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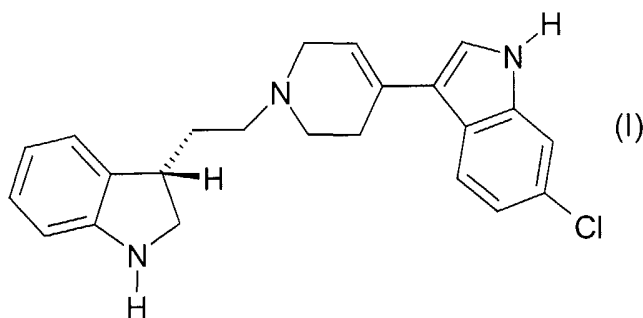
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: S-(+)-3-{1-[2-(2,3-DIHYDRO-1H-INDOL-3-YL)ETHYL]-3,6-DIHYDRO-2H-PYRIDIN-4-YL}-6-CHLORO-1H-INDOLE AND ACID ADDITION SALTS THEREOF



(57) Abstract: The present invention relates to the compound S-(+)-3-[1-[2-(2,3-dihydro-1H-indol-3-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-6-chloro-1H-indole or a pharmaceutically acceptable salt thereof and the use thereof for the preparation of a pharmaceutical composition for the treatment diseases and disorders responsive to 5-HT reuptake inhibition and/or diseases and disorders responsive to dopamine D₄ receptor antagonism.

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S-(+)-3-{1-[2-(2,3-Dihydro-1H-indol-3-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl}-6-chloro-1H-indole and acid addition salts thereof

The present invention relates to S-(+)-3-[1-[2-(2,3-dihydro-1H-indol-3-yl)ethyl]-3,6-dihydro-2H-pyridin-4-yl]-6-chloro-1H-indole and pharmaceutically acceptable salts thereof and the use thereof for the treatment of diseases or disorders responsive to 5-HT reuptake inhibition and/or diseases responsive to dopamine D₄ receptor antagonism.

Background of the Invention

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The present invention relates to a compound which has antagonistic effect at dopamine D₄ receptors and 5-HT reuptake inhibiting effect.

There are mounting evidences showing that blockade of 5-HT reuptake has antidepressant effects in patients (Montgomery *Psychopharmacology: The fourth generation of progress*, ed: Meltzer HY, Raven Press, New York, 1995, pp 1043-1051) and today, treatment with 5-HT reuptake inhibitors is the standard first-line treatment for major depression (Berman et al. *Neurobiology of mental illness*, eds: Charney DS, Nestler EJ, Bunney BS, Oxford University Press, Oxford, 1999, 31, 419-432). Furthermore, it is well recognised that 5-HT reuptake inhibitors are effective in the treatment of dysthymic disorder (Thase et al. *Arch Gen Psychiatry*, 1996, 53, 777-784).

5-HT reuptake inhibitors may also be useful in the treatment of anxiety disorders. Clinical studies have shown that 5-HT reuptake inhibitors have beneficial effects in generalized anxiety disorder (see e.g. Rocca et al. *Acta Psychiatr Scand*, 1997, 95, 444-450). It is also well accepted that 5-HT reuptake inhibitors are effective against panic anxiety/panic disorder (see e.g. Sheehan and Harnett-Sheehan *J Clin Psychiatry*, 1996, 10, 51-58). Clear efficacy of 5-HT uptake inhibitors has also been demonstrated in obsessive compulsive disorder (McDougle *Neurobiology of mental illness*, eds: Charney DS, Nestler EJ, Bunney BS, Oxford University Press, Oxford, 1999, 37, 518-533). There is accumulating data implicating the central 5-HT system in the pathogenesis of post traumatic stress disorder (Charney et al. *Arch Gen Psychiatry*, 1993, 50, 295-305). In line with this, 5-HT reuptake inhibitors have been shown efficacious in post traumatic stress disorder and these type of agents are generally the first line of treatment

of this disorder (Rothbaum et al. *J Trauma Stress*, 1996, 9, 865-871; Goddard et al. *Neurobiology of mental illness*, eds: Charney DS, Nestler EJ, Bunney BS, Oxford University Press, Oxford, 1999, 39, 548-563). Furthermore, clinical data indicate that blockade of the 5-HT reuptake has beneficial effects in the treatment of acute stress disorder (Robert et al. *J Burn Care Rehabil*, 1999, 20, 250-258.) 5-HT reuptake inhibitors are also useful in the treatment of phobia, particularly social phobia/anxiety disorder. Thus, clinical studies have indicated a role of the central 5-HT system in the pathophysiology of phobias (Potts et al. *Int Clin Psychopharmacol*, 1996, 11, Suppl 3, 43-48) and it is well accepted that 5-HT reuptake inhibitors are effective in treating social phobia/anxiety disorder (see e.g. van den Linden et al. *Int Clin Psychopharmacol*, 2000, 15, Suppl 2, 15-23).

5-HT reuptake inhibitors appear also effective in the treatment of impulse control disorders (Durst et al. *CNS Drugs*, 2001, 15, 185-195; Hollander et al. *Psychiatr Clin North Am*, 2000, 23, 629-642; Christenson and Crow *J Clin Psychiatry*, 1996, Suppl 8, 42-47). In particular, 5-HT reuptake inhibition may reduce aggression, probably due to positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour directed towards oneself or others (for review see Walsh & Dinan *Acta Psychiatr Scand*, 2001, 104, 84-91).

20

Both clinical and preclinical studies indicate that the central 5-HT system is involved in cognitive functions. For example, drug-induced destruction of 5-HT terminals, as evident by a reduction in 5-HT reuptake sites, is associated with impaired memory in both animals and humans (Morgan *Psychopharmacology*, 1999, 141, 30-36). It has also been shown that blockade of the 5-HT reuptake improves cognitive function in elderly depressed patients (Meltzer et al. *Neuropsychopharmacology*, 1998, 18, 407-430). Finally, treatment with agents that increase serotonergic neurotransmission has been reported to ameliorate cognitive deficits in schizophrenic patients (Sumiyoshi et al. *Am J Psychiatry*, 2001, 158, 1722-1725). These findings collectively suggest that 5-HT reuptake inhibitors may be effective in the treatment of cognitive disorders.

30

It has previously been described that 5-HT reuptake inhibitors are effective in the treatment of premenstrual syndrom (see e.g. Eriksson et al. *Neuropsychopharmacology*, 1995, 12, 167-176).

Several findings support that serotonergic mechanisms are involved in the discriminative, reinforcing and subjective effects of drugs of abuse (see e.g. Walsh and Cunningham *Psychopharmacology*, 1997, 130,41-58). Thus, studies in humans have
5 shown that blockade of the 5-HT reuptake attenuates the subjective effects of psychomotor stimulants such as cocaine (Walsh et al. *J Clin Psychopharmacology*, 1994, 14, 396-407). 5-HT reuptake inhibitors may also be useful in treatment of alcohol abuse (see Sellers et al. *J Clin Psychiatry*, 1991, 52, 49-54). Therefore, 5-HT reuptake inhibitors may be beneficial in the treatment of drug abuse.

10

5-HT reuptake inhibitors have been demonstrated to be effective in the treatment of both bulimia nervosa as well as in anorexia nervosa (see Kaye et al. *Biol Psychiatry*, 1998, 44, 825-838). Clinical studies have indicated that treatment with 5-HT reuptake inhibitors show superiority over placebo in reducing the frequency of binge eating
15 episodes (Goldstein et al. *Br J Psychiatry*, 1995, 166, 660-666). Moreover, published data suggest that 5-HT reuptake inhibitors improves outcome and prevents relapse in people with anorexia nervosa (Kaye et al. *Biol Psychiatry*, 1998, 44, 825-838). Thus, it seems clear that 5-HT reuptake inhibitors are useful in the pharmacotherapy of eating disorders including bulimia and anorexia.

20

Finally, clinical studies have indicated a beneficial role of 5-HT reuptake inhibitors in pharmacological intervention of obesity. Thus, treatment with 5-HT reuptake inhibitors has been reported to be effective in inducing significant weight loss in both obese males and females (Ricca et al. *J Endocrinol Invest*, 1996, 19, 727-733; Lawton et al. *Obes*
25 *Res*, 1995, 3, 345-356).

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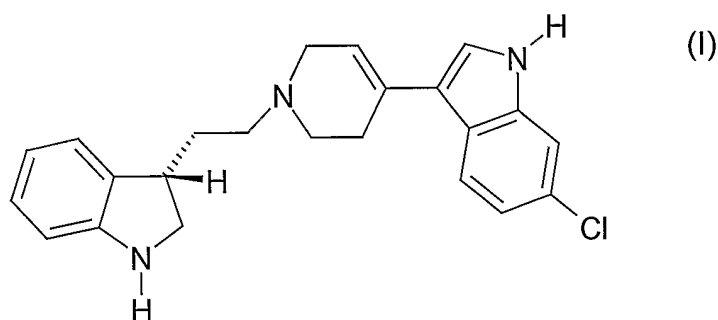
Compounds with combined effects at the 5-HT transporter and the dopamine D₄ receptor have the further benefit of improved effect on depressive and negative symptoms in schizophrenic patients.

WO 98/28293 describes a series of substituted indane or dihydroindole compounds having effect at dopamine D₄ receptors. The compounds described are considered useful for the treatment of a range of psychiatric and neurological disorders, including the positive and negative symptoms of schizophrenia and other psychoses. This

application contains a disclosure of the racemate of 3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole as the oxalate salt and the (+) and (-) form of a closely related compound having an acetyl group instead of hydrogen in position 1 of the 2,3 -dihydro-indole.

5

It has now been found that S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole having the formula



10 and pharmaceutically acceptable salts thereof have potent 5-HT reuptake inhibiting effect in addition to effect at the dopamine D₄ receptor.

It has also been found that this compound has more optimal properties for use as a pharmaceutical than the S-enantiomer of the corresponding compound having an acetyl group in position 1 of the 2,3-dihydro-indole (i.e the above mentioned (+)-enantiomer).
15 For example, the half-life for the compound in humans appears to be longer and the volume of distribution in humans appears to be smaller than the half life and volume of distribution of the corresponding S-enantiomer having an acetyl group in position 1 of the 2,3-dihydro-indole. These findings indicate a better stability of the compound of the
20 present invention in the human body. Further, the compound of the invention is a metabolite of the corresponding S-enantiomer having an acetyl group in position 1 of the 2,3-dihydro-indole in humans and it may thus be more convenient to use the compound of the invention as a pharmaceutical.

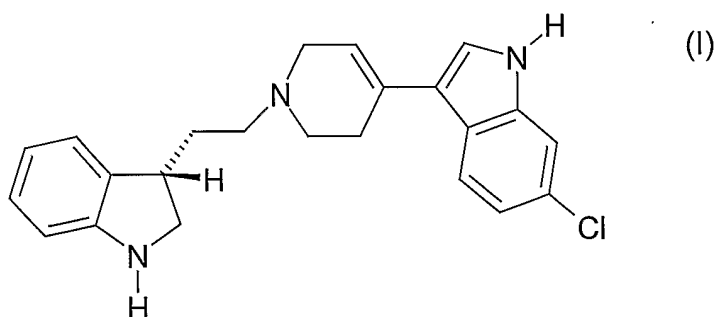
25 In vitro studies show that the compound of the invention is more potent than the corresponding racemate and the corresponding S-enantiomer having an acetyl group in position 1 of the 2,3-dihydro-indole, at the dopamine D₄ receptor and the 5-HT transporter.

Furthermore, preliminary studies indicate that the compound is a safe drug with few side effects.

5 Summary of the Invention

Accordingly, the present invention relates to the compound S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole having the formula

10



or a pharmaceutically acceptable salt thereof and the use of this compound for the treatment diseases and disorders responsive to 5-HT reuptake inhibition.

15

The compound may also be used for the treatment of diseases or disorders responsive to dopamine D₄ receptor antagonism.

20

Diseases and disorders responsive to inhibition of 5-HT reuptake are depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders including aggression and drug abuse.

25

Diseases or disorders responsive to dopamine D₄ receptor antagonists are psychoses, positive and negative symptoms of schizophrenia, cognitive disorders, ADHD and dyskinesia resulting from treatment of Parkinson's disease with L-Dopa.

In particular, the compound of the invention is considered useful in the treatment of positive and negative symptoms of schizophrenia without inducing extrapyramidal side effects and in the treatment of depression.

5

Detailed Description of the Invention

The racemate of the compound S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole was first disclosed in WO 98/28293, an application covering compounds having affinity for the dopamine D₄ receptor.

10 Although it is indicated that some of the compounds disclosed in WO 98/28293 have effect at 5-HT_{1A} and 5-HT₂ receptors and/or have 5-HT reuptake inhibiting effect, the application is silent as regards the effect of 3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole and its enantiomers at these receptors and the 5-HT transporter.

15

It has now surprisingly been found that the compound S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole is a very potent 5-HT reuptake inhibitor. Thus, the present invention covers the use of this compound for the treatment of diseases or disorders responsive to 5-HT reuptake inhibition.

20

An additional advantage of the compound of the invention is that the free base exists in a crystalline form, which have some advantages with regard to formulation of a pharmaceutical composition containing the compound. For example, a crystalline base may be formulated both as an oral solid unit dosage form, e.g. a tablet and in a capsule
25 containing the base in an organic or oily phase.

The compound of formula (I) may be prepared by reduction of the acid group of (+)-(1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-indol-3-yl)acetic acid and conversion of the hydroxy group of the resulting alcohol to a halogen group and thereafter reaction with
30 6-chloro-3-(3,6-dihydro-2*H*-pyridin-4-yl)-1*H*-indole to give the boc-protected analogue of the compound of formula (I). The compound of formula (I) may be obtained by deprotection of the Boc-analogue by the use of trifluoro acetic acid. The compounds

(+)-(1-tert-butoxycarbonyl-2,3-dihydro-1*H*-indol-3-yl)acetic acid and 6-chloro-3-(3,6-dihydro-2*H*-pyridin-4-yl)-1*H*-indole may be prepared as described in WO 98/28293.

Suitable salts of the compound of the invention may suitable be prepared by reacting the compound with either the calculated amount of an organic or inorganic acid in a water miscible solvent, with subsequent isolation of the salt by concentration and cooling, or with an excess of an organic or inorganic acid in a water immiscible solvent, with the salt separating spontaneously.

10 Pharmacological Testing

The compound S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole has been tested in a well-recognised and reliable test for measuring 5-HT reuptake inhibition and dopamine D₄ receptor affinity.

15

Inhibition of [³H]YM-09151-2 binding to D₄ receptor

A D_{4.2} expressing CHO cell line was generated *in house* using standard stable transfection techniques. Cells were harvested, homogenised and tested in 50 mM Tris containing 5 mM MgCl₂, 5 mM EDTA, 5 mM KCl, 1.5 mM CaCl₂, pH 7.4. Clozapine (10 μM) was used as non-specific displacer. The homogenate was incubated with test compound and 0.06 nM [³H]YM-09151-2 for 60 minutes at 25 °C. The assay was terminated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux). The compound of the invention has a KI value of 1.3 nM in this test, whereas the corresponding racemate have a KI value of 4.5 nM and the corresponding S-(+)-enantiomer of a compound having an acetyl group in position 1 of the 2,3-dihydroindole has a KI value of 4.4 in this test.

25

Measurement of [³H]5-HT uptake into rat whole brain synaptosomes

30

Using this method, the ability of the drugs to inhibit the accumulation of [³H]-5-HT into whole rat brain synaptosomes is determined *in vitro*. The assay was performed as described by Hyttel, J. *Psychopharmacology* 1978, 60, 13.

S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole have an IC₅₀ value of 5.3 nM in this test and the S-(+)-enantiomer having an acetyl group in position 1 of the 2,3-dihydroindole has a IC₅₀ value of 8.7 in this test.

5 Functional Dopamine D₄ assay

The compound of the invention has also been tested in a functional assay described by Gazi et al. in *Br. J. Pharmacol.* **1999**, 128, 613-629. In this test, the compound of the invention, the racemate and the S-(+)-enantiomer having an acetyl group in position 1
10 of the 2,3-dihydroindole were shown to be an antagonists at dopamine D₄ receptors.

Example

S-(+)-3-{1-[2-(2,3-Dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl}-6-
15 chloro-1*H*-indole

S-(+)-(1-*tert*-Butoxycarbonyl-2,3-dihydro-1*H*-indol-3-yl)acetic acid (compound 33a, WO 98/28293) (7.4 g) was dissolved in tetrahydrofuran (100 mL) and subsequently added to a suspension of LiAlH₄ (3.0 g) in tetrahydrofuran (250 mL) at 5 °C. The reaction was quenched by sequential addition of water (6 mL), 15% NaOH (3 mL) and
20 water (15 mL), and then added MgSO₄. The mixture was stirred at room temperature for 30 min, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (heptane/ethyl acetate 1:1) to give a colorless oil (5.4 g). A mixture of the crude oil (5.4 g), triethylamine (3.4 mL) and tetrahydrofuran (100 mL) was cooled (5 °C) and subsequently added a solution of methanesulfonyl chloride (1.7 mL) in
25 tetrahydrofuran (50 mL) at 5-10 °C. The resulting mixture was stirred at room temperature for 30 min, filtered and concentrated *in vacuo*. The residue was dissolved in acetone (100 mL), added LiBr (8.9 g) and boiled under reflux for 2 h. The mixture was filtered, concentrated *in vacuo*, and the residue was purified by flash chromatography (heptane/ethyl acetate 4:1) to give a colorless oil (5.9 g). The crude oil (4.0 g) was then
30 dissolved in butanone (100 mL) and subsequently added drop wise to a mixture of 6-chloro-3-(3,6-dihydro-2*H*-pyridin-4-yl)-1*H*-indole (3.4 g) and TEA (8.6 mL) in butanone (300 mL). The resulting mixture was boiled under reflux for 12 h, concentrated *in vacuo* and purified by flash chromatography (ethyl

acetate/ethanol/triethylamine 20:2:1) to give a crude amorphous product (3.9 g). The crude product was dissolved in a mixture of dichloromethane (40 mL) / tetrahydrofuran (25 mL) and cooled (5 °C) and subsequently added trifluoro acetic acid (30 mL). The mixture was stirred at room temperature for 16 h and then poured onto an ice/water
5 mixture. The aqueous phase was made alkaline with aqueous ammonia and extracted with ethyl acetate. The combined organic phase was washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate/ethanol/triethylamine 100:4:4) to give crude target product that was crystallized from ethyl acetate and subsequent ethanol to give pure target product (0.5 g). Analysis:
10 enantiomeric excess > 98.0 %; $[\alpha]_D = +58.1^\circ$ (c = 0.21, methanol); mp 166-169 °C; ¹H NMR (DMSO-*d*₆) δ 1.60-1.70 (m, 1H); 1.90-2.05 (m, 1H); 2.40-2.55 (m, 4 H); 2.60-2.70 (m, 2H); 3.05-3.15 (m, 3H); 3.15-3.25 (m, 1H); 3.55 (t, 1H); 5.40 (s, 1H); 6.10 (s, 1H); 6.50 (d, 1H); 6.55 (t, 1H); 6.90 (t, 1H); 7.00-7.05 (m, 2H); 7.40-7.45 (m, 2H); 7.80 (d, 1H); 11.25 (s, 1H).

15

Formulation

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

20

Thus, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or fillers and diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants, diluents or fillers comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any
25 other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Alternatively, capsules containing the compound of the invention in an organic and/or
30 oily phase may be used.

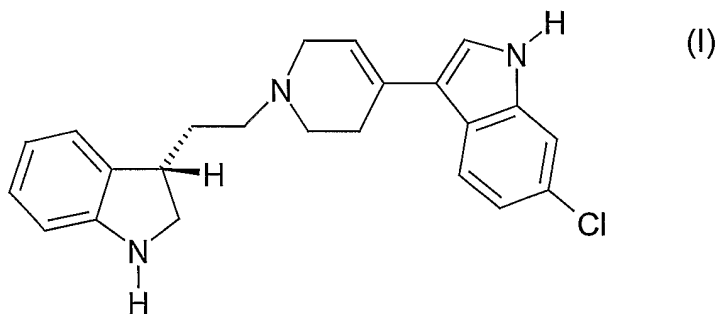
Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water,

adjusting the solution to desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

- 5 The daily dose of the compound of the invention may depend on the disease or disorder to be treated. A suitable daily dose is 0.1-500 mg, more suitable 1-150 mg and more suitable 5-100 mg, even more suitable 10-50 mg, an still more suitable 20-30 mg, depending on the condition to be treated.

Patent Claims

1. The compound S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole having the formula



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or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein the compound is S-(+)-3-[1-[2-(2,3-dihydro-1*H*-indol-3-yl)ethyl]-3,6-dihydro-2*H*-pyridin-4-yl]-6-chloro-1*H*-indole in the form of the crystalline free base.

3. A pharmaceutical composition comprising a compound according to any of claims 1-2 together with pharmaceutically acceptable carriers, fillers or diluents.

15

4. The use of the compound of any of claims 1-2 for the preparation of a pharmaceutical composition for the treatment diseases and disorders responsive dopamine D₄ receptor antagonism.

5. The use of the compound of any of claims 1-2 for the preparation of a pharmaceutical composition for the treatment diseases and disorders responsive to 5-HT reuptake inhibition.

6. The use according to claim 4 wherein diseases or disorders responsive to dopamine D₄ antagonism is psychoses, positive and negative symptoms of schizophrenia, cognitive disorders, ADHD and dyskinesia resulting from treatment of Parkinson's disease with L-Dopa.

25

7. The use according to claim 6 wherein the disease or disorder responsive to dopamine D₄ antagonism is psychosis and the positive and negative symptoms of schizophrenia.
- 5 8. The use according to claim 5 wherein the diseases or disorders responsive to 5-HT reuptake inhibition is selected from depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia,
10 premenstrual syndrome, cognitive disorders, impulse control disorders including aggression and drug abuse.
9. The use according to claim 8 wherein the diseases or disorders responsive to 5-HT reuptake inhibition is depression.
- 15 10. A method for the treatment of diseases or disorders responsive to dopamine D₄ antagonism comprising administering a compound according to claim 1 or a pharmaceutically acceptable salts thereof to an individual in need thereof.
- 20 11. A method for the treatment of diseases or disorders responsive to 5-HT reuptake inhibition comprising administering a compound according to claim 1 or a pharmaceutically acceptable salts thereof to an individual in need thereof.
12. The method according to claim 10 wherein the diseases or disorders responsive
25 to dopamine D₄ ligands are psychoses, positive and negative symptoms of schizophrenia, cognitive disorders, ADHD and dyskinesia resulting from treatment of Parkinson's disease with L-Dopa.
13. The method according to claim 12 wherein the diseases or disorders responsive to
30 dopamine D₄ ligands are psychoses and positive and negative symptoms of schizophrenia.
14. The method according to claim 11 wherein the diseases or disorders responsive to 5-HT reuptake inhibition is selected from depression, anxiety disorders and other affective disorders, including generalized anxiety disorder, panic anxiety, obsessive

compulsive disorder, acute stress disorder, post traumatic stress disorder or social anxiety disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders including aggression and drug abuse.

5

15. The method according to claim 14 wherein the disease or disorder responsive to 5-HT reuptake inhibition is depression.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 03/00564

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/14, A61K 31/4439, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9828293 A1 (H. LUNDBECK A/S), 2 July 1998 (02.07.98) --	1-15
A	WO 9967237 A1 (H. LUNDBECK A/S), 29 December 1999 (29.12.99) --	1-15
A	WO 0200645 A1 (H. LUNDBECK A/S), 3 January 2002 (03.01.02) --	1-15
A	WO 0196328 A1 (H. LUNDBECK A/S), 20 December 2001 (20.12.01) -- -----	1-15

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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

"&" document member of the same patent family

Date of the actual completion of the international search

12 November 2003

Date of mailing of the international search report

17-11-2003

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK03/00564

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☒ Claims Nos.: **10-15**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
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, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ 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 claims Nos.:

Remark on Protest

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

Claims 10-15 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.

PCT/DK 03/00564

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INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.

PCT/DK 03/00564

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