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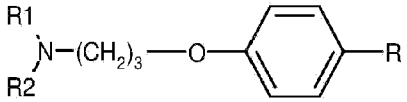
(54) Benævnelse: **Ny terapeutisk anvendelse af H3-ligander**

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DESCRIPTION

[0001] The present invention concerns new therapeutical use, including low dosage administration of a highly potent histamine H3-receptor ligand.

[0002] WO 2006/117609 discloses non-imidazole histamine H3 ligands of formula:



and their use for treating treating and/or preventing CNS disorders such as Alzheimer's disease; attention; wakefulness and memorization disorders; cognitive deficits in psychiatric pathologies; disorders in aged persons; depressive or asthenic states; Parkinson's disease; obstructive sleep apnea; dementia with Lewy bodies; vascular dementia; vertigo; motion sickness; alcohol and other substance abuse; chronic pain; obesity; diabetes and the metabolic syndrome; sleep disorders; stress; psychotropic disorders; convulsion; depression; narcolepsy ; disorders of the hypothalamohypophyseal secretion, the cerebral circulation and/or immune system; and/or for facilitating night works or adaptation to time shift in healthy humans.

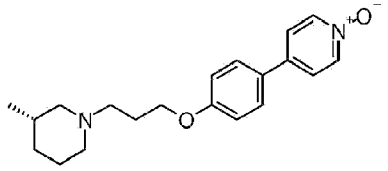
[0003] WO 2006/117609 discloses that said ligands are generally suitable for administration to humans of unit doses generally comprised between 0.1 mg to 1000 mg per day, preferably from 1 to 500 mg administered one to four times a day, and even more preferably from 10 mg to 300 mg, two times a day.

[0004] Similarly, pitolisant, another non-imidazole H3 antagonist authorized for treating narcolepsy is marketed in unit dosage forms (coated tablets) of 4.5 mg and 18 mg. The optimal authorized therapeutical dose can be up to 36 mg a day.

[0005] Generally speaking, it is desired to identify drug candidates that are as potent as possible. Higher potency is generally associated with high selectivity towards the target, lower risks to bind to off-targets and, therefore higher clinical safety.

[0006] It is thus desirable to identify drug candidates that are as high potent as possible and that have effective doses as low as possible.

[0007] Among the H3 ligands disclosed in WO 2006/117609 and despite the disclosed doses of H3-ligands, the inventors have now found that (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide of formula:

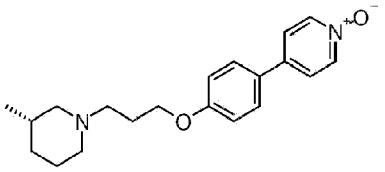


(A)

herein referred as "compound (A)",

unexpectedly exhibits an outstanding profile which thus allows substantially low effective doses.

[0008] According to a first object, the present invention thus concerns (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide of formula (A):



(A)

or its pharmaceutically acceptable salts and/or the solvates of said compound (A) or of its salts, for use for treating and/or preventing in a human patient disorders selected from Alzheimer's disease; attention; wakefulness and memorization disorders; cognitive deficits in psychiatric pathologies; cognitive, mood and vigilance disorders in particular in aged persons; depressive or asthenic states; Parkinson's disease; obstructive sleep apnea; dementia with Lewy bodies; vascular dementia; vertigo; motion sickness; obesity; diabetes and the metabolic syndrome; sleep disorders; stress; psychotropic disorders; epilepsy; depression; narcolepsy with or without cataplexy; substance abuse, notably alcohol abuse disorders, prevention of substance abuse withdrawal syndromes; cognitive disorders in autism; chronic pain and chronic fatigue; post-stroke fatigue, mood, vigilance and cognitive disorders; attention and vigilance disorders of ADHD (attention-deficit hyperactivity disorder) in children or adults or following cerebrovascular accidents; disorders of the hypothalamohypophyseal secretion, the cerebral circulation and/or immune system; excessive daytime sleepiness, such as excessive daytime sleepiness and fatigue associated with Parkinson's disease, obstructive sleep apnea or dementia; and/or for facilitating night works or adaptation to time shift in healthy humans,
where said use comprises the administration of (A) in a human at a dose comprised between 10 and 90 µg a day (relative to compound (A) in the form of the base).

[0009] It is also disclosed herein a method of prevention and/or treatment of the above disorders comprising the administration of compound (A) at a dose comprised between 10 and 90 µg a day (relative to compound (A) in the form of the base), with a pharmaceutically acceptable carrier or excipient, to a patient in the need thereof.

[0010] According to an embodiment, the use is for treating and/or preventing sleep disorders such as insomnia, disorders of sleep initiation and maintenance, sleep fragmentation, parasomnias, REM sleep disorders, sleep disordered breathing, circadian dysrhythmia, narcolepsy with or without cataplexy, excessive daytime sleepiness (including "sleep attacks"), such as fatigue or excessive daytime sleepiness associated with Parkinson's disease, obstructive sleep apnea or dementia. Another use is for the treatment and/or prevention of substance abuse disorders, notably alcohol abuse. Another use is for the treatment and/or prevention of mood, cognitive and vigilance disorders associated with stroke. Another use is for treating and/or preventing cognitive and attention disorders in ADHD or following cerebrovascular accidents.

[0011] According to an embodiment, the compound (A) is in the form of its base, as depicted in

formula (A). Alternatively, compound (A) may be in the form of pharmaceutically acceptable salts such as hydrochloride, oxalate, dihydrochloride, hydrobromide, dihydrobromide, naphthalene-1,5-disulfonate, sulfate, ethane-1,2-disulfonate, cyclamate, toluenesulfonate, paratoluenesulfonate, thiocyanate, nitrate, methanesulfonate, dodecylsulfate, naphthalene-2-sulfonate, benzenesulfonate, dichloroacetate, glycerophosphate, 2-hydroxyethanesulfonate, aspartate, maleate, phosphate, ethanesulfonate, camphor-10-sulfonate, glutamate, alginate, pamoate, 2-oxo-glutarate, 1-hydroxy-2-naphthoate, malonate, gentisate, salicylate, tartrate, fumarate, galactarate, citrate, glucuronate, lactobionate, 4-aminosalicylate, glycolate, sesquiglycolate, glucoheptonate, pyroglutamate, mandelate, malate, hippurate, formate, gluconate, lactate, oleate, ascorbate, benzoate, succinate, 4-acetamidobenzoate, glutarate, cinnamate, adipate, sebacate, camphorate, acetate, caproate, nicotinate, isobutyrate, proionate, carate, laurate, palmitate, stearate, undecen-10-oate, caprylate, orotate, carbonate, 5-sulfocalicylate, 1-hydroxy-2-naphtoate, 3-hydroxy-2-naphtoate; and/or solvates such as hydrates, ethanolate, hemiethanolate.

[0012] Accordingly, the expression "compound (A)" as used herein also refers to the pharmaceutically acceptable salts thereof and/or the solvates of said compound of formula (A) or of the salts thereof, unless specified otherwise. The dihydrochloride salt is particularly mentioned.

[0013] The expression "compound (A) in the form of a base corresponds to compound (A) as depicted above.

[0014] According to an embodiment, Compound (A) may be in the form of the following pharmaceutically acceptable salts:

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dihydrochloride tetrahydrate

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide oxalate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide L-tartrate and its trihydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide pamoate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide fumarate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide para-toluenesulfonate and its sestertihydrate (2.5)

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,5-naphtalenedisulfonate and its hemiethanolate monohydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide phosphate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide bromhydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,2-ethanedisulfonate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sulfate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dibromhydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide orotate and its dihydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 5-sulfosalicylate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1-hydroxy-2-naphtoate and its monohydrate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 3-hydroxy-2-naphtoate;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide (sesqui)glycolate and its monohydrate.

[0015] According to an embodiment, it is in the form of the tetrahydrate form of the dihydrochloride of compound (A).

[0016] The tetrahydrate of compound (A) is stable for relative humidity ranging from at least 30% to 70% which is an improved property as compared to the hygroscopic nature of the previously described dihydrochloride. The tetrahydrate of compound (A) is also stable for temperatures ranging from 20°C to 40°C.

[0017] The tetrahydrate of compound (A) exhibits one or more of the following features: According to an embodiment, the tetrahydrate form of compound (A) exhibits a melting peak around 191°C when measured by capillary tube method.

[0018] According to another embodiment, analysis by differential scanning calorimetry shows two endothermic events with onset around 53°C and 83°C which correspond to the loss of four water molecules; a last event is observed with an onset around 191°C.

[0019] According to another embodiment, the water content of the tetrahydrate of compound (A) is comprised between 14 and 16%, generally about 15.3±0.7% in weight.

[0020] According to an embodiment, the tetrahydrate form of compound (A) exhibits one or more of the powder X-ray diffractogram lines described below:

Angle (2-Theta °)	d value (Angstrom)	Intensity (Count)	Relative Intensity (%)
5.1	17.5	476	20.9
9.7	9.1	998	43.8
10.2	8.7	438	19.2

Angle (2-Theta °)	d value (Angstrom)	Intensity (Count)	Relative Intensity (%)
11.1	8.0	312	13.7
12.5	7.1	2276	100
13.1	6.8	517	22.7
14.6	6.1	700	30.8
15.2	5.8	624	27.4
15.8	5.6	375	16.5
16.5	5.4	1051	46.2
17.4	5.1	275	12.1
18.2	4.9	553	24.3
19.0	4.7	698	30.7
19.5	4.6	969	42.6
20.5	4.3	555	24.4
21.0	4.2	374	16.4
22.0	4.1	1000	43.9
22.5	3.9	446	19.6
23.7	3.8	467	20.5
24.3	3.7	588	25.8
24.8	3.6	1386	60.9
25.2	3.5	408	17.9
26.2	3.4	1352	59.4
26.7	3.3	370	16.3
27.2	3.3	292	12.8
27.5	3.2	336	14.8
28.4	3.1	1058	46.5
29.5	3.0	527	23.2

[0021] More particularly, the following peaks:

2-theta (°)	d (Ångstroms)
9.	9.1
12.5	7.1
14.6	6.1
15.2	5.8
16.5	5.4
19.0	4.7

2-theta (°)	d (Ångstroms)
19.5	4.6
22.0	4.1
24.3	3.7
24.8	3.6
26.2	3.4
28.4	3.1

[0022] The tetrahydrate form of the dihydrochloride salt of compound (A) has been shown to be very stable.

[0023] The tetrahydrate of the dihydrochloride of compound (A) can be prepared by usual methods such as in solubilisation from a solvent by concentration, addition of an anti-solvent, and/or lowering the temperatures.

[0024] According to an embodiment, the tetrahydrate of the dihydrochloride salt of compound (A) may be prepared by a process comprising the steps of:

- dissolving the dihydrochloride of (A) into water;
- concentrating until the solid separates; and
- drying the solid up to a final water content of 15.3±0.7% in weight.

[0025] Alternatively, the tetrahydrate of the dihydrochloride of (A) can be prepared as follows:

- adding aqueous hydrochloric acid to the base (A);
- adding acetone;
- seeding until the solid separates;
- filtering; and
- drying the solid up to a final water content of 15.3±0.7% in weight.

[0026] According to an embodiment, the daily dose of compound (A) for administration to a human is comprised between 20 and 50 µg a day, preferably 30 to 45 µg of the base a day (relative to the compound (A) in the form of the base).

[0027] According to another embodiment, the invention may comprise the administration of said doses of the compound (A), at a frequency comprised between once every three days, once every other day (qod), once-a-day (qd). Preferably, the administration may take place, once-a-day.

[0028] It is to be understood that the dose of the invention is the cumulative dose of each administration dose given within a day.

[0029] The identification of those subjects who are in need of treatment of herein-described diseases and conditions is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination, genetic tests and medical/family history, those subjects who are in need of such treatment.

[0030] Actual dosage levels of the compound of formula (A) of the invention may be varied so as to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, on the route of administration, on the desired duration of treatment and other factors, e.g. the condition of the patient.

[0031] A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of subject; its size, age, and general health; the specific disease involved; the degree of involvement or the severity of the disease; the response of the individual subject; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

[0032] The amount of compound (A) which is required to achieve the desired biological effect will vary depending upon a number of factors, including the dosage of the drug to be administered, the type of disease, the disease state of the patient and the route of administration.

[0033] In general terms, the preferred dosage of a drug to be administered is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, and formulation of the compound excipient, and its route of administration. The daily dose of the compound (A) is generally lower than 90 µg (relative to the base) a day per patient.

[0034] According to a further embodiment, the invention also comprises the administration of one or more further active ingredient, selected from anti-Parkinson drugs such as levodopa, ropinorole, lisuride, bromocriptine, pramixepole or selected from anti-narcoleptic or purported anti-narcoleptic drugs from another class including modafinil. Compound (A) can be formulated into pharmaceutical compositions by admixture with one or more pharmaceutically acceptable excipients.

[0035] The compositions may conveniently be administered in unit dosage form and may be prepared by any of the methods well known in the pharmaceutical art, for example, as

described in Remington: The Science and Practice of Pharmacy, 20th ed.; Gennaro, A. R., Ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2000.

[0036] Compound (A) may be administered by various administration routes such as oral; parenteral including sub-cutaneous, intramuscular, intra-venous; sublingual, topical; local; intratracheal; intranasal; transdermal or rectal, the active ingredient being combined with a pharmaceutically acceptable excipient or vehicle in a pharmaceutical composition.

[0037] According to another object, the present invention thus also concerns the pharmaceutical composition comprising compound (A) and a pharmaceutically acceptable excipient or vehicle for use in treating and/or preventing the above disorders, where compound (A) is administered at a dose comprised between 10 and 70 µg a day (relative to compound (A) in the form of the base).

[0038] For the topical application, the compositions of the invention may be used as creams, gels, ointments or lotions.

[0039] In particular, the formulations suitable for parenteral administration are sterile and include emulsions, suspensions, aqueous and non-aqueous injection solutions, which may contain suspending agents and thickening agents and anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic, and have a suitably adjusted pH, with the blood of the intended recipient.

[0040] According to the invention, oral administration of the compound or composition in an appropriate formulation is advantageously used. Formulations which are suitable to be administered orally to a patient include discrete units such as capsules, such as soft or hard gelatine, tablets, each containing a predetermined amount of the compound of formula (A). They also include powder; granules; solutions or suspensions in an aqueous liquid or a non-aqueous liquid, or oil-in-water liquid emulsion or water-in-oil liquid emulsion.

[0041] "Pharmaceutically" or "pharmaceutically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

[0042] As used herein, "pharmaceutically acceptable excipient, vehicle or carrier" includes in particular diluents, adjuvants, excipients, or vehicles. The use of such ingredients for pharmaceutical active substances is well known in the art.

[0043] In the context of the invention, the term "treating" or "treatment", as used herein, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition.

[0044] "Therapeutically effective amount" means an amount of a compound/ medicament according to the present invention effective in producing the desired therapeutic effect.

[0045] According to the invention, the term "patient", or "patient in need thereof", is intended for a human or non-human mammal affected or likely to be affected with the above disorders. Preferably, the patient is a human.

[0046] Compound (A) may administered in unit dosage forms, wherein the term "unit dose" means a single dose which is capable of being administered to a patient, and which can be readily handled and packaged, remaining as a physically and chemically stable unit dose comprising either the active compound itself, or as a pharmaceutically acceptable composition.

[0047] The appropriate unitary dosage forms comprise the oral forms; the sublingual, buccal, intratracheal, intraocular, intranasal forms, by inhalation, the topical, transdermal, sub-cutaneous, intramuscular or intra-venous, and the rectal forms and the implants.

[0048] The daily dose of between 10 and 90 µg according to the invention may be achieved by administering half a unit dosage form, a single unit dosage form or two or more unit dosage forms, according to the marketed unit dosage form, the daily dose to be administered and the frequency of administration that is prescribed by the practitioner.

[0049] Some salts of compound (A) are novel. According to another object, the present invention also concerns the following compound *per se:*
(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dihydrochloride tetrahydrate.

[0050] The following examples are given for illustrative, non-limiting embodiments of the present invention.

EXAMPLES

Example 1: PK results in human

[0051] C_{max} of Compound (A) given orally once-a-day at doses of either 60 or 90 µg was reached about 2.5 to 3.5 h post administration at Day 1 and Day 10 with an average of 121 and 171 pg/mL after a single dose, and 172 and 344 pg/mL after repeated dose for 60 and 90 µg, respectively.

[0052] The activity of Compound (A) on vigilance at a dose as low as 30 µg daily was evidenced by a delay in falling asleep when going to bed at night whereas repeated treatment at 90 µg once-a-day for 10 days led to some insomnia.

[0053] The mean $t_{1/2}$ was about 33 h determined at Day 10 after multiple administrations. The

total body clearance (Clss/F) was decreased by 65% and 74% after repeated dosing with 60 and 90 µg of Compound (A), respectively. The serum levels of Compound (A) after the 60 µg dose administration were higher after repeated dosing (Day 10) than after a single dose (Day 1) as reflected in a 42 % higher C_{max} and a 73% higher AUC_{0-24h}. The % accumulation after repeated administration was more marked for 90 µg dose with a 101 % higher C_{max} and a 113% higher AUC_{0-24h}.

[0054] Based on mean C_{max} and AUC_{0-24h} dose normalized ratios, Compound (A) serum exposure in human volunteers had a tendency to increase more than dose-proportionally between 60 and 90 µg o.d. between Day 1 and Day 10.

[0055] Steady state seems to be attained after 7 to 8 days of treatment for the 60 µg dose.

Example 2: Determination of the active dose of Compound (A)

[0056] The therapeutic activity of histamine H3-receptor antagonists/inverse agonists drugs can be predicted by evaluation of the degree of occupancy of their target in brain i.e. the H3 receptor.

[0057] This occupancy by drugs can be measured reliably in human through their displacing the binding of a selective radioactive probe, labelled with a radioisotope of short half-life like 11-C. In this way PET imaging allows for the non-invasive measurement of receptor occupancy. The process of imaging requires the injection of a positron-emitting radiotracer that binds to the receptor followed by the measurement of this binding using the PET scanner. Radioligands selective for the H3 receptor have been developed among which [^{11}C]GSK189254 is a histamine H3 receptor antagonist with a high affinity . It has good brain penetration and a terminal half-life of 1.6 + 0.4 hours. This tracer has been used recently to characterize the dose-response occupancy of novel histamine H3 antagonists, providing validation for the ability of [^{11}C]-GSK189254 to measure H3 receptors in humans using PET(Ashworth, S., et al., Evaluation of 11C-GSK189254 as a novel radioligand for the H3 receptor in humans using PET. J Nucl Med, 2010. 51(7): p. 1021-9).

[0058] This method allows to predict the therapeutic dose of a new H3 receptor inverse agonist/antagonist in two steps: 1/the degree of receptor occupancy associated with the dose ensuring therapeutic efficacy of a known drug A is determined, 2/ the dose of the new drug B ensuring the same receptor occupancy as A at therapeutic dose is evaluated. This strategy was applied by comparing H3R occupancy in healthy volunteers receiving pitolisant, an approved and marketed H3R inverse agonist, at its oral maximal therapeutic dose of 40 mg to occupancy by Compound (A) given at several dosages.

[0059] H3R occupancy after 40 mg pitolisant in 6 healthy volunteers was found of 82,33 ± 8.71 %.

[0060] As shown below, very close H3R occupancy was found at a dose of 60 µg of Compound (A) and, at a dose of 30 µg of Compound (A) very high degree of occupancy was still present, particularly after treatment repeated once-a-day for 10 days when steady state is reached.

Compound (A) dose	**Percent H3R occupancy ± SD**	
	at t_{max} (3h)	**At through (24h)**
30µg once	- 70.75 ± 2.94	- 46.50 ± 12.71
60µg once	- 82.00 ± 2.60	
60 µg repeated	- 87.25 ± 3.6	-75.50 ± 2.6

[0061] Since dose-response trials of pitolisant indicate therapeutic activity in various pathologies (narcolepsy, excessive daytime sleepiness associated with Parkinson's disease or Obstructive Sleep Apnea) at oral doses of 20 to 40 mg, the results above lead to the conclusion that the therapeutic dose of the Compound (A) is around 30 to 60 µg. Hence the latter compound appears 1,000-fold more potent than the marketed drug pitolisant.

[0062] Melting points are determinated on Büchi capillary melting point apparatus.

[0063] Proton NMR spectra are recorded on a Varian 400 MHz NMR instrument. The chemical shifts δ are expressed in ppm. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, ms = massif. The spectra recorded are consistent with the proposed structures.

[0064] Infrared spectra (range 4000-450 cm-1) are recorded on a THERMO Electron Corporation Nicolet 380 FT-IR equipped with an attenuated total reflection system. Wavelenghts are in cm-1.

Example 3: (3*S*)-4-{4-[3-(3-Methylpiperidin-1-yl)propoxylphenyl}pyridine 1-oxvde dihydrochloride tetrahydrate.

[0065] (3*S*)-4-{4-[3-(3-Methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxyde dihydrochloride (210 g) and water (200 g) are charged in evaporation vessel. Temperature of bath in evaporation system is set to about 40°C and mixture is agitated until all the precipitate is dissolved. Water is evaporated until product separates as solid form.

[0066] Evaporation vessel containing the product is transferred in vacuum tray drier and product is dried at 30°C. Product is transferred from evaporation vessel into actual drying vessel and drying is continued at 30°C until water content of product is 15.3±0.5% in weight.

Example 4: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dihydrochloride tetrahydrate

[0067] Acetone (10 kg) and (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxyde (2.5 kg) are charged. Temperature is set at 30-40°C. The mixture is stirred until (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dissolves, filtered through pressure filter, and concentrated. A solution of hydrochloric acid (32%, 1.84 kg, 2.1 equivalents) in water (2 kg) is added. Temperature is set to 22-30°C and acetone (6 to 7 L) is added. After seeding acetone is added up to a total amount of 20 kg at 22-30°C. The suspension is agitated at 18-24°C for 1-2 hours and filtered. The cake is rinsed with a mixture of acetone (3.5 kg) and water (240 g). product is dried in vacuum tray dryer with nitrogen flow (Tmax = 30°C) until water content is 15.0 - 16.5% in weight.

Example 5: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base

[0068] (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide, dihydrochloride is treated with ethyl acetate, water, concentrated sodium hydroxide and potassium carbonate to free the base. The phases are filtered through a pad of celite and decantated. The organic phase is washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered and concentrated under reduced pressure to yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base. The crude base is refluxed in diisopropyl ether and let crystallize at room temperature. The obtained solid is filtered and dried at 40°C under vacuum for 2 days to give pure (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base as a white solid, melting at 91°C.

[0069] 1H NMR (DMSO-d6): 8.17 (d,2H), 7.69 (d,2H), 7.68 (d,2H), 7.00 (d,2H), 4.02 (t,2H), 2.72 (m,2H), 2.35 (t, 2H), 1.90-1.70 (ms,3H), 1.65-1.35 (ms,5H), 0.85-0.75 (ms,4H).

[0070] IR (main bands): 2929, 2766, 1606, 1473, 1465, 1241, 1177, 1061, 1029, 822, 569, 515.

Example 6: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide oxalate

[0071] (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base is dissolved in acetone and treated with a solution of one equivalent of oxalic acid in acetone. The obtained white suspension is stirred for 15 hours at room temperature, filtered, rinsed with acetone and dried at 40°C under vacuum for 2 days to yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide oxalate as an off-white solid melting at 102°C.

[0072] 1H NMR (D_2O): 8.12 (d,2H), 7.65 (d,2H), 7.58 (d,2H), 6.95 (d,2H), 4.06 (m,2H), 3.41

[0073] (m,1H), 3.34 (m,1H), 3.16 (m, 2H), 2.70 (t,1H), 2.43 (t,1H), 2.150 (m, 2H), 1.85-1.50 (ms,4H), 0.98 (m,1H), 0.79 (s,3H).

[0074] IR (main bands): 2963, 2501, 1704, 1602, 1470, 1449, 1409, 1391, 1287, 1256, 1225, 1169, 1052, 826, 815, 766, 695, 574, 449.

Example 7: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide L-tartrate trihydrate

[0075] (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base is dissolved in ethanol and treated with a solution of one equivalent of L-tartaric acid in ethanol. The obtained white suspension is sonicated and then stirred for 15 hours at room temperature, filtered, rinsed with ethanol and dried at 45°C under vacuum for 15 hours to yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide L-tartrate trihydrate as a white solid melting at 86°C.

[0076] 1H NMR (D_2O): 8.19 (d,2H), 7.73 (d,2H), 7.66 (d,2H), 7.02 (d,2H), 4.40 (s,2H), 4.12 (m,2H), 3.46 (m,1H), 3.39 (m,1H), 3.21 (m, 2H), 2.75 (t,1H), 2.45 (t,1H), 2.15 (m, 2H), 1.89-1.61 (ms,4H), 1.05 (m,1H), 0.84 (s,3H).

[0077] IR (main bands): 2982, 2882, 2500, 1650, 1600, 1470, 1260, 1213, 1114, 1070, 1046, 883, 674, 576, 477.

Example 8: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide pamoate

[0078] (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base and one equivalent of pamoic acid is refluxed in ethanol. The obtained yellow suspension is stirred for 15 hours at room temperature and filtered. The solid (which contains an excess of acid) is refluxed in ethanol, filtered while hot and the filtrate concentrated under reduced pressure then dissolved in a minimum of hot ethanol. Methyl tert-butylether is added to induce precipitation of the salt. After stirring at room temperature for 2 days, filtration, rinse with methyl tert-butylether and filtration the solid is dried at 45°C under vacuum for 15 hours to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide pamoate as a yellow solid melting at 179°C.

[0079] 1H NMR (DMSO-d6): 8.24 (s,2H), 8.17 (d,2H), 8.14 (d,2H), 7.71-7.65 (ms,6H), 7.18 (m,2H), 7.06-7.01 (ms,4H), 4.69 (s,2H), 4.09 (t,2H), 2.77 (t,1H), 2.14 (m, 2H), 1.85-1.61 (ms,4H), 1.07 (m,1H), 0.88 (s,3H). Missing signals are hidden by deuterated solvent peaks.

[0080] IR (main bands): 2984, 2500, 1644, 1567, 1510, 1445, 1392, 1354, 1214, 1196, 810,

751, 596, 482, 401.

Example 9: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide fumarate

[0081] (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base is dissolved in hot acetone and treated with a solution of one equivalent of fumaric acid in hot acetone. The obtained white gum is refluxed and then stirred for 15 hours at room temperature to give a white solid. After filtration, rinse with acetone and drying at 45°C under vacuum for 15 hours (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide fumarate is obtained as a white solid melting at 135°C.

[0082] 1H NMR (DMSO-d6): 8.18 (d,2H), 8.14 (d,2H), 7.70 (d,2H), 7.68 (d,2H), 7.01 (d,2H), 6.53 (s,2H), 4.04 (t,2H), 2.90 (m,2H), 2.56 (m, 2H), 2.06-1.85 (ms,3H), 1.75 (m,1H), 1.70-1.50 (ms,3H), 1.49 (m,1H), 0.88 (m, 1H), 0.82 (s,3H).

[0083] IR (main bands): 3161, 2500, 1713, 1656, 1574, 1470, 1403, 1339, 1257, 1235, 1144, 1110 1038, 983, 918, 840, 790, 756, 627, 573, 454.

Example 10: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide para-toluenesulfonate sestertihydrate (2.5)

[0084] A suspension of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in water is treated with a solution of one equivalent of para-toluenesulfonic acid in water. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for two days to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide para-toluenesulfonate sestertihydrate as an off-white solid melting at 201°C.

[0085] 1H NMR (D_2O): 8.10 (d,2H), 7.62 (d,2H), 7.55 (d,2H), 7.49 (d,2H), 7.17 (d,2H), 6.92 (d,2H), 4.40 (s,2H), 4.03 (t,2H), 3.37 (m,1H), 3.30 (m,1H), 3.14 (m,2H), 2.71 (m,1H), 2.44 (m,1H), 2.20 (s,3H), 2.06 (m, 2H), 1.85-1.50 (ms,4H), 1.00 (m,1H), 0.79 (s,3H).

[0086] IR (main bands): 2541, 2353, 1651, 1601, 1469, 1402, 1284, 1224, 1205, 1163, 1119, 1030, 1007, 943, 850, 820, 680, 628, 559, 521, 487.

Example 11: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,5-naphtalenedisulfonate monohydrate hemiethanolate

[0087] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in ethanol is treated with a solution of one equivalent of 1,5 naphtalene disulfonic acid in

ethanol. The resulting suspension is stirred at room temperature for 15 hours, filtered, rinsed with ethanol and dried at 40°C under vacuum for 2 days to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,5-naphtalenedisulfonate monohydrate hemiethanolate as a white solid melting at 276°C.

[0088] 1H NMR (D_2O): 8.65 (d,2H), 8.11 (d,2H), 8.00 (d,2H), 7.60 (d,2H), 7.53 (m,2H), 7.49 (m,2H), 6.86 (d,2H), 3.98 (t,2H), 3.37 (m,1H), 3.29 (m,1H), 3.09 (m,2H), 2.64 (t,1H), 2.36 (t,1H), 2.05 (m, 2H), 1.80-1.50 (ms,4H), 0.95 (m,1H), 0.77 (s,3H).

[0089] IR (main bands): 3026, 1601, 1487, 1416, 1261, 1213, 1114, 1030, 983, 806, 764, 665, 609, 580, 526, 502.

Example 12: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide phosphate

[0090] A suspension of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in water is treated with one equivalent of 85% phosphoric acid in water. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for two days to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide phosphate as a white solid melting at 116°C.

[0091] 1H NMR (D_2O): 8.11 (d,2H), 7.64 (d,2H), 7.57 (d,2H), 6.95 (d,2H), 4.05 (m,2H), 3.42 (m,1H), 3.34 (m,1H), 3.15 (m, 2H), 2.70 (t,1H), 2.43 (t,1H), 2.10 (m, 2H), 1.85-1.50 (ms,4H), 0.99 (m,1H), 0.79 (s,3H).

[0092] IR (main bands): 2975, 2883, 2398, 2351, 1603, 1470, 1259, 1216, 1046, 932, 871, 812, 524, 502, 485, 450.

Example 13: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide bromhydrate

[0093] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in tetrahydrofuran is treated with one equivalent of 48% bromhydric acid in water. The resulting suspension is stirred at room temperature for 15 hours, concentrated under reduced pressure and azeotroped with ethanol twice to yield a sticky solid. Dilution in hot acetonitrile, concentration under reduced pressure and drying at 40°C under vacuum for 2 days afford (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide bromhydrate as a white solid melting at 76°C.

[0094] 1H NMR (D_2O): 8.15 (d,2H), 7.68 (d,2H), 7.62 (d,2H), 6.98 (d,2H), 4.09 (t,2H), 3.44 (m,1H), 3.36 (m,1H), 3.18 (m, 2H), 2.72 (m,1H), 2.45 (m,1H), 2.13 (m, 2H), 1.85-1.55 (ms,4H),

1.05 (m,1H), 0.82 (s,3H).

[0095] IR (main bands): 3390, 2930, 2633, 2541, 2360, 1604, 1469, 1227, 1173, 1054, 1029, 945, 821, 568, 518, 487.

Example 14: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,2-ethanedisulfonate

[0096] A suspension of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in water is treated with a solution of one equivalent of 1,2 ethanedisulfonic acid in water. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for two days to yield a hygroscopic solid. Trituration in tetrahydrofuran, filtration and drying at 40°C under vacuum for 2 days give (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,2-ethanedisulfonate as a beige solid melting at 155°C.

[0097] 1H NMR (D_2O): 8.16 (d,2H), 7.69 (d,2H), 7.61 (d,2H), 6.98 (d,2H), 4.08 (t,2H), 3.44 (m,1H), 3.36 (m,1H), 3.18 (m, 2H), 2.72 (m,1H), 2.45 (t,1H), 2.12 (m, 2H), 1.85-1.55 (ms,4H), 1.02 (m,1H), 0.81 (s,3H).

[0098] IR (main bands): 3390, 2944, 2726, 2355, 1600, 1472, 1218, 1166, 1131, 1022, 997, 823, 760, 544, 524, 500.

Example 15: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sulfate

[0099] A suspension of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in water is treated with one equivalent of aqueous 5N sulfuric acid. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for two hours to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sulfate as an off-white solid melting at 71°C.

[0100] 1H NMR (D_2O): 8.14 (d,2H), 7.67 (d,2H), 7.61 (d,2H), 6.97 (d,2H), 4.08 (t,2H), 3.42

[0101] (m,1H), 3.35 (m,1H), 3.18 (m, 2H), 2.73 (m,1H), 2.45 (m,1H), 2.12 (m, 2H), 1.85-1.55 (ms,4H), 1.03 (m,1H), 0.82 (s,3H).

[0102] IR (main bands): 3377, 2931, 2357, 1604, 1470, 1285, 1229, 1174, 1027, 945, 821, 602, 568, 518, 487.

Example 16: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dibromhydrate

[0103] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in ethanol is treated with two equivalents of aqueous 48% bromhydric acid in water. The resulting solution is precipitated with ethyl acetate and stirred at room temperature for 15 hours. After filtration, rinse with ethyl acetate and drying at 40°C under vacuum for 15 hours (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide dibromhydrate is obtained as an off-white solid melting at 215°C.

[0104] 1H NMR (D_2O): 8.24 (d,2H), 7.76 (d,2H), 7.67 (d,2H), 7.03 (d,2H), 4.13 (t,2H), 3.49

[0105] (m,1H), 3.41 (m,1H), 3.25 (m, 2H), 2.78 (m,1H), 2.50 (t,1H), 2.18 (m, 2H), 1.90-1.60 (ms,4H), 1.08 (m,1H), 0.87 (s,3H).

[0106] IR (main bands): 2930, 2632, 2352, 1601, 1471, 1410, 1292, 1261, 1210, 1182, 1050, 945, 823, 704, 678, 625, 569, 502, 485.

Example 17: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide orotate dihydrate

[0107] A suspension of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in water is treated with a suspension of one equivalent of orotic acid in water. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for 24 hours to yield (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide orotate dihydrate as a white solid melting at 125°C.

[0108] 1H NMR (D_2O): 8.14 (d,2H), 7.66 (d,2H), 7.59 (d,2H), 6.95 (d,2H), 5.98 (s,1H), 4.07 (t,2H), 3.43 (m,1H), 3.36 (m,1H), 3.18 (m, 2H), 2.72 (m,1H), 2.45 (m,1H), 2.11 (m, 2H), 1.85-1.55 (ms,4H), 1.04 (m,1H), 0.82 (s,3H).

[0109] IR (main bands): 2957, 2789, 1667, 1633, 1605, 1472, 1409, 1355, 1285, 1226, 1176, 819, 765, 572, 539, 418.

Example 18: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 5-sulfosalicylate

[0110] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in ethanol is treated with a solution of one equivalent of 5-sulfosalicylic acid dihydrate in ethanol. The resulting suspension is stirred at room temperature for 20 hours, filtered, rinsed with ethanol and dried at 45°C under vacuum for 24 hours to yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 5-sulfosalicylate as a white solid melting

at 213°C.

[0111] 1H NMR (D_2O): 8.13 (d,2H), 8.06 (s,1H), 7.67 (d,1H), 7.63 (d,2H), 7.53 (d,2H), 6.90 (d,2H), 6.86 (d,2H), 4.04 (m,2H), 3.42 (m,1H), 3.34 (m,1H), 3.16 (m, 2H), 2.70 (m,1H), 2.43 (m,1H), 2.09 (m, 2H), 1.85-1.55 (ms,4H), 1.02 (m,1H), 0.81 (s,3H).

[0112] IR (main bands): 2963, 2671, 2556, 2358, 1667, 1602, 1471, 1366, 1290, 1240, 1164, 1149, 1117, 1021, 878, 771, 667, 584, 503.

Example 19: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1-hydroxy-2-naphtoate monohydrate

[0113] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in ethanol is treated with a solution of one equivalent of 1-hydroxy-2-naphtoic acid in ethanol and water. The resulting homogeneous phase is lyophilized and let evolve at room temperature in open air for 24 hours to yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1-hydroxy-2-naphtoate monohydrate as a beige solid melting at 140°C.

[0114] 1H NMR (DMSO-d6): 8.18 (d,2H), 8.15 (m,1H), 7.75-7.65 (ms,6H), 7.43 (m,1H), 7.35 (m,1H), 7.01 (d,2H), 6.97 (d,2H), 4.08 (t,2H), 3.10 (m,2H), 2.60 (m,1H), 2.10 (m, 2H), 1.85-1.60 (ms,4H), 1.02 (m,1H), 0.87 (s,3H). Missing signals are hidden by deuterated solvent peaks.

[0115] IR (main bands): 3500, 2356, 1609, 1580, 1471, 1402, 1367, 1313, 1239, 1175, 1035, 984, 806, 774, 578, 491, 447, 426.

Example 20: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 3-hydroxy-2-naphtoate

[0116] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in ethanol is treated with a solution of one equivalent of 3-hydroxy-2-naphtoic acid in ethanol. The resulting homogeneous phase is concentrated under reduced pressure to yield an oily residue. Acetone is then added and the solution concentrated under reduced pressure to yield a yellow solid. A minimum of acetone and a drop of water are added and the resulting suspension sonicated and stirred at room temperature for 20 hours. Filtration, rinse with acetone and drying under vacuum at 45°C for 24 hours yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 3-hydroxy-2-naphtoate as an off-white solid melting at 199°C.

[0117] 1H NMR (DMSO-d6): 8.26 (s,1H), 8.18 (d,2H), 7.72 (d,1H), 7.70-7.65 (ms,4H), 7.56

(d,2H), 7.31 (t,1H), 7.13 (t,1H), 7.01 (d,2H), 6.94 (s, 1H), 4.08 (t,2H), 3.11 (m,2H), 2.64 (m,1H), 2.11 (m, 2H), 1.85-1.60 (ms,4H), 1.02 (m,1H), 0.87 (s,3H). Missing signals are hidden by deuterated solvent peaks.

[0118] IR (main bands): 2931, 2355, 1645, 1603, 1519, 1464, 1446, 1351, 1238, 1173, 841, 818, 739, 594, 577, 478.

Example 21: (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sesquiglycolate monohydrate

[0119] A solution of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide base in tetrahydrofuran is treated with a solution of one equivalent of glycolic acid in tetrahydrofuran. The resulting suspension is stirred at room temperature for 24 hours. Filtration, rinse with tetrahydrofuran and drying under vacuum at 45°C for 24 hours yield (3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sesquiglycolate monohydrate as an off-white solid melting at 82°C.

[0120] 1H NMR (D_2O): 8.19 (d,2H), 7.71 (d,2H), 7.65 (d,2H), 7.01 (d,2H), 4.12 (t,2H), 3.48

[0121] (m,1H), 3.41 (m,1H), 3.22 (m, 2H), 2.76 (m,1H), 2.49 (t,1H), 2.17 (m, 2H), 1.90-1.60 (ms,4H), 1.06 (m,1H), 0.86 (s,3H).

[0122] IR (main bands): 3258, 3102, 2930, 2356, 1603, 1470, 1411, 1287, 1232, 1177, 1059, 947, 819, 696, 568, 509, 456.

Example 22: Comparative pharmacokinetic data in mice.

[0123] Compounds were administered to male swiss mice at a dose close to 1 mg of base/kg. Sampling was performed on a 24 hours time for plasma and brain. Results are presented in *Table 1* with normalization at 1 mg of base/kg.

Table 1: pharmacokinetic data of the exemplified compounds

	AUC (ng/mg*hr)	
example	plasma	brain
Example 5	769	860
Example 6	562	923
Example 4	619	1039
Example 7	447	814
Example 8	587	952
Example 9	448	882

	AUC (ng/mg*hr)	
example	plasma	brain
Example 10	718	862
Example *11*	453	812
Example 12	350	630
Example 13	395	565
Example 14	438	676
Example 15	466	639
Example 16	357	474
Example 17	389	529
Example 18	400	513
Example 19	393	528
Example 20	388	467
Example 21	348	484

[0124] To some extent, the exemplified compounds display similar rates of absorbtion. Ratios of the AUC of the examples over the AUC of the dihydrochloride tetrahydrate are diplayed in Table 2. The ratios all fit within the interval 0.6 to 1.2 which is relevant for similarity with respect to experimental errors associated with the test.

Table 2: comparison of the plasma AUC

example	ratio
Example 5	1.2
Example 6	0.9
Example 4	1.0
Example 7	0.7
Example 8	0.9
Example 9	0.7
Example 10	1.2
Example *11*	0.7
Example 12	0.6
Example 13	0.6
Example 14	0.7
Example 15	0.8
Example 16	0.6
Example 17	0.6
Example 18	0.6

example	ratio
Example 19	0.6
Example 20	0.6
Example 21	0.6

[0125] Striking result is the one from the pamoate (Example 8). The pamoate (embonate) salts are generally used for making slow release drugs (See for example zypadhera / zyprexa relprevv the pamoate of olanzapine which is only given every two to four weeks). Example 8 shows similar AUC and similar time to reach Cmax when compared to the dihydrochloride tetrahydrate (Example 4).

[0126] The compound A as presently claimed thus allows a low dosage, irrespective of its salts and:or solvates therefrom.

Example 23: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide L-tartrate

[0127]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
10.622	8.32195	1103	1.7
11.815	7.48397	65935	100
14.195	6.23436	21253	32.2
14.523	6.09411	2936	4.5
15.153	5.84212	1283	1.9
15.434	5.73636	804	1.2
16.086	5.50553	1990	3
16.205	5.46533	1154	1.7
16.543	5.35441	2062	3.1
16.731	5.2947	4284	6.5
18.055	4.90925	9130	13.8
18.695	4.74257	1523	2.3
19.319	4.59073	3270	5
19.675	4.50851	34400	52.2
20.425	4.34473	1578	2.4
21.416	4.14573	2992	4.5
22.083	4.02212	6703	10.2

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
22.785	3.89966	1791	2.7
23.396	3.79927	9372	14.2
23.634	3.76141	6562	10
24.514	3.62836	4959	7.5
24.614	3.61395	6019	9.1
24.985	3.56111	4404	6.7
25.261	3.52277	10605	16.1
26.032	3.42021	4443	6.7
26.383	3.37547	4383	6.6
27.058	3.29282	3008	4.6
27.855	3.20034	4765	7.2
28.226	3.15911	929	1.4
28.716	3.10633	815	1.2
31.766	2.81465	857	1.3
30.996	2.88282	525	0.8

Example 24: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide pamoate

[0128]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
5.74	15.38566	5136	25.9
6.409	13.77904	4797	24.2
6.832	12.92799	4537	22.8
8.57	10.3099	3843	19.4
8.999	9.81895	4646	23.4
9.605	9.20102	13254	66.7
9.99	8.84695	8769	44.2
11.314	7.81432	6689	33.7
11.516	7.67772	7979	40.2
11.849	7.46299	3230	16.3
14.738	6.00572	15601	78.6
15.776	5.6129	11553	58.2
17.6	5.03509	2409	12.1

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
18.051	4.91034	2694	13.6
18.829	4.70924	3321	16.7
18.971	4.6741	4602	23.2
19.087	4.64614	5624	28.3
19.621	4.5207	4491	22.6
20.044	4.42624	19857	100
20.962	4.23449	3648	18.4
21.471	4.13528	2728	13.7
23.446	3.79125	6076	30.6
23.724	3.74742	11594	58.4
24.432	3.64041	2329	11.7
25.084	3.54727	4040	20.3
25.333	3.51291	3953	19.9
25.814	3.44857	4063	20.5
26.463	3.36542	9057	45.6
27.088	3.28922	4364	22
29.486	3.02694	2704	13.6
29.637	3.01185	3246	16.3
30.105	2.9661	6383	32.1
30.719	2.90813	2487	12.5

Example 25: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide fumarate

[0129]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
7.379	11.97131	9660	42.2
10.544	8.38328	2567	11.2
10.821	8.16977	4686	20.5
11.069	7.98684	11911	52
11.442	7.72714	2661	11.6
12.41	7.12691	2199	9.6
12.642	6.99664	4495	19.6

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
12.893	6.86064	9427	41.1
13.265	6.66933	3425	14.9
14.807	5.97805	8722	38.1
15.243	5.80815	22909	100
16.761	5.28508	5012	21.9
17.523	5.05717	3554	15.5
17.629	5.02701	2430	10.6
18.163	4.88022	4355	19
18.457	4.80316	3981	17.4
18.697	4.74204	4875	21.3
19.043	4.65678	4965	21.7
19.58	4.53026	3167	13.8
20.355	4.35932	3559	15.5
20.701	4.28734	4613	20.1
21.231	4.18149	2619	11.4
21.686	4.09481	6203	27.1
21.78	4.0773	8303	36.2
22.083	4.02208	3892	17
22.497	3.94889	4153	18.1
22.912	3.87837	6378	27.8
23.273	3.81905	2879	12.6
23.628	3.76242	3160	13.8
24.056	3.69642	3078	13.4
24.673	3.60534	5099	22.3
25.749	3.45709	3993	17.4
26.263	3.39054	3935	17.2
26.371	3.37691	3257	14.2
28.371	3.14324	3205	14

Example 26: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide para-toluenesulfonate

[0130]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
8.126	10.87193	1220	4.3
8.672	10.18799	6320	22.5
13.043	6.782	1515	5.4
13.486	6.56057	2082	7.4
13.656	6.47898	2341	8.3
14.21	6.22769	1138	4
14.806	5.97829	2474	8.8
15.73	5.62906	8864	31.5
16.164	5.479	2933	10.4
16.903	5.24124	3707	13.2
17.419	5.08696	2268	8.1
18.628	4.75947	4913	17.5
19.312	4.59241	15833	56.3
20.289	4.37334	19600	69.6
20.797	4.26778	28145	100
21.268	4.17435	2009	7.1
21.599	4.11104	1072	3.8
22.363	3.97233	5381	19.1
22.629	3.92615	3120	11.1
22.912	3.87837	1881	6.7
23.649	3.75905	3082	10.9
23.714	3.74893	3090	11
24.37	3.64951	2706	9.6
25.812	3.44881	2104	7.5
26.505	3.36022	2945	10.5
27.153	3.28146	3658	13
27.541	3.23608	2573	9.1
27.781	3.20865	2650	9.4
28.673	3.11083	1953	6.9
28.92	3.0849	1536	5.5
29.771	2.99854	2149	7.6
29.939	2.98218	2140	7.6
30.581	2.92095	1503	5.3

Example 27: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,5-naphtalenedisulfonate

[0131]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.053	14.58946	3344	7.1
6.743	13.09747	9176	19.6
7.78	11.35388	1471	3.1
7.997	11.04653	7287	15.5
8.406	10.51039	1386	3
8.748	10.10043	761	1.6
9.024	9.7917	711	1.5
9.384	9.4165	4822	10.3
10.155	8.70326	2479	5.3
12.492	7.08029	2090	4.5
12.861	6.87769	9724	20.8
13.021	6.79386	9299	19.8
13.648	6.48297	988	2.1
13.911	6.36085	4282	9.1
14.206	6.22946	8003	17.1
14.563	6.07743	14657	31.3
14.884	5.94722	3561	7.6
15.519	5.70533	7539	16.1
15.997	5.53579	13027	27.8
16.693	5.30644	6992	14.9
16.97	5.22063	8861	18.9
17.171	5.1598	3936	8.4
17.374	5.10017	7022	15
18.039	4.91345	1201	2.6
18.571	4.77386	3537	7.5
18.888	4.69447	27322	58.3
19.086	4.64637	4783	10.2
19.807	4.47874	1710	3.6
20.286	4.37401	6783	14.5
20.494	4.33024	4507	9.6

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
20.919	4.24316	7847	16.7
21.599	4.11104	4775	10.2
21.875	4.05972	1370	2.9
22.84	3.8904	12628	26.9
23.389	3.8004	2704	5.8
23.971	3.70929	3139	6.7
24.146	3.68284	46862	100
24.829	3.58314	3736	8
24.978	3.56206	5320	11.4
25.394	3.50459	3987	8.5
25.9	3.43725	1812	3.9
26.371	3.37699	6140	13.1
27.04	3.29487	16001	34.1
29.238	3.05198	1261	2.7
29.689	3.00669	1091	2.3
31.068	2.87632	885	1.9

Example 28: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide phosphate

[0132]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.479	13.6312	632	0.9
7.199	12.26997	71454	100
7.919	11.15605	5719	8
8.126	10.87193	3362	4.7
10.831	8.16165	54565	76.4
11.82	7.48098	2027	2.8
13.444	6.5806	1147	1.6
14.479	6.11247	12840	18
15.309	5.78298	828	1.2
17.001	5.21115	2216	3.1
18.702	4.74095	2239	3.1
19.319	4.59078	1051	1.5

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
19.785	4.48366	1969	2.8
19.886	4.46122	1099	1.5
20.029	4.42972	1024	1.4
20.632	4.30154	673	0.9
21.141	4.19901	546	0.8
21.658	4.09993	2586	3.6
22.714	3.91164	2414	3.4
22.886	3.88275	1299	1.8
23.374	3.80267	1359	1.9

Example 29: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide bromhydrate phase A

[0133]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
7.366	11.99193	3142	16.5
10.083	8.76605	8965	47.1
10.314	8.56959	4251	22.4
10.682	8.27515	2574	13.5
10.976	8.05473	15003	78.9
12.824	6.89744	1589	8.4
13.081	6.76278	1596	8.4
13.171	6.7164	1628	8.6
14.168	6.24609	3950	20.8
14.616	6.05576	14499	76.2
15.195	5.82609	6833	35.9
15.726	5.63059	2119	11.1
16.511	5.36452	2974	15.6
16.771	5.28195	2759	14.5
16.929	5.23308	2462	12.9
17.592	5.03747	1616	8.5
18.377	4.82405	4106	21.6
19.131	4.6355	7769	40.9

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
20.126	4.40844	3962	20.8
20.573	4.31372	3258	17.1
21.923	4.0511	19018	100
26.172	3.40217	14595	76.7
26.863	3.31621	4859	25.5
31.199	2.86449	9683	50.9

Example 30: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide bromhydrate phase B

[0134]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.744	13.09621	1050	1.8
7.228	12.2209	1932	3.2
8.673	10.18673	12130	20.3
9.849	8.97367	8381	14
10.514	8.40736	17844	29.9
10.89	8.11809	642	1.1
11.392	7.76128	8500	14.2
11.995	7.37228	1390	2.3
13.032	6.78819	1501	2.5
13.413	6.59598	9133	15.3
13.759	6.43071	4006	6.7
14.403	6.14466	40322	67.5
16.315	5.42855	3092	5.2
17.128	5.17278	6865	11.5
17.448	5.07871	21423	35.9
17.918	4.94657	23891	40
18.528	4.78494	3852	6.5
19.482	4.55284	760	1.3
19.87	4.46475	8806	14.7
20.097	4.41485	59707	100
21.743	4.08418	12279	20.6
21.888	4.05736	30357	50.8

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
22.782	3.90019	6438	10.8
23.672	3.75554	962	1.6
24.002	3.70461	7607	12.7
24.678	3.60464	3017	5.1
25.006	3.55819	4063	6.8
26.367	3.37752	17805	29.8
26.962	3.30427	7319	12.3
27.265	3.26825	3138	5.3
27.894	3.19596	6098	10.2
28.171	3.1651	3293	5.5
29.188	3.05709	2873	4.8
29.933	2.98271	956	1.6
30.305	2.94696	625	1
30.661	2.91352	1732	2.9
31.203	2.86414	10127	17
31.479	2.83963	4690	7.9
31.885	2.80442	1430	2.4

Example 31: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1,2-ethanedisulfonate

[0135]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.076	14.53457	2470	3.9
7.191	12.28301	1088	1.7
7.912	11.16587	63580	100
8.915	9.91132	1306	2.1
10.515	8.40664	1685	2.7
11.567	7.64396	23675	37.2
12.114	7.30033	16226	25.5
12.328	7.17374	1378	2.2
12.883	6.8659	1225	1.9
14.001	6.32031	1401	2.2

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
14.203	6.23063	1507	2.4
14.621	6.05375	12806	20.1
15.457	5.72797	1808	2.8
15.753	5.6209	34565	54.4
16.208	5.46428	995	1.6
16.683	5.30977	22245	35
17.275	5.12924	3929	6.2
17.73	4.99852	4056	6.4
17.999	4.9245	8781	13.8
18.866	4.69994	33732	53.1
19.029	4.66019	16126	25.4
19.507	4.54702	11670	18.4
20.333	4.36405	5760	9.1
20.543	4.31997	4220	6.6
21.136	4.20011	32904	51.8
22.152	4.00969	7803	12.3
22.369	3.97133	26731	42
23.257	3.82154	8128	12.8
23.485	3.78505	26515	41.7
23.741	3.74477	24996	39.3
24.363	3.65057	4500	7.1
25.216	3.52896	1605	2.5
26.199	3.39876	2022	3.2
26.4	3.37332	1808	2.8
27.127	3.28459	2074	3.3
28.374	3.14301	12166	19.1
29.061	3.07018	899	1.4
29.374	3.03823	2634	4.1
29.486	3.02694	2110	3.3
30.02	2.97426	2448	3.9
30.518	2.92685	3091	4.9
30.996	2.88282	1407	2.2
31.384	2.84805	1061	1.7
31.609	2.8283	847	1.3
31.962	2.79787	1459	2.3

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %

Example 32: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sulfate phase A

[0136]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.656	13.26963	2744	19.2
7.161	12.33535	2286	16
7.46	11.84024	6576	46
9.95	8.88266	2999	21
11.175	7.91137	5640	39.4
11.511	7.68092	2387	16.7
13.438	6.58388	4784	33.4
14.105	6.27406	2251	15.7
14.971	5.9127	2505	17.5
15.074	5.87279	2830	19.8
15.963	5.54771	3902	27.3
16.405	5.3991	3514	24.6
16.749	5.28906	10566	73.8
18.628	4.75947	2239	15.6
19.694	4.50416	14309	100
20.244	4.38303	9373	65.5
21.055	4.21607	2762	19.3
23.179	3.83432	9224	64.5
23.568	3.77192	3028	21.2
26.813	3.32229	3858	27
29.312	3.04443	3593	25.1

Example 33: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide sulfate phase B

[0137]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
7.208	12.25347	15062	100
7.567	11.67291	6023	40
11.312	7.81562	8017	53.2
11.93	7.41239	4515	30
14.186	6.23803	3984	26.5
14.934	5.92757	5282	35.1
15.143	5.84614	3131	20.8
16.904	5.24091	7584	50.4
17.18	5.15723	1304	8.7
17.663	5.01733	10940	72.6
17.943	4.93966	2540	16.9
18.285	4.84791	1930	12.8
19.51	4.54637	2589	17.2
20.389	4.35229	3820	25.4
20.703	4.28689	2852	18.9
20.979	4.23104	6185	41.1
21.256	4.17666	4124	27.4
22.209	3.99947	1596	10.6
23.056	3.8544	6004	39.9
24.7	3.60148	10306	68.4
26.751	3.3298	5273	35
27.087	3.28933	9892	65.7
28.575	3.12132	2804	18.6
29.431	3.03244	3483	23.1
29.822	2.9936	3436	22.8
30.098	2.96674	3503	23.3

Example 34: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide orotate

[0138]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.813	12.96356	14761	39.6

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
9.3	9.50134	18344	49.2
10.122	8.73237	3418	9.2
11.855	7.45922	7872	21.1
12.343	7.16534	3390	9.1
12.501	7.07484	3560	9.5
13.478	6.56449	11038	29.6
13.917	6.35833	7063	18.9
14.698	6.02225	37281	100
15.431	5.73774	21914	58.8
15.989	5.53869	4110	11
16.864	5.25309	4780	12.8
17.276	5.12873	3309	8.9
17.681	5.01219	3628	9.7
18.559	4.777	5347	14.3
19.312	4.59236	3299	8.8
19.872	4.46431	14550	39
20.148	4.4037	24954	66.9
20.709	4.2857	12916	34.6
21.67	4.09771	7765	20.8
22.132	4.01324	2894	7.8
22.587	3.93339	6133	16.5
23.543	3.77583	6696	18
23.714	3.74903	17914	48.1
24.57	3.62024	4148	11.1
24.773	3.59103	4372	11.7
26.78	3.32627	9867	26.5
27.489	3.24215	5566	14.9

Example 35: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 5-sulfosalicylate

[0139]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
9.06	9.75257	62819	100
10.527	8.3971	16700	26.6
12.577	7.03267	5252	8.4
13.308	6.64783	1079	1.7
13.584	6.5132	926	1.5
14.254	6.20861	1613	2.6
15.037	5.88707	1759	2.8
15.684	5.64577	2314	3.7
16.393	5.40291	1195	1.9
16.486	5.37284	1259	2
17.265	5.13193	3028	4.8
17.687	5.01041	15149	24.1
18.031	4.91572	17071	27.2
18.728	4.7344	2909	4.6
19.457	4.55849	900	1.4
19.734	4.49526	1532	2.4
20.329	4.36498	1242	2
21.038	4.21934	53363	84.9
21.4	4.14883	8088	12.9
22.087	4.0214	1663	2.6
22.497	3.94889	1674	2.7
25.608	3.47579	2201	3.5
26.327	3.38247	10817	17.2
26.943	3.30654	1451	2.3
28.177	3.16447	1393	2.2
28.314	3.14945	1695	2.7
28.958	3.08091	1642	2.6
30.641	2.91539	1824	2.9

Example 36: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 1 -hydroxy-2-naphtoate

[0140]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.468	13.65521	3347	5.4
7.141	12.36906	40644	65.1
9.093	9.71746	4334	6.9
11.546	7.65819	1516	2.4
12.784	6.91889	62472	100
13.168	6.71807	46091	73.8
14.379	6.15501	4351	7
15.312	5.78209	1350	2.2
16.007	5.53236	3604	5.8
16.916	5.23712	1499	2.4
17.313	5.11804	4582	7.3
18.162	4.88047	4156	6.7
18.877	4.69727	4259	6.8
19.337	4.5866	2607	4.2
20.286	4.37401	35807	57.3
20.632	4.30154	4252	6.8
21.257	4.17639	4957	7.9
21.503	4.12927	30954	49.5
21.993	4.03835	10314	16.5
23.084	3.84988	5338	8.5
23.2	3.83085	4238	6.8
23.75	3.74343	3716	5.9
24.787	3.58902	1870	3
25.123	3.54186	1231	2
25.665	3.46825	31154	49.9
26.265	3.39038	9578	15.3
26.643	3.34311	1547	2.5
27.343	3.2591	3973	6.4
27.44	3.24775	5471	8.8
28.073	3.176	9106	14.6
28.802	3.09719	8293	13.3
29.31	3.04465	2719	4.4
31.423	2.84464	2681	4.3

Example 37: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 3-hydroxy-2-naphtoate phase A

[0141]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
7.446	11.86322	30252	49.7
8.748	10.10043	1368	2.2
9.024	9.7917	1609	2.6
9.937	8.8938	6257	10.3
11.27	7.84506	60862	100
13.293	6.6553	2270	3.7
15.072	5.87339	43369	71.3
19.59	4.52783	6152	10.1
19.98	4.44042	2834	4.7
24.813	3.5854	7358	12.1
25.124	3.54169	3602	5.9
26.85	3.31777	4592	7.5

Example 38: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide 3-hydroxy-2-naphtoate phase B

[0142]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
6.311	13.99407	6977	9.6
7.159	12.3387	72823	100
8.95	9.87282	7257	10
11.342	7.79538	966	1.3
12.631	7.00249	2500	3.4
13.122	6.7414	13203	18.1
14.111	6.27121	1300	1.8
15.45	5.73069	1989	2.7
15.864	5.58187	25710	35.3
17.022	5.20487	3579	4.9
17.934	4.9421	8356	11.5

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
18.147	4.88456	1440	2
18.916	4.68768	5385	7.4
20.202	4.39198	15208	20.9
20.29	4.37317	14155	19.4
21.317	4.16482	40284	55.3
21.92	4.05165	4786	6.6
22.918	3.87737	1388	1.9
23.873	3.72441	2539	3.5
24.888	3.57474	4225	5.8
25.607	3.47602	846	1.2
26.162	3.40345	1922	2.6
27.012	3.29822	7527	10.3
27.403	3.25209	1911	2.6
27.913	3.19376	1445	2
28.62	3.11652	3777	5.2
31.941	2.79964	1710	2.3

Example 39: XRPD of (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridine 1-oxide glycolate

[0143]

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
7.495	11.78525	29684	51
11.196	7.89645	22907	39.3
14.884	5.94733	58231	100
15.032	5.88902	37813	64.9
18.675	4.74765	13995	24
18.833	4.70819	10947	18.8
22.371	3.97094	3746	6.4
23.744	3.74433	2259	3.9
24.252	3.66704	1859	3.2

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patent documents cited in the description

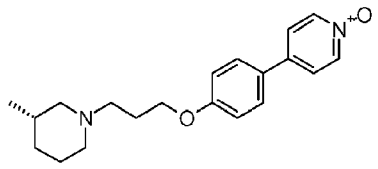
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Patentkrav

1. (3*S*)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid med formlen (A):



(A)

eller farmaceutisk acceptable salte deraf og/eller solvaterne af forbindelsen (A) eller af salte deraf til anvendelse til behandling og/eller forebyggelse hos en human patient af lidelser udvalgt blandt Alzheimers sygdom; opmærksomheds-; vågenheds- og erindringsforstyrrelser; kognitive mangler i psykiatriske patologier; kognitive, humørmæssige og årvågenhedsforstyrrelser, især hos ældre personer; depressive eller asteniske tilstande; Parkinsons sygdom; obstruktiv søvnapnø; demens med Lewy-legemer; vaskulær demens; svimmelhed; køresyge; fedme; diabetes og det metaboliske syndrom; søvnforstyrrelser; stress; psykotrope lidelser; epilepsi; depression; narkolepsi med eller uden kataplexi; lidelser i den hypothalamohypofyseale sekretion, den cerebrale cirkulation og/eller immunsystemet; overdreven søvnighed i dagtimerne, såsom overdreven søvnighed i dagtimerne og træthed forbundet med Parkinsons sygdom, obstruktiv søvnapnø eller demens og/eller for at lette natarbejde eller tilpasning til tidsforskydning hos raske mennesker; lidelser forbundet med stofmisbrug, især alkoholmisbrug; forebyggelse af stofmisbrugsabstinenssyndromer; opmærksomhedsforstyrrelser; træthed efter slagtilfælde, humør, kognitive og årvågenhedsforstyrrelser; kognitive forstyrrelser i autisme; kroniske smerter og kronisk træthed; opmærksomheds- og årvågenhedsforstyrrelser af ADHD (attention-deficit hyperactivity disorder) hos børn eller voksne eller efter cerebrovaskulære ulykker,

hvor anvendelsen omfatter administration af forbindelse (A) eller de farmaceutisk acceptable salte deraf og/eller solvaterne af disse salte eller af forbindelsen (A) i et menneske ved en basedosis på mellem 10 og 90 µg om dagen (i forhold til forbindelse (A) i form af basen).

2. Forbindelse (A) til anvendelse ifølge krav 1, hvor søvnforstyrrelser omfatter søvnløshed, forstyrrelser i søvnstart og -vedligeholdelse, søvnfragmentering, parasomnier, REM-søvnforstyrrelser, søvnforstyrret vejrtrækning, døgnrytmeforstyrrelser, narkolepsi med eller uden kataplexi, overdreven søvnighed i dagtimerne (herunder "søvnanfald"), såsom overdreven søvnighed i dagtimerne forbundet med Parkinsons sygdom, obstruktiv søvnapnø eller demens.

3. Forbindelse (A) til anvendelse ifølge krav 1 eller 2, hvor forbindelse (A) er i form af de farmaceutisk acceptable salte deraf, såsom hydrochlorid, oxalat, dihydrochlorid, hydrobromid, dihydrobromid, naphthalen-1,5-disulfonat, sulfat, ethan-1,2-disulfonat, cyclamat, toluensulfonat, paratoluensulfonat, thiocyanat, nitrat, methansulfonat, dodecylsulfat, naphthalen-2-sulfonat, benzensulfonat, dichloracetat, glycerophosphat, 2-hydroxyethansulfonat, aspartat, maleat, phosphat, ethansulfonat, camphor-10-sulfonat, glutamat, alginat, pamoat, 2-oxo-glutarat, 1-hydroxy-2-naphthoat, malonat, gentisat, salicylat, tartrat, fumarat, galactarat, citrat, glucuronat, lactobionat, 4-aminosalicylat, glycolat, sesquiglycolat, glucoheptonat, pyroglutamat, mandelat, malat, hippurat, formiat, gluconat, lactat, oleat, ascorbat, benzoat, succinat, 4-acetamidobenzoat, glutarat, cinnamat, adipat, sebacat, camphorat, acetat, caproat, nicotinat, isobutyrat, proionat, carat, laurat, palmitat, stearat, undecen-10-oat, caprylat, orotat, carbonat, 5-sulfocalicylat, 1-hydroxy-2-naphtoat, 3-hydroxy-2-naphtoat; og/eller solvater såsom hydrater, ethanolat, hemiethanolat.

4. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge krav 1, 2 eller 3, hvor forbindelse (A) er i form af en hydrochloridform.

5. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor forbindelse (A) er i form af dihydrochloridsaltet.

6. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor forbindelse (A) er i form af tetrahydratet af dihydrochlorid.

7. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor den daglige dosis til indgivelse til en human patient ligger mellem 20 og 50 µg om dagen (i forhold til forbindelse (A) i form af basen).

8. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor den daglige dosis til indgivelse til et menneske ligger mellem 30 og 45 µg om dagen (i forhold til forbindelse (A) i form af basen).

9. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor forbindelse (A) indgives én gang om dagen eller én gang hver anden dag.

10. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor forbindelse (A) indgives én gang dagligt.

11. Forbindelse (A) eller et farmaceutisk acceptabelt salt deraf til anvendelse ifølge et hvilket som helst af de foregående krav, hvor forbindelse (A) indgives ad oral vej.

12. Forbindelse (A) til anvendelse ifølge et hvilket som helst af de foregående krav valgt fra gruppen bestående af:

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin 1-oxid dihydrochlorid-tetrahydrat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-oxalat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-L-tartrat og trihydrat deraf;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-pamoat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-fumarat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-para-toluenesulfonatog sestertihydrat deraf (2.5)

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-1,5-naphtalenedisulfonat og hemiethanolatmonohydrat deraf;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-phosphat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-bromhydrat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-1,2-ethandisulfonat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-sulfat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-dibromhydrat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-orotat og dihydrat deraf;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-5-sulfosalicylat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-1-hydroxy-2-naphtoat og monohydrat deraf;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-3-hydroxy-2-naphtoat;

(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-(sesqui)glycolat og monohydrat deraf.

13. Forbindelse valgt fra gruppen bestående af:
(3S)-4-{4-[3-(3-methylpiperidin-1-yl)propoxy]phenyl}pyridin-1-oxid-dihydrochlorid-tetrahydrat.