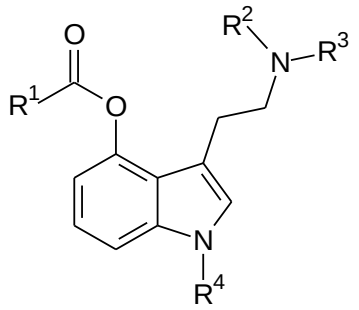
Summary

In an aspect of the present disclosure, there is provided a psilocin derivative according to the general formula (I):



(I),

wherein:

R^1 is selected from -O-(C_{1-12} alkyl), -O-CH_2-phenyl, -CH_2-NH_2, -CH(-NH_2)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_3, -CH(-NH_2)-CH_2-CH(-CH_3)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_2CH_3, -CH(-NH_2)-CH_2CH_2-S-CH_3, -CH(-NH_2)-CH_2-SH, -CH(-NH_2)-CH_2-OH, -CH(-NH_2)-CH(-CH_3)-OH, -CH(-NH_2)-CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2-COOH, -CH(-NH_2)-CH_2CH_2-COOH, -CH(-NH_2)-$CH_2CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=NH)-NH_2, -CH(-NH_2)-CH_2-(1H-imidazol-4-yl), -CH(-NH_2)-CH_2-phenyl, -CH(-NH_2)-CH_2-(4-hydroxyphenyl), -CH(-NH_2)-CH_2-(1H-indol-3-yl), -(pyrrolidin-2-yl), -(4-hydroxypyrrolidin-2-yl), -CH(-NH_2)-CH_2-S-S-CH_2-CH(-NH_2)-COOH, -CH(-NH_2)-$CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=O)-NH_2, -CH_2-NH-CH_3, -CH(-NH_2)-CH_2CH_2-SH, -CH(-NH_2)-CH_2CH_2-OH, -CH(-NH_2)-CH_2-(3,4-dihydroxyphenyl), -CH(-NH_2)-CH_2-(5-hydroxy-1H-indol-3-yl), -CH_2CH_2-NH_2, -$CH_2CH_2CH_2$-NH_2, -CH(-CH_3)-CH_2-NH_2, -C(-NH_2)=CH_2, -O-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -O-(C_{1-12} alkylene)-O-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2CH_2-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2-S-S-CH_2-CH(-NH_2)-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -O-(5-(aminomethyl)isoxazol-3-yl), and -CH(-NH_2)-(3-hydroxy-isoxazol-5-yl);

R^2 and R^3 are each independently selected from hydrogen, methyl and ethyl, provided that R^2 and R^3 are not both hydrogen; and

R^4 is hydrogen or -C(=O)-O-(C_{1-6} alkyl);

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising at least one psilocin derivative disclosed herein and optionally one or more pharmaceutically acceptable excipients.

In a further aspect of the present disclosure, there is provided a psilocin derivative disclosed herein or the pharmaceutical composition disclosed herein for use in the treatment of a serotonin $5\text{-}HT_{2A}$ receptor associated disease/disorder.

In another aspect of the present disclosure, there is provided a use of the psilocin derivative disclosed herein in the manufacture of a medicament for the treatment of a serotonin 5-HT_{2A} receptor associated disease/disorder.

In a further aspect of the present disclosure, there is provided a method for producing a psilocin derivative disclosed herein, comprising the steps of:

(a) preparing a suspension of psilocin in a solvent I;
(b) adding an activating agent under a protective gas atmosphere;
(c) adding a derivatization agent;
(d) stirring the mixture under a protective gas atmosphere for at least 3 hours;
(e) stopping the reaction by dilution with solvent;
(f) concentrating the solvent;
(g) dissolving the residue in a solvent II;
(h) extracting with 1 M HCl, water and saturated saline solution;
(i) drying the organic phase over a desiccant at 40-60°C under vacuum;
(j) obtaining the crude product;
(k) purifying the crude product by recrystallization and/or column chromatography;
(l) obtaining the psilocin derivative disclosed herein.

Brief Description of the Drawings:

FIG. 1: Thin layer chromatograms of the starting material psilocin (**E**), the end product psilocin-4-yl ethyl carbonate (**CO3**) and the intermediate product psilocin-4-yl-Fmoc-tryptophanate (**AS**) in chloroform/ethanol 10:1 (left panel) and dichloromethane/methanol 7:3 (right panel), respectively.

FIG. 2: Thin layer chromatograms of the starting material psilocin (**E**), the end product psilocin-4-yl ethyl carbonate (**CO3**) and the intermediate product psilocin-4-yl-Fmoc-tryptophanate (**AS**) in tert-butyl methyl ether/ethanol 8:2 (left panel), hexane/ethyl acetate 7:3 (central panel), and tert-butyl methyl ether/isopropanol 8:2 (right panel), respectively.

FIG. 3: HPLC-MS spectrum of psilocin-4-yl ethyl carbonate from the reaction solution.

FIG. 4: HPLC-MS spectrum of psilocin-4-yl-Fmoc-tryptophanate from the reaction solution.

FIG. 5: Stability of novel psilocin carbonates in HCl. (**A**) % of parent compound remaining following incubation in 1% HCl solution over 24 hours. (**B**) % of psilocin liberated from test compounds during incubation in 1% HCl. (**C**) % of psilocin tert-butylcarbonate remaining following incubation in 1% HCl solution for over 24 hours. (**D**) % of psilocin liberated from test compounds during incubation in 1% HCl. See Example 9.

FIG. 6: Pharmacokinetics of novel psilocin carbonates in the mouse. (**A**) Plasma psilocin concentrations following intravenous dosing of mice with test compounds. Data shown as mean±SEM. (**B**) Plasma psilocin concentrations following oral dosing of mice with test compounds. Data shown as mean±SEM. (**C**) Plasma psilocin concentrations following intravenous dosing of mice with psilocybin or psilocin-4-yl-ethylcarbonate. Data shown as mean±SEM. (**D**) Plasma psilocin concentrations following oral dosing of mice with psilocybin or psilocin-4-yl-ethylcarbonate. Data shown as mean±SEM. (**E**) Plasma psilocin concentrations following intravenous dosing of mice with psilocybin or psilocin-4-yl-tert-butylcarbonate. Data shown as mean±SEM. (**F**) Plasma psilocin concentrations following oral dosing of mice with psilocybin or psilocin-4-yl-tert-butylcarbonate. Data shown as mean±SEM. (**G**) Plasma psilocin concentrations following intravenous dosing of mice with psilocybin or psilocin-4-yl-benzylcarbonate. Data shown as mean±SEM. (**H**) Plasma psilocin concentrations following oral dosing of mice with psilocybin or psilocin-4-yl-benzylcarbonate. Data shown as mean±SEM. See Example 12.

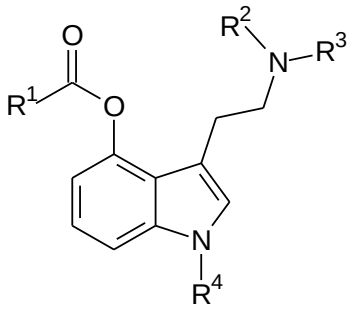
Detailed Description:

Definitions:

For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

CLAIMS

1. A psilocin derivative according to the general formula (I):



(I),

wherein:

R^1 is selected from -O-(C_{1-12} alkyl), -O-CH_2-phenyl, -CH_2-NH_2, -CH(-NH_2)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_3, -CH(-NH_2)-CH_2-CH(-CH_3)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_2CH_3, -CH(-NH_2)-CH_2CH_2-S-CH_3, -CH(-NH_2)-CH_2-SH, -CH(-NH_2)-CH_2-OH, -CH(-NH_2)-CH(-CH_3)-OH, -CH(-NH_2)-CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2-COOH, -CH(-NH_2)-CH_2CH_2-COOH, -CH(-NH_2)-$CH_2CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=NH)-NH_2, -CH(-NH_2)-CH_2-(1H-imidazol-4-yl), -CH(-NH_2)-CH_2-phenyl, -CH(-NH_2)-CH_2-(4-hydroxyphenyl), -CH(-NH_2)-CH_2-(1H-indol-3-yl), -(pyrrolidin-2-yl), -(4-hydroxypyrrolidin-2-yl), -CH(-NH_2)-CH_2-S-S-CH_2-CH(-NH_2)-COOH, -CH(-NH_2)-$CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=O)-NH_2, -CH_2-NH-CH_3, -CH(-NH_2)-CH_2CH_2-SH, -CH(-NH_2)-CH_2CH_2-OH, -CH(-NH_2)-CH_2-(3,4-dihydroxyphenyl), -CH(-NH_2)-CH_2-(5-hydroxy-1H-indol-3-yl), -CH_2CH_2-NH_2, -$CH_2CH_2CH_2$-NH_2, -CH(-CH_3)-CH_2-NH_2, -C(-NH_2)=CH_2, -O-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -O-(C_{1-12} alkylene)-O-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2CH_2-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -CH(-NH_2)-CH_2-S-S-CH_2-CH(-NH_2)-COO-(1-[R^4]-3-[(-CH_2CH_2-N(-R^2)-R^3)]-1H-indol-4-yl), -O-(5-(aminomethyl)isoxazol-3-yl), and -CH(-NH_2)-(3-hydroxy-isoxazol-5-yl);

R^2 and R^3 are each independently selected from hydrogen, methyl and ethyl, provided that R^2 and R^3 are not both hydrogen; and

R^4 is hydrogen or -C(=O)-O-(C_{1-6} alkyl);

or a pharmaceutically acceptable salt thereof.

2. The psilocin derivative according to claim 1, wherein R^1 is -O-(C_{1-12} alkyl) or -O-CH_2-phenyl.

3. The psilocin derivative according to claim 1, wherein R^1 is selected from -CH_2-NH_2, -CH(-NH_2)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_3, -CH(-NH_2)-CH_2-CH(-CH_3)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_2CH_3, -CH(-NH_2)-CH_2CH_2-S-CH_3, -CH(-NH_2)-CH_2-SH, -CH(-NH_2)-CH_2-OH, -CH(-NH_2)-CH(-CH_3)-OH, -CH(-NH_2)-CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2-COOH, -CH(-NH_2)-CH_2CH_2-COOH, -CH(-NH_2)-$CH_2CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=NH)-NH_2, -CH(-NH_2)-CH_2-(1H-imidazol-4-yl), -CH(-NH_2)-CH_2-phenyl, -CH(-NH_2)-CH_2-(4-hydroxyphenyl), -CH(-NH_2)-CH_2-(1H-indol-3-yl), and -(pyrrolidin-2-yl).

4. The psilocin derivative according to claim 1, wherein R^1 is selected from -CH(-NH_2)-CH(-CH_3)-CH_3, -CH(-NH_2)-CH_2-CH(-CH_3)-CH_3, -CH(-NH_2)-CH(-CH_3)-CH_2CH_3, -CH(-NH_2)-CH_2CH_2-S-CH_3, -CH(-NH_2)-CH_2-SH, -CH(-NH_2)-CH_2-OH, -CH(-NH_2)-CH(-CH_3)-OH, -CH(-NH_2)-CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2CH_2-C(=O)-NH_2, -CH(-NH_2)-CH_2-COOH, -CH(-NH_2)-CH_2CH_2-COOH, -CH(-NH_2)-$CH_2CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=NH)-NH_2, -CH(-NH_2)-CH_2-(1H-imidazol-4-yl), -CH(-NH_2)-CH_2-phenyl, -CH(-NH_2)-CH_2-(4-hydroxyphenyl), -CH(-NH_2)-CH_2-(1H-indol-3-yl), and -(pyrrolidin-2-yl).

5. The psilocin derivative according to claim 1, wherein R^1 is selected from -(4-hydroxypyrrolidin-2-yl), -CH(-NH_2)-CH_2-S-S-CH_2-CH(-NH_2)-COOH, -CH(-NH_2)-$CH_2CH_2CH_2$-NH_2, -CH(-NH_2)-$CH_2CH_2CH_2$-NH-C(=O)-NH_2, -CH_2-NH-CH_3, -CH(-NH_2)-CH_2CH_2-SH, -CH(-NH_2)-CH_2CH_2-OH, -CH(-NH_2)-CH_2-(3,4-dihydroxyphenyl), -CH(-NH_2)-CH_2-(5-hydroxy-1H-indol-3-yl), -CH_2CH_2-NH_2, -$CH_2CH_2CH_2$-NH_2, -CH(-CH_3)-CH_2-NH_2, and -C(-NH_2)=CH_2.

6. The psilocin derivative according to any one of claims 1 to 5, wherein R^2 and R^3 are each methyl.

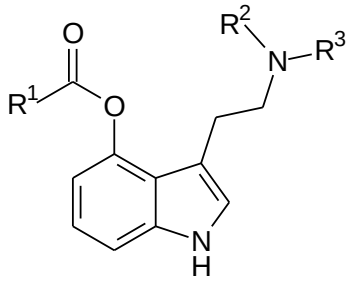
7. The psilocin derivative according to any one of claims 1 to 5, wherein R^2 is methyl and R^3 is hydrogen.

8. The psilocin derivative according to any one of claims 1 to 5, wherein R^2 is methyl and R^3 is ethyl.

9. The psilocin derivative according to any one of claims 1 to 8, wherein R^4 is hydrogen.

10. The psilocin derivative according to any one of claims 1 to 8, wherein R^4 is -C(=O)-O-(C_{2-4} alkyl).

11. The psilocin derivative according to claim 1, wherein said psilocin derivative is a compound of the following formula:



wherein:

R^1 is selected from -O-(C_{2-5} alkyl), -O-CH_2-phenyl, -CH_2-NH_2, -CH(-NH_2)-CH_2-COOH, and -CH(-NH_2)-CH_2-(1H-indol-3-yl);

R^2 is methyl or ethyl; and

R^3 is methyl or ethyl;

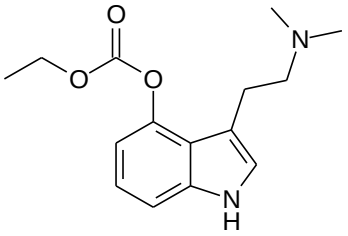
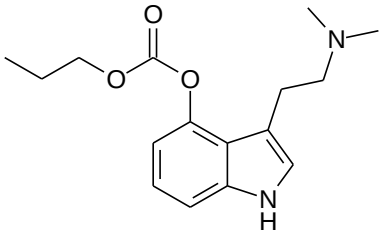
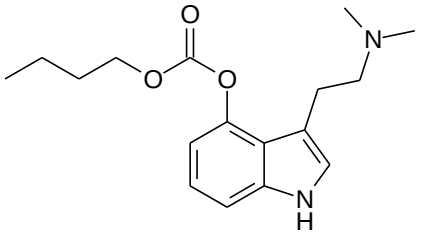
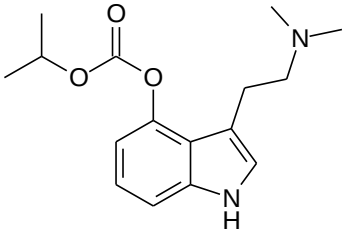
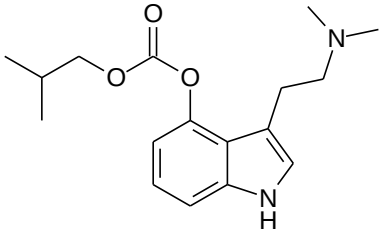
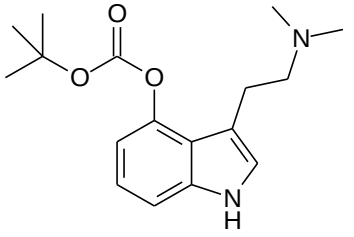
or a pharmaceutically acceptable salt thereof.

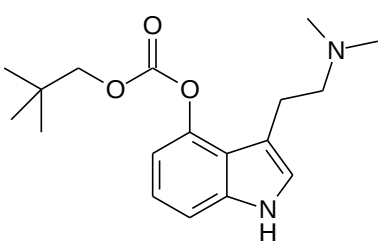
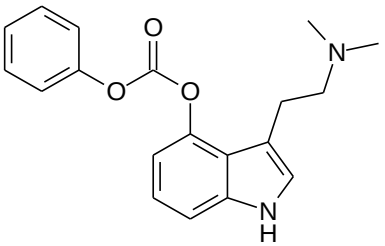
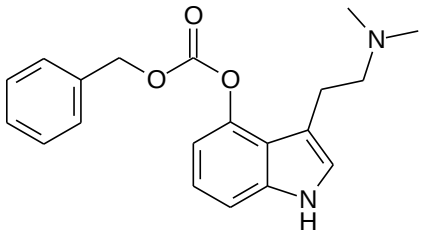
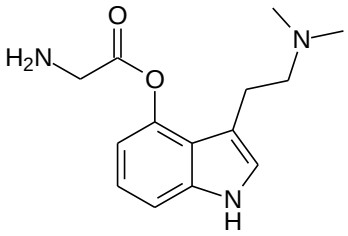
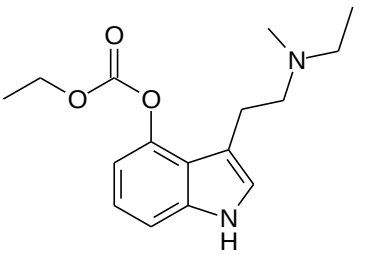
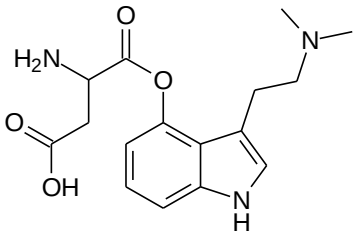
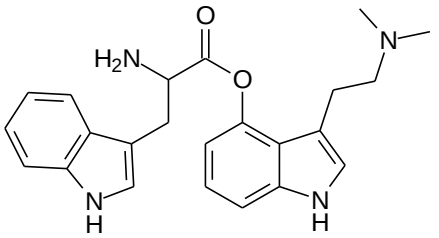
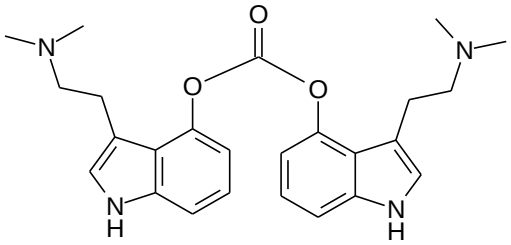
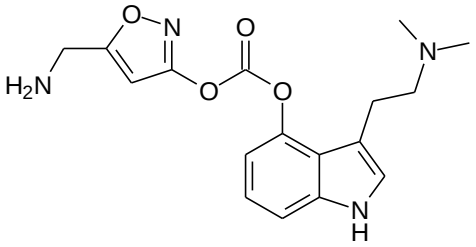
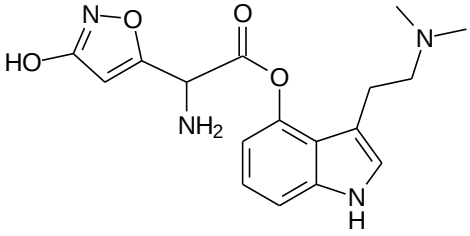
12. The psilocin derivative according to claim 11, wherein R^1 is -O-(C_{2-5} alkyl) or -O-CH_2-phenyl.

13. The psilocin derivative according to claim 11, wherein R^1 is selected from -CH_2-NH_2, -CH(-NH_2)-CH_2-COOH, and -CH(-NH_2)-CH_2-(1H-indol-3-yl).

14. The psilocin derivative according to any one of claims 11 to 13, wherein R^2 and R^3 are each methyl.

15. The psilocin derivative according to claim 1, wherein said psilocin derivative is selected from any one of the following compounds or a pharmaceutically acceptable salt thereof:


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16. The psilocin derivative according to any one of claims 1 to 15, wherein said psilocin derivative is in the form of a pharmaceutically acceptable salt;
wherein said pharmaceutically acceptable salt is preferably a fumarate salt, a maleate salt, an oxalate salt, a malate salt, a tartrate salt, or a mesylate salt, more preferably an oxalate salt or a fumarate salt.

17. A pharmaceutical composition comprising at least one psilocin derivative according to any one of claims 1 to 16 and optionally one or more pharmaceutically acceptable excipients.

18. The psilocin derivative according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 17 for use in the treatment of a serotonin 5-HT_{2A} receptor associated disease/disorder.

19. The psilocin derivative for use according to claim 18 or the pharmaceutical composition for use according to claim 18, wherein said psilocin derivative or said pharmaceutical composition is for use in the treatment of an anxiety disorder, attention deficit hyperactivity disorder (ADHD), depression, cluster headache, a condition associated with cancer, diminished drive, burn-out, bore-out, migraine, Parkinson's disease, pulmonary hypertension, schizophrenia, an eating disorder, nausea, or vomiting.

20. Use of the psilocin derivative according to any one of claims 1 to 16 in the manufacture of a medicament for the treatment of a serotonin 5-HT_{2A} receptor associated disease/disorder.

21. The use according to claim 20, wherein said disease/disorder is an anxiety disorder, attention deficit hyperactivity disorder (ADHD), depression, cluster headache, a condition associated with cancer, diminished drive, burn-out, bore-out, migraine, Parkinson's disease, pulmonary hypertension, schizophrenia, an eating disorder, nausea, or vomiting.

~~22. A method of treating a serotonin 5-HT_{2A} receptor associated disease/disorder in a subject in need thereof, the method comprising administering a therapeutically effective amount of the psilocin derivative according to any one of claims 1 to 16 to said subject.~~

~~23. The method according to claim 22, wherein said disease/disorder is an anxiety disorder, attention deficit hyperactivity disorder (ADHD), depression, cluster headache, a condition associated with cancer, diminished drive, burn-out, bore-out, migraine, Parkinson's disease, pulmonary hypertension, schizophrenia, an eating disorder, nausea, or vomiting.~~

~~24~~22. A method for producing a psilocin derivative according to any one of claims 1 to 16, comprising the steps of:

(a) preparing a suspension of psilocin in a solvent I;
(b) adding an activating agent under a protective gas atmosphere;
(c) adding a derivatization agent;
(d) stirring the mixture under a protective gas atmosphere for at least 3 hours;
(e) stopping the reaction by dilution with solvent;
(f) concentrating the solvent;
(g) dissolving the residue in a solvent II;
(h) extracting with 1 M HCl, water and saturated saline solution;
(i) drying the organic phase over a desiccant at 40-60°C under vacuum;
(j) obtaining the crude product;
(k) purifying the crude product by recrystallization and/or column chromatography;

(l) obtaining the psilocin derivative according to any one of claims 1 to 16.

~~25~~23. The method according to claim ~~24~~22, wherein:

(i) the activating agent is a nitrogen base, a carbodiimide, or a combination thereof; preferably wherein the activating agent is triethylamine, diisopropylethylamine, pyridine, 4-dimethylaminopyridine, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride, dicyclohexylcarbodiimide, diisopropylcarbodiimide, or a combination thereof; and/or

(ii) the derivatization agent is ethyl chloroformate, di-tert-butyl pyrocarbonate, N-carbobenzoxy-glycine, N-(9-fluorenylmethyloxycarbonyl)-L-tryptophan, 4-benzyl N-carbobenzoxy-L-aspartate, N-carbobenzoxy-L-tryptophan, or N-benzyloxycarbonyl-L-tryptophan; and/or

(iii) the solvent I is tetrahydrofuran, 2-methyltetrahydrofuran, or dioxane; and/or

(iv) the solvent II is ethyl acetate, diethyl ether, dichloromethane, or a combination thereof; and/or

(v) the yield of the psilocin derivative is at least 60 wt-% relative to the starting materials.