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The synthesis of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine, its use for the treatment of Alzheimer's disease, and pharmaceutical compositions comprising this compound are disclosed in U.S. Patent No. 7,157,488 ("the '488 patent"). The '488 patent further describes the preparation of the hydrochloride salt of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine.

N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine can be produced according to the method described in WO 11/76212.

By using the methods in the '488 patent and in WO 11/76212, the N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride is obtained as a solid.

Pharmaceutical solids can exist in amorphous, glass or crystalline states. Furthermore crystalline materials can be found as hydrates or other solvates. If such a compound can exist in more than one crystalline arrangement (polymorphic form) the compound is said to show polymorphism.

In order to be able to provide an active pharmaceutical ingredient of high and reproducible quality and with well-defined biological activity, it is desirable to have the active pharmaceutical ingredient in the most thermodynamically stable form.

The inventors of the present invention have found a new and thermodynamically stable form of the hydrochloride salt of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine.

SUMMARY

The present disclosure relates to polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

In one aspect, the present disclosure relates to polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, characterized by an X-Ray

powder diffractogram showing peaks at the following 2θ-angles: 4.63°, 6.94°, 13.89°, 17.26° and 19.97°.

In another aspect, the present disclosure further relates to a process for preparing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride comprising:

a. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride from a suspension of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine in an organic solvent selected from the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C.

In another aspect, the present disclosure further relates to a process for preparing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride comprising:

a. adding polymorphic form I, form II, amorphous or a mixture of the forms of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride to an organic solvent selected from the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C to produce a suspension;

b. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

In another aspect, the present disclosure further relates to a process for preparing polymorphic form III of N-[2-(6-fluoro-lH indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride comprising:

a. seeding a suspension of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride in an organic solvent selected from the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C with polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride;

b. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

In yet another aspect, the present disclosure further relates to a process for preparing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride comprising:

a. adding polymorphic form I, form II , amorphous or a mixture of the forms of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride to an organic solvent selected from the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, heptane, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C to produce a suspension;

b. seeding with polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride at a temperature below 60°C;

c. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

The present disclosure further relates to polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride for use as a medicament, a pharmaceutical composition comprising polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride and a method of treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment comprising administering an effective daily dose of polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride to a patient in need of such treatment.

In another aspect, the present disclosure relates to a compound as disclosed herein for use as a medicament.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as disclosed herein.

In a further aspect, the present disclosure relates to the use of a compound as disclosed herein for the manufacture of a medicament for treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment.

In yet another aspect, the present disclosure relates to polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, characterized by an FTIR spectrum having relative strong band intensity at the following band positions [cm^{-1}]: 3426, 1586, 1089, 762 and a shoulder at 1099 cm^{-1}.

In another aspect, the present disclosure relates to a pharmaceutical composition prepared from polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, wherein polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride is characterized by an X-Ray powder diffractogram showing peaks at the following 2θ-angles: 4.63°, 6.94°, 13.89°, 17.26°, 18.95°, 19.97°, 22.53° and 23.65°.

In a further aspect, the present disclosure relates to a pharmaceutical composition prepared from polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, wherein the polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride is characterized by an FTIR spectrum having strong band intensity at the following band positions [cm^{-1}]: 3426, 1586, 1089, 762 and a shoulder at 1099 cm^{-1}.

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1: X-ray powder diffractogram of polymorphic form I of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

FIGURE 2: X-ray powder diffractogram calculated from the crystal structure of polymorphic form I.

FIGURE 3: X-ray powder diffractogram of polymorphic form II of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

FIGURE 4: X-ray powder diffractogram calculated from the crystal structure of polymorphic form II.

FIGURE 5: X-ray powder diffractogram of polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C with polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride;

b. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

7. A process for preparing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride comprising:

a. adding polymorphic I, form II, amorphous or a mixture of the forms of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride to an organic solvent selected from the list of acetonitrile, proprionitrile, acetone, methanol, ethanol, heptane, toluene and xylenes (ortho, meta or para) or a mixture thereof, at a temperature below 60°C to produce a suspension;

b. seeding with polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride at a temperature below 60°C;

c. capturing polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride.

8. The process according to any of the claims 4-7, wherein the organic solvent is a mixture of acetone and heptane in the ratio 1:4.

9. The process according to any of the claim 4-7, wherein the organic solvent is a mixture of methanol and toluene in the ratio 1:4.

10. A compound according to any of the claims 1-3 or 15 for use as a medicament.

11. A pharmaceutical composition comprising a compound according to any of the claims 1-3 or 15.

12. Use of a compound according to any of the claims 1-3 or 15 for the manufacture of a medicament for treating Alzheimer's disease as adjunctive therapy to acetylcholinesterase treatment.

13. The use according to claim 12, wherein the dose of said compound is between about 30 and about 60 mg.

14. The process according to any of claims 4 to 7 wherein the suspension is produced in the temperature range 45°C - 55°C.

15. Polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, characterized by an FTIR spectrum having relative strong band intensity at the following band positions [cm^{-1}]: 3426, 1586, 1089, 762 and a shoulder at 1099 cm^{-1}.

16. A pharmaceutical composition prepared from polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, wherein polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride is characterized by an X-Ray powder diffractogram showing peaks at the following 2θ-angles: 4.63°, 6.94°, 13.89°, 17.26°, 18.95°, 19.97°, 22.53° and 23.65°.

17. A pharmaceutical composition prepared from polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride, wherein the polymorphic form III of N-[2-(6-fluoro-lH-indol-3-yl)ethyl]-3-(2,2,3,3-tetrafluoropropoxy)benzylamine hydrochloride is characterized by an FTIR spectrum having strong band intensity at the following band positions [cm^{-1}]: 3426, 1586, 1089, 762 and a shoulder at 1099 cm^{-1}.