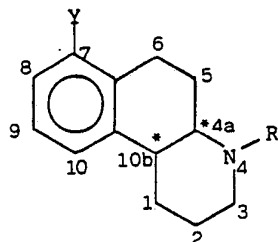


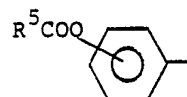


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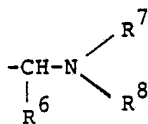
(51) International Patent Classification³ : C07D221/10, 401/12, 413/12 C07D417/12, 419/12; A61K 31/435	A1	(11) International Publication Number: WO 84/ 04303 (43) International Publication Date: 8 November 1984 (08.11.84)
(21) International Application Number: PCT/SE84/00135 (22) International Filing Date: 12 April 1984 (12.04.84) (31) Priority Application Number: 8302361-4 (32) Priority Date: 27 April 1983 (27.04.83) (33) Priority Country: SE (71) Applicant: ASTRA LÄKEMEDEL AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors: ANDERSSON, Bengt, Ronny ; Flintegatan 7B, S-431 33 Mölndal (SE). ARVIDSSON, Folke, Lars-Erik ; Seminariegränd 3, S-752 28 Uppsala (SE). CARLSSON, Per, Arvid, Emil ; Torild Wulffsgatan 50, S-413 19 Göteborg (SE). HJORTH, John, Stephan, Mikael ; Blåvalsgatan 7A, S-414 75 Göteborg (SE). JOHANSSON, Anette, Margareta ; Blodstensvägen 7, S-752 44 Uppsala (SE). LINDBERG, Per, Lennart ; Knapeshall 64, S-436 00 Askim (SE). NILSSON, John, Lars, Gunnar ; Tullinge Strand 30B, S-146 00 Tullinge (SE). SANCHEZ, Domingo ; Snipåsvägen 24, S-448 00 Floda (SE). SVENSSON, Kjell, Anders, Ivan ; Doktor Bex 2, S-413 24 Göteborg (SE). WIKSTRÖM, Håkan, Vilhelm ; Gibsons väg 25, S-433 61 Partille (SE).	(74) Agents: WURM, Bengt, R. et al.; AB Astra, Patent and Trade-mark Department, S-151 85 Södertälje (SE). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, JP, LU (European patent), NL (European patent), NO, SE (European patent). Published <i>With international search report.</i>	

(54) Title: NEW OCTAHYDROBENZO (f) QUINOLINE DERIVATIVES

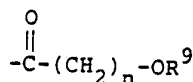
(I)



(II)



(III)



(IV)

(57) Abstract

Compounds of the formula (I), wherein C¹ and N⁴ are in trans configuration to each other, Y is OH, R¹COO, R²R³NCOO- or R⁴O whereby R¹ is an aliphatic hydrocarbon residue having 1-17 carbon atoms, a phenyl, 2,6-dimethylphenyl or 3- or 4-hydroxyphenyl group or a 3- or 4-alkanoyloxyphenyl group with the formula (II), wherein R⁵ is an alkyl group having 1-6 carbon atoms, or R¹ is a group (III) wherein R⁶ is hydrogen, an alkyl group having 1 to 5 carbon atoms or a phenyl group, R⁷ is hydrogen, and alkyl group having 1 to 5 carbon atoms or an acyl group and R⁸ is hydrogen or an alkyl group having 1 to 5 carbon atoms, R² is hydrogen, an alkyl group having 1-5 carbon atoms, a phenethyl, benzyl or phenyl group which may be mono- or disubstituted in the aromatic part with a methyl, methoxy, hydroxy, nitro or cyano group or a halogen, R³ is H, an alkyl group having 1 to 5 carbon atoms of a phenyl group or R² and R³ together with the nitrogen atom form a 5, 6 or 7 membered ring that may contain 1 to 3 double bonds and/or 1 or 2 further heteroatoms selected from N, O and S, and R⁴ is an allyl or benzyl group and R is hydrogen or the group (IV) wherein n is 3 or 4 and R⁹ is hydrogen, an alkanoyl group having 2-6 carbon atoms or benzoyl as bases and pharmaceutically acceptable acid addition salts thereof, processes for their preparation and pharmaceutical preparations and methods of treatment employing such compounds. The compounds are useful for treatment of disorders in the central nervous system.

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NEW OCTAHYDROBENZO(f) QUINOLINE DERIVATIVES

DESCRIPTION

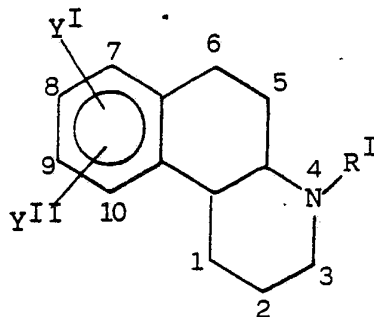
Technical Field

- 5 The present invention is related to new substituted octa-hydrobenzo(f)quinolines, to processes for preparing such compounds as well as to pharmaceutical preparations thereof and methods of treatment employing such compounds.
- 10 An object of the invention is to provide compounds for therapeutic use, especially having a therapeutic activity in the central nervous system.

Background Art

15

Compounds of the formula



25

- are disclosed by a number of references. Thus, Cannon et al. (J. Med. Chem. 19, 987 (1976)) describe i.a. compounds wherein R^I is CH₃ and Y^I and Y^{II} are both H, Y^I is 7-OH (or 7-OCH₃) and Y^{II} is H, or Y^I is 8-OH (or 8-OCH₃) and Y^{II} is H, or Y^I is 7-OH (or 7-OCH₃) and Y^{II} is 8-OH (or 8-OCH₃). Further, compounds wherein R^I is H, C₂H₅, n-C₃H₇ or benzyl and Y^I is 7-OH (or 7-OCH₃) and Y^{II} is 8-OH (or 8-OCH₃), respectively, have been described by Cannon et al. (J. Med. Chem. 22, 341 (1979)). Said
- 35 compounds are

indicated to have central dopaminergic properties although the monohydroxy compounds are reported to be only weakly active and the non-hydroxy compound to be inactive.

5 Cannon et al. (J. Med. Chem. 23, 1 (1980)) also describe compounds wherein Y^I is 8-OH (or 8-OCH₃), Y^{II} is 9-OH (or 9-OCH₃) and R^I is H, CH₃, C₂H₅ or n-C₃H₇. Said compounds are claimed to be inactive in the central nervous system but to be potent dopamine agonists in the periphery.

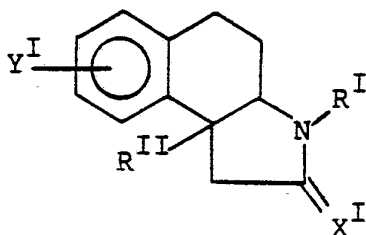
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Wikström et al. (J. Med. Chem., 1982, 25, 925-931) describe compounds under the above formula wherein Y^{II} is H, Y^I is 7-OH, 8-OH, 9-OH and 10-OH and R^I is n-Pr and n-Bu having dopaminergic properties. However, these compounds stimulate
15 both presynaptic and postsynaptic dopamine receptors. The hydroxy compounds mentioned were prepared by demethylating the corresponding methoxy compounds. In the preparation of those methoxy compounds, intermediates are employed wherein Y^{II} is H, Y^I is CH₃O and R^I is H.

20

DE Offenlegungsschrift 20 44 172 describes compounds under the formula

25



30 wherein R^I and R^{II} represent H or alkyl, X^I represents H₂ or O and Y^I represents H, alkoxy or hydroxy. Said compounds are claimed to have analgesic activity.

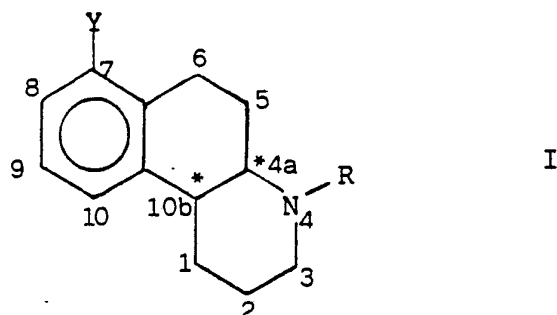
Disclosure of invention

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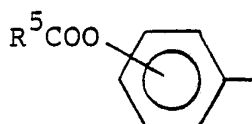
According to the present invention it has been found that novel compounds of the formula



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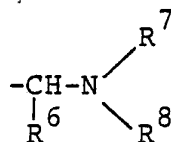


wherein C¹ and N⁴ are in trans configuration to each other,
 Y is OH, R¹COO, R²R³NCOO- or R⁴O whereby R¹ is an aliphatic hydrocarbon residue having 1-17 carbon atoms, a phenyl, 2,6-dimethylphenyl or 3- or 4-hydroxyphenyl group or a 3-
 5 or 4-alkanoyloxyphenyl group with the formula



10

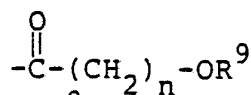
wherein R⁵ is an alkyl group having 1-6 carbon atoms, or R¹ is a group



15

wherein R⁶ is hydrogen, an alkyl group having 1 to 5 carbon atoms or a phenyl group, R⁷ is hydrogen, an alkyl group having 1 to 5 carbon atoms or an acyl group, preferably
 20 an acyl group having 2 to 7 carbon atoms, and R⁸ is hydrogen or an alkyl group having 1 to 5 carbon atoms, R² is hydrogen, an alkyl group having 1-5 carbon atoms, a phenethyl, benzyl or phenyl group which may be mono- or disubstituted in the aromatic part with a methyl, methoxy,
 25 hydroxy, nitro or cyano group or a halogen, R³ is H, an alkyl group having 1 to 5 carbon atoms or a phenyl group or R² and R³ together with the nitrogen atom form a 5, 6 or 7 membered ring that may contain 1 to 3 double bonds and/or 1 to 2 further heteroatoms selected from N, O and
 30 S, and R⁴ is an allyl or benzyl group and R is hydrogen

or the group



wherein n is 3 or 4 and R⁹ is hydrogen, an alkanoyl group having 2-6 carbon atoms or benzoyl, as bases and pharmaceutically acceptable acid addition salts thereof, are potent neuropharmacological agents. Thus, said compounds are active as selective presynaptic dopamine receptor agonists when administered to animals including man. The compounds are thus useful for treatment of disorders in the central nervous system especially psychotic disorders in man.

An alkyl group may be a straight alkyl group or a branched alkyl group having at least 3 carbon atoms.

Symbols for numbers, atoms or groups referred to below have the broadest meaning previously assigned unless specified otherwise.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds of this invention. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic and benzoic acid. These salts are readily prepared by methods known in the art.

In a preferred embodiment the invention is related to compounds of the formula I above wherein Y is OH, R¹COO, or R²R³NCOO-, whereby R¹ is an alkyl group having 1-5 carbon atoms, or a phenyl group, and R² is an alkyl group having 1-5 carbon atoms, a phenethyl, benzyl or phenyl group, and R³ is H or an alkyl group having 1-5 carbon atoms.

One group of preferred compounds are those wherein Y is OH or R²R³NCOO. Further preferred are compounds wherein



R is H or 4-hydroxybutyryl.

Preferred compounds are those wherein Y is OH and R is H or 4-hydroxybutyryl.

5

The compounds of formula I contain two asymmetric carbon atoms in the aliphatic moiety as indicated by asterisks in the above formula. The therapeutic properties of the compounds are ascribed to the trans isomers. The pure enantiomers as well as mixtures thereof are within the scope of the invention. The preferred enantiomers are those with 4aS,10bS-configuration.

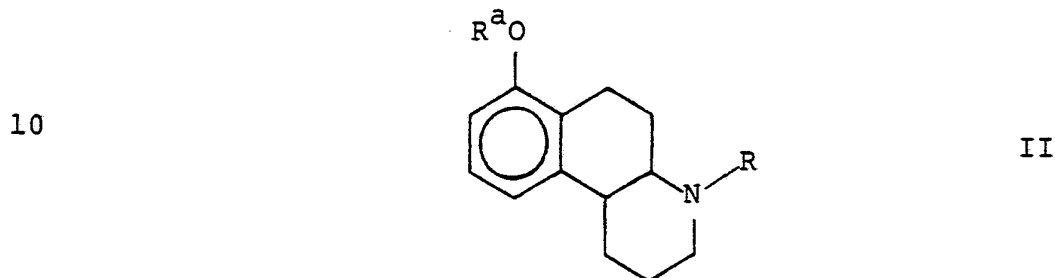
The invention takes into consideration that compounds which structurally deviate from the formula I, after administration to a living organism may be transformed to compounds of the formula I and in this structural form exert their effect. This consideration is a further aspect of the invention. Likewise, certain compounds of formula I may be metabolized into other compounds of formula I before exerting their effect. Compounds of the invention as defined above wherein Y is other than hydroxy and compounds wherein R is other than hydrogen are thus believed to exert their main activity after metabolism to compounds wherein Y is hydroxy and R is hydrogen, respectively.



Methods of Preparation

The compounds of the invention may be obtained by one of the following methods constituting a further aspect of the invention.

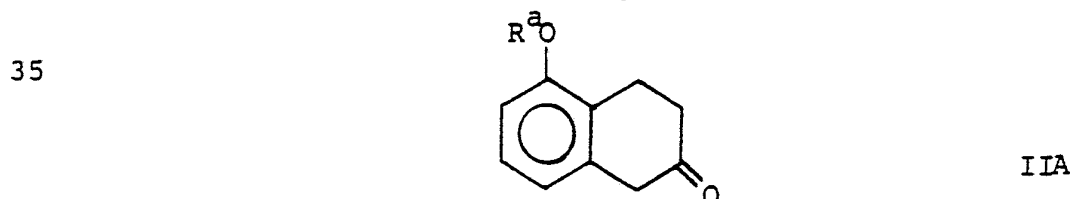
a) An ether or ester of the formula



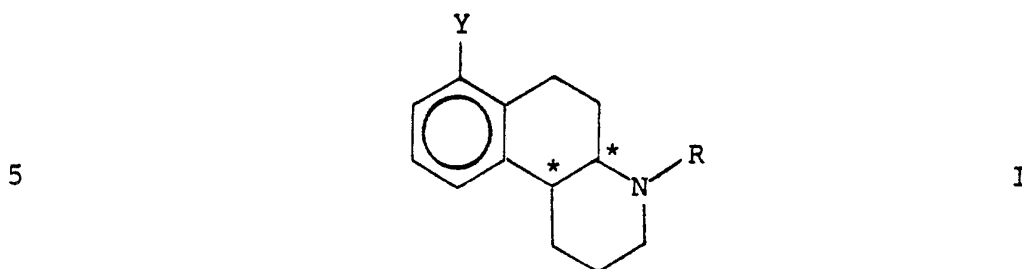
15 wherein R^a represents a hydrocarbon residue, preferably an alkyl group having 1-5 carbon atoms, or a benzyl group, and R is as defined above, may be cleaved to form a compound of formula I wherein Y is a hydroxy group.

20 The cleavage may be carried out by treating the compound of formula II with an acidic nucleophilic reagent such as aqueous HBr, or HI, HBr/ CH_3COOH , BBr_3 , AlCl_3 , pyridine-HCl or $(\text{CH}_3)_3\text{SiI}$, or with a basic nucleophilic reagent such as $\text{CH}_3\text{C}_6\text{H}_4\text{-S}^\ominus$ or $\text{C}_2\text{H}_5\text{-S}^\ominus$. When R^a is a benzyl group the
 25 cleavage may also be carried out by reduction, preferably with hydrogen using Pd or PtO_2 as catalyst.

A compound of formula II wherein R^a is a methyl group is obtained from a compound of formula IIA, as described
 30 in J. Med. Chem. 1982, 25, 925. Compounds of formula II wherein R^a is an alkyl group with 2-5 carbon atoms are synthesized in an analogous manner starting from the appropriately substituted compound IIA.

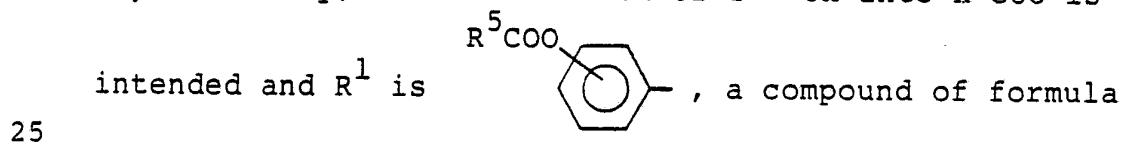


b) A compound of formula

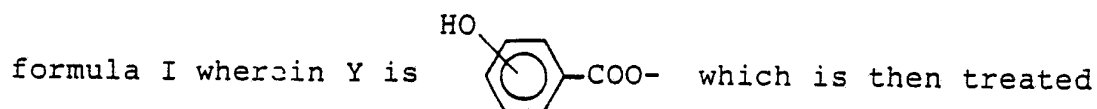


10 wherein Y is OH and R is as defined above may be converted
into a compound of the formula I wherein Y is R^1COO ,
 R^2R^3NCOO or R^4O by treating the first mentioned compound
with an appropriate carboxylic acid halide R^1COX or an-
hydride $(R^1CO)_2O$ or with an appropriate carbamoyl halide
15 R^2R^3NCOX in the presence of a base (only when R is other
than hydrogen) such as triethylamine or pyridine or an acid
such as H_2SO_4 or CF_3COOH or with an appropriate allyl,
benzyl or methyl halide R^4X in the presence of a base such
as triethylamine, pyridine or potassium t-butoxide. X
20 represents a halogen, preferably Cl or Br.

Alternatively, when conversion of $Y = OH$ into R^1COO is

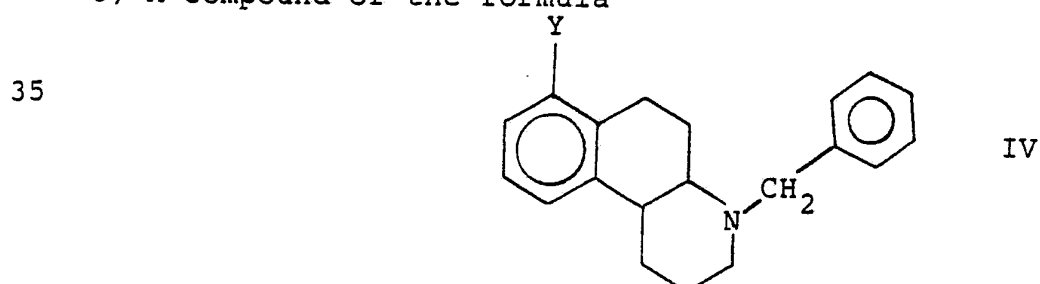


I wherein Y is OH may first be converted to a compound of



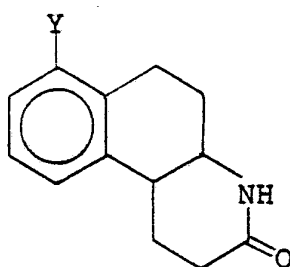
30 with an appropriate carboxylic acid halide R^5COX or an-
hydride $(R^5CO)_2O$ in the presence of a base or an acid.

c) A compound of the formula



wherein Y is other than allyloxy, may be hydrogenated to form a compound of formula I wherein R is H. The hydrogenation is carried out in the presence of a catalyst such as Pd. The starting material of formula IV is obtained by demethylation of the corresponding methoxy compound described in J. Med. Chem. 1982, 25, 925-931, and, when Y other than OH is required, subsequent acylation in analogy with b) above.

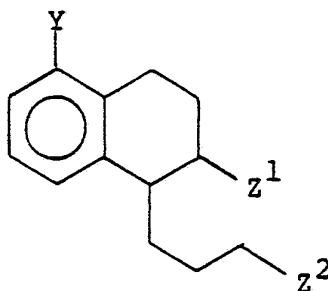
d) An amide of the formula



V

wherein Y is other than $R^2R^3\text{NCOO}$, may be converted into a compound of the formula I by reduction of the amide function and the ester function $R^1\text{COO}$ if present. Thus the compound of formula V may be treated with a reducing agent preferably a hydride reducing agent such as LiAlH_4 or BH_3 in an ethereal solvent or a metal reducing agent such as Na in an alcoholic solvent such as n-butanol. When an ester function is present this is converted to a hydroxy group.

e) A compound according to the formula



VI

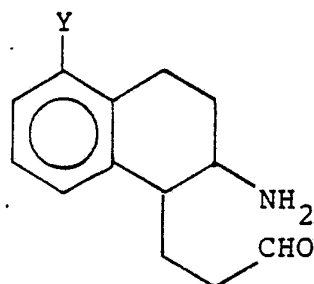
wherein one of the groups Z^1 and Z^2 is a leaving group X

and the other is NH_2 , or Z^1 and Z^2 are both leaving groups X, and X is a leaving group such as Cl, Br, I or $-\text{OSO}_2\text{C}_6\text{H}_4\text{CH}_3$, may be converted to a compound of formula I wherein Y is as defined above and R is H, by treating the compound of formula VI, or when one of Z^1 and Z^2 is NH_2 , an acid addition salt thereof, with a base such as $(\text{C}_2\text{H}_5)_3\text{N}$ or K_2CO_3 , whereby the compound of formula VI is treated together with an equivalent amount of ammonia or an acid addition salt thereof when Z^1 and Z^2 are both X.

The conversion is carried out in a solvent such as tetrahydrofuran, dioxan or acetonitrile, if necessary with simultaneous or subsequent heating of the mixture.

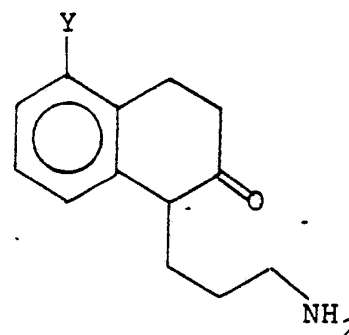
f) A carbonyl-containing compound of the formula

15



or

20



VII

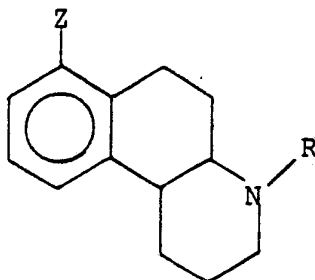
VIII

wherein Y is other than allyloxy, may be subjected to an intramolecular reductive alkylation, preferably by using catalytic hydrogenation, to give a compound of the formula I wherein R is hydrogen. When Y is benzyloxy this is converted to OH.

30

g) In a compound of the formula

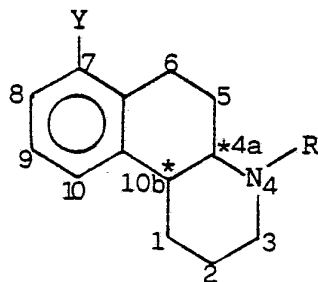
35



IX

wherein Z represents SO_3H , Cl or NH_2 , a hydroxy group may be substituted for the group Z to the formation of a compound of formula I wherein Y represents a hydroxy group. When Z is SO_3H or Cl said reaction may be carried out by treatment with a strong alkali under heating, suitably with an alkali melt such as KOH when Z is SO_3H , and with a strong aqueous alkali such as NaOH or KOH when Z is Cl. When Z is NH_2 the reaction may be carried out by treatment with aqueous nitrous acid to the formation of an intermediate diazonium compound which is then subjected to hydrolysis in water.

h) A racemic mixture or a mixture partly enriched on one of the enantiomers of a compound of formula



may be subjected to enantiomeric separation to obtain the desired enantiomer of compound I. This may be done by methods known in the art. These methods include recrystallization of diastereomeric salts with pure enantiomers of acids such as tartaric acid, O,O'-dibenzoyltartaric acid, mandelic acid and camphor-10-sulphonic acid.

Free bases formed may subsequently be converted into their acid addition salts, and acid addition salts formed may subsequently be converted into the corresponding bases or other acid addition salts.

Pharmaceutical Preparations

Pharmaceutical preparations of the compounds of the invention constitute a further aspect of the invention.

5

In clinical practice the compounds of the present invention will normally be administered orally, rectally, or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or
10 as a pharmaceutically acceptable non-toxic, acid addition salt, e.g. the hydrochloride, lactate, acetate, sulfamate, and the like, in association with a pharmaceutically acceptable carrier.

15 Accordingly, terms relating to the novel compounds of this invention, whether generically or specifically, are intended to include both the free amine base and the acid addition salts of the free base, unless the context in which such terms are used, e.g. in the specific examples,
20 would be inconsistent with the broad concept. The carrier may be a solid, semisolid or liquid diluent or capsule. These pharmaceutical preparations constitute a further aspect of this invention. Usually the active substance will constitute between 0.1 and 99 % by weight of the prepara-
25 tion, more specifically between 0.5 and 20% by weight for preparations intended for injection and between 0.2 and 95 % by weight for preparations suitable for oral administration.

30 Pharmaceutical preparations containing a compound of the invention in a solid form of dosage units for oral application may preferably contain between 2 and 95 % by weight of the active substance, in such preparations the selected compound may be mixed with a solid fine grain carrier, e.g.
35 lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, or gelatin and a lubricant such as magnesium

stearate, calcium stearate, polyethylene glycol waxes, and the like, and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatin, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatin capsules (pearl-shaped closed capsules) consisting of gelatin and, for example, glycerol, or similar closed capsules, the active substance may be admixed with a vegetable oil. Hard gelatin capsules may contain granulates of the active substance in combination with solid, fine grain carriers such as lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatin.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing from about 0.2 % to about 20 % by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl-cellulose as a thickening agent.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5 % to about 10



% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

- 5 In therapeutical treatment the suitable daily doses of the compounds of the invention are 50-10000 mg for oral application, preferentially 200-5000 mg, and 0.005-500 mg for parenteral application, preferentially 0.25-250 mg.

10 Working Examples

The following examples will further illustrate the invention.

15 Preparation of Intermediates

Example 11

(+)-trans-(4aR,10bR)- and (-)-trans-(4aS,10bS)-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrochloride.
20 (Method h)

- Trans-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)-quinoline hydrochloride (0.50 g, 2.0 mmol), R(-)-O-methyl-mandelic acid chloride (0.36 g, 2.2 mmol), methylene
25 chloride (10 ml), water (10 ml) and 5% NaOH (10 ml) were mixed and stirred for 5 min. Extraction with ether, drying and evaporation of the volatiles gave an oil (0.77 g, theoretically 0.72 g). When adding ether to this oil, crystals of isomer 1 melting at 151-153°C were precipitated
30 out (0.20 g, 28%), optical purity according to HPLC 96.3%. After three additional crystallizations giving an additional 0.13 g of isomer 1 the mother liquor was concentrated to an oil (0.26 g). The oil (0.26 g) was chromatographically separated by repeated injections to a semi-preparative
35 HPLC column (SiO₂) using hexane-ethyl acetate-ethanol (95.5:3.75:0.75) as the mobile phase giving isomer 2



(0.16 g) (98.2% of isomer 2 and 1.8% of isomer 1).

Isomer 1 (0.19 g, 0.52 mmol) was dissolved in dry THF (40 ml) and treated with potassium tert. butoxide (0.81 g, 7.1 mmol) and H₂O (64 μ l, 3.6 mmol) and the mixture was stirred overnight and then refluxed for 1 hour. Water was added and the mixture was extracted with ether. The organic layer was dried and the solvent evaporated. The residue was treated with HCl/EtOH, evaporated and recrystallized from ethanol/ether to give the desired (+)-trans-(4aR;10bR) product (120 mg, 87% on the resolved amide isomer 1), m.p. 296-301°C, $[\alpha]_D^{22} +81^\circ$ (c0.96, MeOH).

Isomer 2 (0.16 g; 0.44 mmol) was dissolved in dry THF (20 ml) and treated with potassium tert. butoxide (0.81 g, 7.1 mmol) and H₂O (64 μ l, 3.6 mmol) and the mixture was stirred overnight. The mixture was then refluxed for 1 hour. Water was added and the mixture was extracted with ether. The organic layer was dried and the solvent evaporated. The residue was converted to its hydrochloride, evaporated and recrystallized (ethanol-ether) giving 55 mg (50% on the resolved amide isomer 2) of the desired (-)-trans-(4aS;10bS) product, m.p. 296-301°C, $[\alpha]_D^{22} -88^\circ$ (c 1.05, MeOH).

Example I2

(+)-trans-7-methoxy-4-hydroxybutyryl-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline

(\pm)-trans-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)-quinoline hydrochloride (0.50 g, 1.9 mmol) was converted to the free base by partitioning between CH₂Cl₂ and 10% Na₂CO₃. Drying and evaporation of volatiles gave an oil which was mixed with γ -butyrolactone (0.33 g, 3.8 mmol) and 2-hydroxypyridine (0.36 g, 3.8 mmol) and dry toluene (2 ml). The mixture was refluxed for 25 hours. After one night at room temperature the precipitate (2-hydroxypyridine) was filtered off, the filtrate extracted with



H₂O/CH₂Cl₂, the organic layer washed with 0.5M HCl, dried and evaporated giving an oil. This was purified on a SiO₂-column using ethyl acetate as eluant, giving 0.25 g (46%) of the desired product.

5

Example I3

(±)-trans-7-Phenylcarbamoyloxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrobromide

10 (±)-trans-7-Methoxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydro-(f)quinoline hydrochloride (50 mg, 0.15 mmol) was heated in 48% HBr for 2 hours at 125°C under nitrogen. The hydrobromic acid was evaporated off and the residue alkalized (Na₂CO₃) and extracted with ethyl acetate. Evaporation of
15 the solvent yielded an oil which was dissolved in toluene and refluxed in the presence of phenyl isocyanate (18 mg) for three hours. Extractive work up gave the product (40 mg) as an oil which was debenzylated as described in Example E6.

20

Preparation of end compoundsExample E1

25 (±)-trans-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)-quinoline hydrobromide (Method a)

(±)-trans-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)-quinoline (0.40 g, 1.8 mmol) was refluxed in 48% aqueous HBr under N₂ (g) for two hours. The acid was evaporated
30 and the residue was recrystallized from MeOH-ether giving the desired product (0.39 g, 90%), m.p. 320-330°C (dec.).



Example E2

(-)-trans-(4aS;10bS)-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrobromide (Method a)

- 5 (-)-trans-(4aS,10bS)-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrochloride (50 mg, 0.20 mmol) was heated in 48% aqueous HBr for 2 hours at 125°C under nitrogen. The hydrobromic acid was evaporated off and the residue was recrystallized from MeOH-ether yielding the
10 desired product (59 mg, 92%), 100% optical purity according to HPLC, m.p. 320-330°C (dec.), $[\alpha]_D^{22} -60^\circ$ (c 0.5, MeOH), GC-MS: $M^+ = m/e = 203$.

Example E3

- 15 (+)-trans-(4aR;10bR)-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrobromide (Method a)
-

- (+)-trans-(4aR;10bR)-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrochloride (0.12 g, 0.47 mmol) was
20 heated in 48% aqueous HBr for 2 hours at 125°C under nitrogen. The hydrobromic acid was evaporated off and the residue was recrystallized from MeOH-ether yielding the desired product (0.11 g, 85%), 100% optical purity according to HPLC, m.p. 320-330°C (dec.), $[\alpha]_D^{22} +60^\circ$ (c 0.5,
25 MeOH), GC-MS: $M^+ = m/e = 203$.

Example E4

(±)-trans-7-Hydroxy-4-hydroxybutyryl-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline. (Method a)

- 30 (±)-trans-7-Methoxy-4-hydroxybutyryl-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline (0.25 g, 0.88 mmol) was dissolved in CH_2Cl_2 (15 ml) and the solution was chilled to -70°C. BBr_3 (0.7 ml) was added at this temperature. The
35 mixture was allowed to reach room temperature under stirring. The reaction was quenched with water. The mixture was extracted with ether. The organic layer was dried and the solvent evaporated giving the desired product (0.16 g, 68%).



Example E5

(±)-trans-7-Pivaloyloxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrobromide (Method b)

5 (±)-trans-7-Hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)-quinoline hydrobromide (50 mg, 0.17 mmol) was dissolved in trifluoroacetic acid (1 ml). Pivaloyl chloride (0.2 ml) was added and the mixture was stirred at room temperature
10 overnight. After evaporation of the solvent, the residue was partitioned between H₂O and CH₂Cl₂. The organic layer was concentrated and applied to a SiO₂ column and the product was eluted with CH₂Cl₂-MeOH. Fractions containing the product were collected. The solvent was evaporated
15 yielding 20 mg of an oil. GC-MS: M⁺ at m/e 287.

Example E6

(±)-trans-7-Phenylcarbamoyloxy-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrochloride (Method c)

20 (±)-trans-7-Phenylcarbamoyloxy-4-benzyl-1,2,3,4,4a,5,6,10b-octahydrobenzo(f)quinoline hydrochloride (40 mg, 0.12 mmol) was dissolved in MeOH (5 ml) and hydrogenolyzed in the presence of 10% Pd/C (40 mg) at 25 psig at room
25 temperature. After filtration of the catalyst and evaporation of the solvent the desired product (20 mg) was obtained. MS shows M⁺ at m/e 322.



Pharmaceutical Preparations

The following examples illustrate how the compounds of the present invention may be included into pharmaceutical
5 preparations.

Example P1. Preparation of soft gelatine capsules

500 g of active substance are mixed with 500 g of corn oil,
10 whereupon the mixture is filled in soft gelatine capsules,
each capsule containing 100 mg of the mixture (i.e. 50 mg
of active substance).

Example P2. Preparation of tablets

15 0.5 kg of active substance are mixed with 0.2 kg of silicic
acid of the trade mark Aerosil. 0.45 kg of potato starch
and 0.5 kg of lactose are mixed therewith and the mixture
is moistened with a starch paste prepared from 50 g of
20 potato starch and distilled water, whereupon the mixture
is granulated through a sieve. The granulate is dried and
sieved, whereupon 20 g of magnesium stearate are mixed into
it. Finally the mixture is pressed into tablets each
weighing 172 mg.

25

Example P3. Preparation of a syrup

100 g of active substance are dissolved in 300 g of 95%
ethanol, whereupon 300 g of glycerol, aroma and colouring
30 agents (q.s.) and 1000 ml of water are mixed therein. A
syrup is obtained.



Example P4. Preparation of an injection solution

Active substance (hydrobromide) (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) are dissolved in
5 sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance per ml, is used in filling ampoules, which are sterilized by heating at 120°C for 20 minutes.

10 The compounds of the invention under consideration are centrally acting selective dopamine autoreceptor stimulating agents, and thus of great clinical interest in the treatment of psychotic disorders such as schizophrenia and a number of other disease states such as tardive
15 dyskinesia, Huntington's chorea, alcoholism and drug abuse, said psychotic disorders and other disease states possibly being associated with a pathological increase in central dopamine transmission.

20 Best mode of carrying out the invention

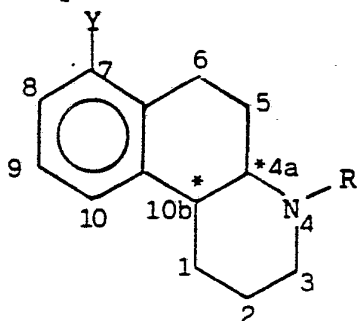
The compound (-)-trans-(4aS;10bS)-7-hydroxy-1,2,3,4,4a,5,6,-
10b-octahydrobenzo(f)quinoline and its salts, processes
for preparing said compound and methods of employing said
25 compound in therapy, in particular for treatment of schizophrenia represents the best mode of carrying out the invention known to the inventors at present.



CLAIMS

1. A novel compound of the formula

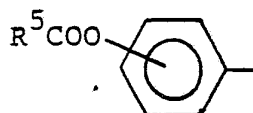
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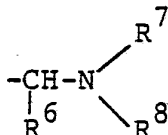
I

10

wherein C¹ and N⁴ are in trans configuration to each other, Y is OH, R¹COO, R²R³NCOO- or R⁴O whereby R¹ is an aliphatic hydrocarbon residue having 1-17 carbon atoms, a phenyl, 2,6-dimethylphenyl or 3- or 4-hydroxyphenyl group or a 3-
15 or 4-alkanoyloxyphenyl group with the formula



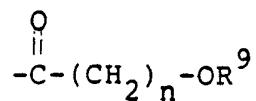
20 wherein R⁵ is an alkyl group having 1-6 carbon atoms, or R¹ is a group



25

wherein R⁶ is hydrogen, an alkyl group having 1 to 5 carbon atoms or a phenyl group, R⁷ is hydrogen, an alkyl group having 1 to 5 carbon atoms or an acyl group and R⁸ is hydrogen or an alkyl group having 1 to 5 carbon atoms, R² is hydrogen or an alkyl group having 1 to 5 carbon atoms, a phenethyl, benzyl or phenyl group which may be mono- or disubstituted in the aromatic part with a methyl, methoxy, hydroxy, nitro or cyano group or a halogen, R³ is H, an alkyl group having 1 to 5 carbon atoms or a phenyl group or R² and R³ together
30 with the nitrogen atom form a 5, 6 or 7 membered ring that may contain 1 to 3 double bonds and/or 1 to 2 further hetero-atoms selected from N, O and S, and R⁴ is an allyl or benzyl
35

group, and R is hydrogen or the group



5

wherein n is 3 or 4 and R⁹ is hydrogen, an alkanoyl group having 2-6 carbon atoms or benzoyl, as the base or a pharmaceutically acceptable acid addition salt thereof.

- 10 2. A compound according to claim 1, characterized in that Y is OH, R¹COO or R²R³NCOO-, whereby R¹ is an alkyl group having 1-5 carbon atoms, a phenethyl, benzyl or phenyl group, R² is an alkyl group having 1-5 carbon atoms or a phenyl group and R³ is H or an alkyl group having 1-5 carbon atoms.

15

3. A compound according to claim 1, characterized in that Y is OH or R²R³NCOO.

20 4. A compound according to claim 1, characterized in that R is hydrogen or 4-hydroxybutyryl.

5. A compound according to claim 1, characterized in that Y is OH and R is hydrogen or 4-hydroxybutyryl.

25 6. A compound according to one or more of the preceding claims, characterized by 4aS, 10bS configuration.

7. A compound which after administration to a living organism is transformed into a compound according to claim 1 in which
30 Y is OH and R is H, and exerting its effect in this structural form, characterized in that Y and R are as defined in claim 1, provided that Y is other than OH and/or R is other than H, as the base or a pharmaceutically acceptable acid addition salt thereof.

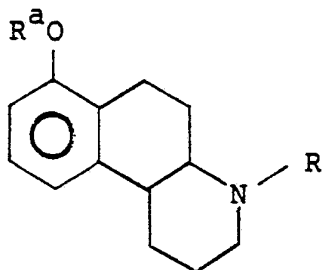
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8. A process for preparation of a compound of formula I according to claim 1, characterized in that

a) an ether or ester of the formula

5



II

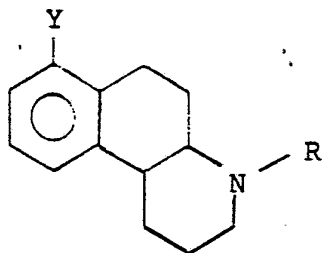
10

wherein R^a represents a hydrocarbon residue, preferably an alkyl group having 1-5 carbon atoms or a benzyl group, and R is as defined above, is cleaved to form a compound or formula I wherein Y is a hydroxy group, or

15

b) a compound of formula

20



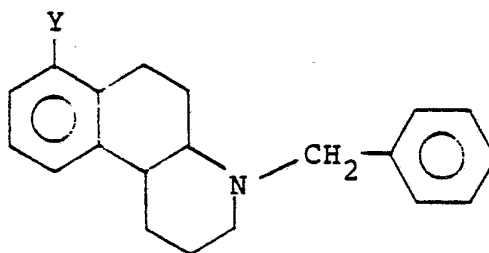
III

25

wherein Y is OH and R is as defined above is converted into a compound of the formula I wherein Y is R^1COO , R^2R^3NCOO or R^4O by ester or ether formation, or

c) a compound of the formula

30



IV

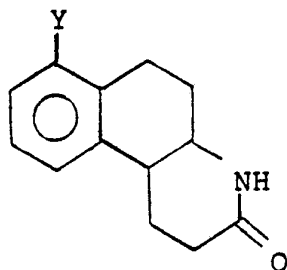
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wherein Y is other than allyloxy, is hydrogenated to form a compound of formula I wherein R is H, or

d) an amide of the formula

5



V

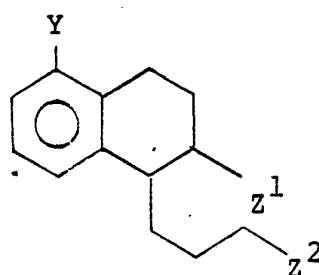
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wherein Y is other than R^2R^3NCOO , is converted into a compound of the formula I by reduction of the amide function and the ester function R^1COO if present, or

15

e) a compound according to the formula

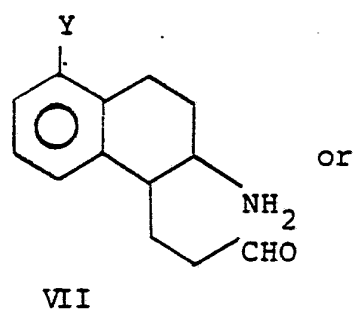
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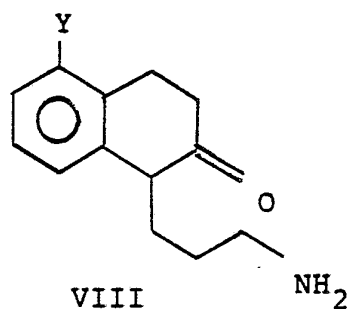
VI

wherein one of the groups Z^1 and Z^2 is a leaving group X and the other is NH_2 , or Z^1 and Z^2 are both leaving groups X, and X is a leaving group such as Cl, Br, I or $-OSO_2C_6H_4CH_3$, is converted to a compound of formula I wherein Y is as defined above, and R is H by treating the compound of formula VI, or when one of Z^1 and Z^2 is NH an acid addition salt thereof, with a base such as $(C_2H_5)_3N$ or K_2CO_3 , whereby the compound of formula VI is treated together with an equivalent amount of ammonia or an acid addition salt thereof when Z^1 and Z^2 are both X, or

35 f) a carbonyl-containing compound of the formula



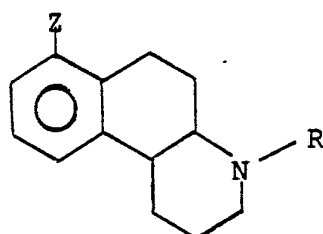
or



wherein Y is other than allyloxy is subjected to an intra-molecular reductive alkylation to give a compound of the formula I, wherein R is hydrogen, when Y is benzyloxy this is converted to OH, or

5

g) in a compound of the formula



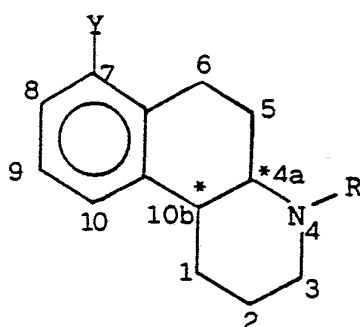
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wherein Z represents SO_3H , Cl or NH_2 , a hydroxy group is substituted for the group Z to the formation of a compound of formula I wherein Y represents a hydroxy group, or

15

h) a racemic mixture or a mixture partly enriched in one of the enantiomers of a compound of the formula

20



25

is subjected to enantiomeric separation to obtain the desired enantiomer of compound I; whereupon optionally a free base formed is subsequently converted into an acid addition salt thereof, an acid addition salt formed is subsequently converted

30

into the corresponding base or another acid addition salt thereof, or an enantiomeric mixture is separated into the pure enantiomers.

5 9. A process according to claim 8 characterized in preparing a compound of formula I as defined in any of claims 2-7.

10 10. A pharmaceutical preparation comprising as an active ingredient a compound according to one or more of claims 1 to 7, in conjunction with a pharmaceutically acceptable carrier.

15 11. A method of treatment of disorders in the central nervous system, comprising administering to a host in need of treatment a therapeutically effective amount of a compound according to one or more of claims 1 to 7.

20 12. Compounds, processes, pharmaceutical preparations and methods of treatment as claimed in any of claims 1-11, and substantially as described.



INTERNATIONAL SEARCH REPORT

International Application No PCT/SE84/00135

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC ³ C 07 D 221/10, 401/12, 413/12, 417/12, 419/12, A 61 K 31/435											
II. FIELDS SEARCHED Minimum Documentation Searched ⁴ <table border="1"> <thead> <tr> <th>Classification System</th> <th>Classification Symbols</th> </tr> </thead> <tbody> <tr> <td>IPC 2,3</td> <td>C 07 D 221/00, 02, 06, 10; A 61 K 31/435, 47</td> </tr> <tr> <td>IPC 1</td> <td>C 07 d 39/00</td> </tr> <tr> <td>National C112p5</td> <td>.../...</td> </tr> </tbody> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵ SE, NO, DK, FI classes as above			Classification System	Classification Symbols	IPC 2,3	C 07 D 221/00, 02, 06, 10; A 61 K 31/435, 47	IPC 1	C 07 d 39/00	National C112p5	.../...	
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IPC 2,3	C 07 D 221/00, 02, 06, 10; A 61 K 31/435, 47										
IPC 1	C 07 d 39/00										
National C112p5	.../...										
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ <table border="1"> <thead> <tr> <th>Category ⁶</th> <th>Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷</th> <th>Relevant to Claim No. ¹⁸</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>EP, A, 0 059 553 (SMITHKLINE CORPORATION) 8 September 1982 & US, 4341786</td> <td>1-10, 12</td> </tr> <tr> <td>X</td> <td>DE, A, 2 801 576 (SANDOZ-PATENT-GMBH) 27 July 1978 & NL, 7800719 FR, 2378015 BE, 863215 JP, 53092778 AU, 32654/78 GB, 1596170 CA, 1105468 AT, 367404 AT, 367405 AT, 367406 CH, 630902 CH, 630903 CH, 630904 CH, 633270 SE, 7800452 .../...</td> <td>1-10, 12</td> </tr> </tbody> </table>			Category ⁶	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸	X	EP, A, 0 059 553 (SMITHKLINE CORPORATION) 8 September 1982 & US, 4341786	1-10, 12	X	DE, A, 2 801 576 (SANDOZ-PATENT-GMBH) 27 July 1978 & NL, 7800719 FR, 2378015 BE, 863215 JP, 53092778 AU, 32654/78 GB, 1596170 CA, 1105468 AT, 367404 AT, 367405 AT, 367406 CH, 630902 CH, 630903 CH, 630904 CH, 633270 SE, 7800452 .../...	1-10, 12
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<div style="display: flex; justify-content: space-between;"> <div> <p>* Special categories of cited documents: ¹⁶</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>											
IV. CERTIFICATION <table border="1"> <tr> <td> Date of the Actual Completion of the International Search ¹ 1984-07-09 </td> <td> Date of Mailing of this International Search Report ² 1984-07-30 </td> </tr> <tr> <td> International Searching Authority ¹ Swedish Patent Office </td> <td> Signature of Authorized Officer ¹⁰ <i>Gunilla Claesson</i> Gunilla Claesson </td> </tr> </table>			Date of the Actual Completion of the International Search ¹ 1984-07-09	Date of Mailing of this International Search Report ² 1984-07-30	International Searching Authority ¹ Swedish Patent Office	Signature of Authorized Officer ¹⁰ <i>Gunilla Claesson</i> Gunilla Claesson					
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International Searching Authority ¹ Swedish Patent Office	Signature of Authorized Officer ¹⁰ <i>Gunilla Claesson</i> Gunilla Claesson										

L.E.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields searched (cont).

US CI 260:239, 283, 286
424:256, 258, 267
546:101

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers 11 because it relates to subject matter ¹² not required to be searched by this Authority, namely:

a method for treatment of the human or animal body by therapy.

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁶ with Indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
X	Journal of Medicinal Chemistry, Vol. 25, No.8, 1982, H. Wikström et al., "Monophenolic octahydrobenzo (f) quinolines: Central dopamine- and serotonin- receptor stimulating activity", pages 925-931	1-10, 12
X	Journal of Medicinal Chemistry, Vol. 22, No.4, 1979, J.G. Cannon et al., "Rigid congeners of dopamine based on octahydrobenzo (f) quinoline: Peripheral and central effects", pages 341-347	1-10, 12
X	Journal of Medicinal Chemistry, Vol. 19, No.8, 1976, J.G. Cannon et al., "Centrally acting emetics. 10. Rigid dopamine congeners derived from octahydrobenzo (f) quinoline", pages 987-993	1-10, 12
X	Journal of Medicinal Chemistry, Vol. 23, No.1, 1980, J.G. Cannon et al., "Congeners of the β conformer of dopamine derived from cis- and trans- octahydrobenzo (f) quinoline and trans- octahydrobenzo (g) quinoline," pages 1-5.	1-10, 12
X	Chemical Abstracts, Vol. 86 (1977), abstract No. 37497u, J. Pharmacol. Exp. Ther. 1976, 199 (3), 630-8.	1-7
X	GB, A, 1 277 789 (LABORATOIRES JACQUES LOGEAIS) 14 June 1972	1-10, 12