicable law.

COMPOUNDS OF THE INVENTION

5 *Table 1: Exemplified compounds of the invention*

Example	Compound
(Id-ia)	(2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(((4aR,10aR)-7-hydroxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-6-yl)oxy)tetrahydro-2H-pyran-2-carboxylic acid
(Id-ib)	(2S,3S,4S,5R,6S)-3,4,5-trihydroxy-6-(((4aR,10aR)-6-hydroxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-7-yl)oxy)tetrahydro-2H-pyran-2-carboxylic acid
(Id-iaa)	(4aR,10aR)-7-hydroxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-6-yl hydrogen sulfate
(Id-iib)	(4aR,10aR)-6-hydroxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinolin-7-yl hydrogen sulfate
(Id-iab)	(2S,2'S,3S,3'S,4S,4'S,5R,5'R,6S,6'S)-6,6'-(((4aR,10aR)-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-6,7-diyl)bis(oxy))bis(3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid)
(Id-iiab)	(4aR,10aR)-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline-6,7-diyl bis(hydrogen sulfate)

EXPERIMENTAL SECTION

Preparation of the compounds of the invention

The compounds of formula (Id) may be prepared by methods described below,
 10 together with synthetic methods known in the art of organic chemistry, or modifications that are familiar to those of ordinary skill in the art. The starting materials used herein are available commercially or may be prepared by routine methods known in the art, such as those methods described in standard reference books such as "Compendium of Organic Synthetic Methods, Vol. I-XII" (published with Wiley-Interscience). Preferred methods
 15 include, but are not limited to, those described below.

13.10 min 2 % B

18.00 min 2 % B

Total run time: 18 min

- 5 Method 222: LC-MS were run on a Shimadzu LCMS-2020 consisting of PDA detector operating at 190-800 nM and MS equipped with ESI source operating in positive mode.

LC-conditions: The column was Phenomenex Kinetex EVO C18 2.6 μ m; 2.1x100 mm operating at 25°C with 0.5 ml/min of a gradient consisting of water + 0.1 % formic acid (A) and acetonitrile (B).

- 10 Gradient:

0.00 min 2 % B

1.00 min 2% B

10.00 min 90 % B

13.00 min 90 % B

- 15 13.10 min 2 % B

18.00 min 2 % B

Total run time: 18 min

Preparative LCMS was performed using the method identified below.

- 20 Waters AutoPurification system using combined mass/UV detection.

Column: Sunfire 30x100 mm, 5 μ m particles. Operating at 40°C with 90 ml/min of a binary gradient consisting of water + 0.05 % trifluoroacetic acid (A) and acetonitrile/water (3:5) + 0.05 % trifluoroacetic acid.

Gradient:

- 25 0.00 min 98% A

5.00 min 50% A

5.50 min 98% A

6.00 min 98% A

room temperature. cAMP-d2 tracer was added to wells and followed by addition of Anti-cAMP antibody-cryptate preparation and incubated for 1h at room temperature in dark. HTRF cAMP was measured by excitation of the donor with 337 nm laser (the “TRF light unit”) and subsequent (delay time 100 microseconds) measurement of cryptate and d2 emission at 615 nm and 665 nm over a time window of 200 microseconds with a 2000 microseconds time window between repeats /100 flashes). HTRF measurements were performed on an Envision microplate reader (PerkinElmer). The HTRF signal was calculated as the emission-ratio at 665 nm over 615 nm. The HTRF ratio readout for test compounds was normalized to 0% and 100% stimulation using control wells with DMSO-solvent or 30uM dopamine. Test compound potency (EC50) was estimated by nonlinear regression using the sigmoidal dose-response (variable slope) using Xlfit 4 (IDBS, Guildford, Surrey, UK, model 205).

$$y = (A + ((B - A) / (1 + ((C/x)^D))))$$

where y is the normalized HTRF ratio measurement for a given concentration of test compound, x is the concentration of test compound, A is the estimated efficacy at infinite compound dilution, and B is the maximal efficacy. C is the EC50 value and D is the Hill slope coefficient. EC50 estimates were obtained from an independent experiment and the logarithmic average was calculated.

20 *Dopamine D2 receptor agonism*

Dopamine D2 receptor agonism was measured using a calcium mobilization assay protocol developed by HD Biosciences (China). Briefly, HEK293/G15 cells expressing human D2 receptor were plated at a density of 15000 cells/well in clear-bottomed, Matrigel-coated 384-well plates and grown for 24 hrs at 37°C in the presence of 5% CO₂. The cells were incubated with calcium-sensitive fluorescent dye, Fluo8, for 60-90 minutes at 37°C in the dark. Test compounds were prepared at 3-fold concentrated solution in 1xHBSS buffer with Ca²⁺ and Mg²⁺. Calcium Flux signal was immediately recorded after compounds were added from compound plate to cell plate at FLIPR (Molecular Devices). The fluorescence data were normalized to yield responses for no stimulation (buffer) and full stimulation (1 μM of dopamine) of 0% and 100% stimulation, respectively. Test compound potency (EC50) was

5-HT2B binding assay

Evaluation of the affinity of compounds (Id-ia), (Id-ib), (Id-ia), (Id-iib) and (Id-iab) for the human 5-HT2B receptor was determined in a radioligand binding assay at Eurofins/Cerep (France). Membrane homogenates prepared from CHO cells expressing the human 5HT2B receptor were incubated for 60 min at room temperature with 0.2 nM [125I](±)DOI (1-(4-iodo-2, 5-dimethoxyphenyl)propan-2-amine) in the absence or presence of the test compound in a buffer containing 50 mM Tris-HCl (pH 7.4), 5 mM MgCl₂, 10 μM pargyline and 0.1% ascorbic acid. Nonspecific binding is determined in the presence of 1 μM (±)DOI. Following incubation, the samples were filtered rapidly under vacuum through glass fiber filters (GF/B, Packard) presoaked with 0.3% polyethyleneimine (PEI) and rinsed several times with ice-cold 50 mM Tris-HCl using a 96-sample cell harvester (Unifilter, Packard). The filters were dried and counted for radioactivity in a scintillation counter (Topcount, Packard) using a scintillation cocktail (Microscint 0, Packard). The results are expressed as a percent inhibition of the control radioligand specific binding. The standard reference compound was (±)DOI, which was tested in each experiment at several concentrations to obtain a competition curve from which its IC₅₀ is calculated.

Table 2. In vitro activities for the compounds of the invention obtained according to Examples 2 and 3.

	Compound	D1 EC ₅₀ (nM)/Emax	D2 EC ₅₀ (nM)/Emax	5-HT2B EC ₅₀ (nM)/Emax
Parent compound	(I)	3.3/99%	1.3/91%	2900nM/50%
Prior art prodrugs	(Ia)	>1000	>1000	>6000nM,58%@30uM
	(Ib)	>1000	46nM/100%	3.8nM/79%
	(Ic)	nd	nd	-5%@10μM
Compounds of the invention	(Id-ia)	2700/98%	1100/92%	-25%@10μM*
	(Id-ib)	1800/94%	1300/100%	-39%@10μM*
	(Id-ia)	>30000/49%	>30000/48%	6%@10μM*
	(Id-iib)	>30000/42%	>30000/54%	25%@10μM*
	(Id-iab)	nd	nd	17%@10μM
	(Id-iiab)	nd	nd	nd

* indicate binding affinity (% inhibition of control, specific binding at concentration indicated)

nd: not determined

were administered a single dose of apomorphine either subcutaneously or orally by gavage, or administered a single dose of apomorphine conjugates orally by gavage. From rats administered 3000 µg/kg (apomorphine) or 3899 µg/kg (sulfate conjugate) or 4977 µg/kg (glucuronide conjugates), blood samples from 3 male animals were collected on the following time points at Day 1: 0.25, 0.5, 1, 2, 4 and 8 hours SC administration and 0.5, 1, 2, 4, 8 and 24 h PO administration after dosing.

Table 3. PK parameters for (4aR,10aR)-1-n-Propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinoline-6,7-diol (compound (I)) after oral dosing of 0.300 mg/kg (Ia), 0.300 mg/kg (Ib), 0.633 mg/kg of (Id-ia) 0.633 mg/kg of (Id-ib), 0.392 mg/kg of (Id-ia), 0.392 mg/kg (Id-iib), 793 µg/kg (Id-iab), 703 µg/kg (Id-iib) and 494 µg/kg (Ic) to Wistar rats according to Example 4.

	compound	T _{max} (h)	C _{max} (pg/mL)	AUC ₀₋₂₄ (pg*h/mL)	t _{1/2} (h)	24 h exposure (pg/mL)
Prior art prodrugs	(Ia)	1.0	3160	13600	4.09	48 ± 26
	(Ib)	0.5	4990	31000	N/A	147 ± 28
	(Ic)	1.0	14	104	N/A	N/A
Compounds of the invention	(Id-ia)	4.0	1350	15500	6.8	208 ± 89
	(Id-ib)	4.0	2150	21100	7.1	270 ± 112
	(Id-ia)	6.0	945	11300	7.7	192 ± 14
	(Id-iib)	8.0	665	7800	8.0	166 ± 94
	(Id-iab)	4.0	964	18900	N/A	800 ± 244
	(Id-iib)	24	68	1040	N/A	68 ± 38

Example 5: PK experiments in minipigs

Blood samples of approximately 0.5 mL was drawn from the V. jugularis via a syringe and put into precooled EDTA tubes with stabilizing solution as described for rats in example 4. Concentrations of the compounds were measured in plasma. Plasma samples were

(Id-ib)	5.3	1300	14300
(Id-ia)	7.3	501	6280
(Id-iib)	12	328	4160

Example 6: PK/PD of compound (Id-ia)/compound (I) in rat hyperactivity assay

Animals

In total, 206 male CD rats (Charles River, Germany) weighing 200-250 grams (165-190 grams upon arrival) were used in the study. Animals were housed at a standard temperature (22 ± 1 °C) and in a light-controlled environment (lights on from 7 am to 8 pm) with ad libitum access to food and water. The experiment described below was performed in accordance with the standard operating procedures of Charles River Discovery Research Services Finland Ltd. and in accordance with the national Animal Experiment Board of Finland (Eläinkoelautakunta, ELLA) authority on animal testing.

Locomotor activity testing, open field

The test device is a square Plexiglass-arena (measuring 40×40×40 cm), in which the movement paths of the rats are recorded by an activity monitor (Med. Associates Inc.). Before the test period is initiated, rats are habituated to their test cage for 60 minutes. Upon completion of habituation, animals were treated with either compound or vehicle and placed back into the open field apparatus. The main test parameter measured is ambulatory distance (recorded in 5 minute segments). Overall time of measurement after receiving initial treatment was 360 minutes. Total follow up period in the study was 420 min, including 60 min of habituation.

Results

Oral administration of compound (Id-ia) was assessed in the rat locomotor activity assay, and this functional readout was then correlated to plasma concentrations of compound (I). Apomorphine and pramipexole were also concomitantly tested in this assay as comparators (i.e. known standard-of-care (SoC) in the Parkinson's Disease field), and plasma concentration was analyzed for apomorphine.

As shown in figure 3, compound (Id-ia) (10 to 300 µg/kg, p.o.) increases locomotor activity with an effect starting approximatively 2 hours' post-administration (around the 180-minute