Rotigotine Behenate, and Preparation Method and Use thereof

Technical Field

The present invention relates to a rotigotine derivative, a preparation method and use thereof, in particular to a rotigotine long-chain ester, a preparation method thereof and use thereof.

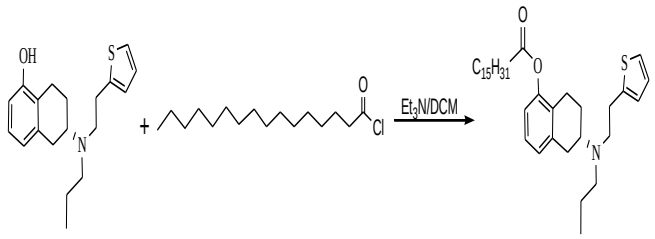
Background Art

Rotigotine is a non-ergot selective dopamine receptor agonist that produces an anti-Parkinson effect by activating D3/D2/D1 dopamine receptors. Due to the first-pass effect of the liver, the oral bioavailability of rotigotine is extremely low (about 1%-5%), which renders it unsuitable for oral administration. Currently there is no cure for Parkinson's disease. Patients thus require long-term treatment or management by drugs. Therefore, it is of great clinical significance to develop a drug characterized by a concise preparation process, low cost, and long-term steady release to improve the drug accessibility.

WO 2012/068783 discloses a rotigotine microsphere preparation capable of maintaining an effective blood drug concentration for more than two weeks. Although the microsphere preparation could achieve the objective of sustained steady release, the preparation process are complicated and accompanied by high production costs.

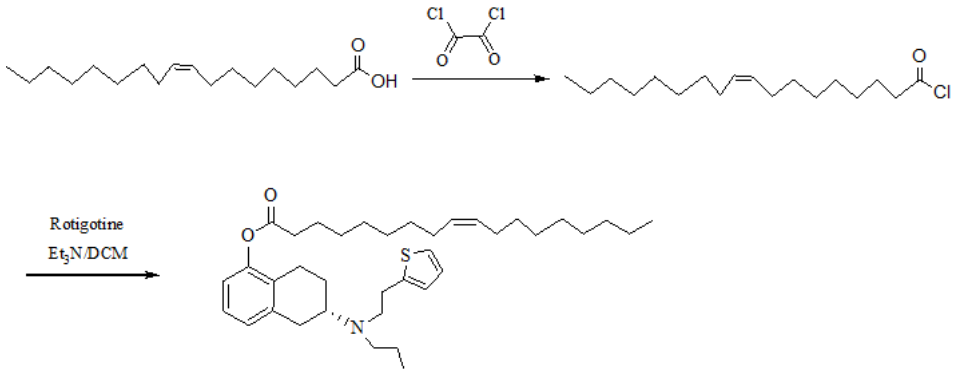
WO 2016/014242 discloses a series of structurally-modified derivatives of rotigotine, including rotigotine and its esters with saturated long chain of up to 16 carbons, which overcome the defect of low blood drug concentration of rotigotine for oral administration. Nevertheless, such oral dosage forms cannot achieve the objective of sustained steady release for longer than two weeks. Experiments conducted by the inventors of the present invention have revealed that injecting the saturated long-chain esters of rotigotine disclosed in WO 2016014242, such as rotigotine caprylate and rotigotine palmitate, can cause the blood drug concentration fluctuate significantly. As such, the

dichloromethane (DCM), which was referred to as solution II; Solution I was added dropwise to Solution II. The above reaction solution was washed with an equal volume of water after completion of the reaction, and the solvent of the organic phase was evaporated under reduced pressure. The residue was purified by column chromatography eluting with a 1:3 (v/v) ethyl acetate-petroleum ether system as the eluent, to provide a light yellow oil (31.8 g) in a yield of 72.1%.



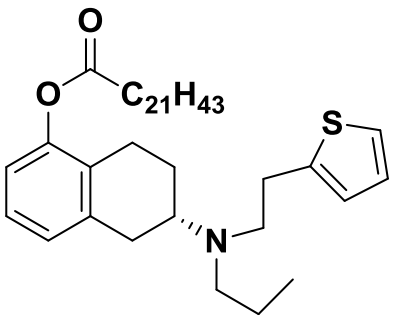
^{1}H NMR($CDCl_3$,400MHz)$\delta_{H:}$ 7.01 (m, 2H, H-7&H-14), 6.88 (d, *J*=7.56 Hz, 1H, H-6), 6.81 (t, *J*=3.46 Hz, 1H,H-15), 6.72 (t, *J*=2.78 Hz, 2H, H-8&H-13), 2.92 (m 4H, H-1&H-4), 2.78 (m, 4H, H-19&H-20), 2.49 (m, 5H, H-2,H-22&H-16), 2.04 (m, 1H, H-3), 1.77 (m, 2H, H-23), 1.58 (m, 1H, H-3), 1.39 (m, 2H, H-17), 1.23 (m, 8H, H-24~H-27), 0.96 (m, 6H, H-18&H-28).

Comparative Example 2: Rotigotine oleate



28.3 g (0.1 mol) of oleic acid was dissolved in 300 ml of dichloromethane (DCM) under nitrogen at room temperature, and 12.7 g (0.1 mol) of oxalyl chloride was added dropwise to the above mixed solution within 30 min, and the resulting solution after completion of the reaction at room temperature was referred to as Solution I; 31.5 g (0.1 mol) of rotigotine was dissolved in a mixed

1. Rotigotine behenate, as shown in formula (I):



(I).

2. A crystal form I of rotigotine behenate, wherein the crystal form I has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 21.563, 21.156, 23.295, 21.955 and 20.838 in a powder X-ray diffraction pattern obtained using Cu-Kα radiation.

3. The crystal form I according to claim 2, wherein the crystal form I has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 21.563, 21.156, 23.295, 21.955, 20.838, 16.154, 19.403, 11.749, 14.518 and 17.875 in a powder X-ray diffraction pattern obtained using Cu-Kα radiation.

4. The crystal form I according to claim 3, wherein the crystal form I has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 21.563, 21.156, 23.295, 21.955, 20.838, 16.154, 19.403, 11.749, 14.518, 17.875, 19.729, 20.299, 13.583, 11.962, 22.949, 23.772, 16.424, 15.749, 12.586 and 22.430. in a powder X-ray diffraction pattern obtained using Cu-Kα radiation

5. The crystal form I according to claim 4, wherein the crystal form I has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 21.563, 21.156, 23.295, 21.955, 20.838, 16.154, 19.403, 11.749, 14.518, 17.875, 19.729, 20.299, 13.583, 11.962, 22.949, 23.772, 16.424, 15.749, 12.586, 22.430, 12.238, 23.995, 18.626, 16.614, 28.574, 24.530, 25.169, 27.044, 36.329, 27.764, 29.127 and 31.490 in a powder X-ray diffraction pattern obtained using Cu-Kα radiation.

6. The crystal form I according to claim 5, wherein the crystal form I has a powder X-ray diffraction pattern substantially as shown in Fig. 4.

7. The crystal form I according to claim 2, wherein the crystal form I has a TGA/DSC curves substantially as shown in Fig. 6.

8. A crystal form Ⅱ of rotigotine behenate, wherein the crystal form II has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 21.481, 23.887 in a powder X-ray diffraction pattern obtained using Cu-Kα radiation.

9. The crystal form Ⅱ according to claim 8, wherein the crystal form II has characteristic peaks expressed in degrees 2θ(±0.2 2θ) at 3.274, 21.481, 23.887 in a powder X-ray diffraction pattern obtained using Cu-Kα radiation.

10. The crystal form Ⅱ according to claim 9, wherein the crystal form II has a powder X-ray diffraction pattern substantially as shown in Fig. 5.

11. The crystal form Ⅱ according to claim 8, wherein the crystal form II has a TGA/DSC curves substantially as shown in Fig.7.

12. A method for preparing a compound of claim 1, comprising: reacting behenoyl chloride with rotigotine to provide rotigotine behenate; or reacting behenic acid with rotigotine to provide rotigotine behenate; or reacting behenic anhydride with rotigotine to provide rotigotine behenate.

13. The method of claim 12, wherein the method comprises adding rotigotine to a mixed solution of triethylamine and dichloromethane (DCM) under nitrogen at room temperature, and then adding behenoyl chloride, washing after completion of the reaction, evaporating solvent under reduced pressure, and purifying to provide rotigotine behenate; or dissolving behenic acid, rotigotine and 4-(dimethylamino)pyridinium *p*-toluene sulfonate (DPTS) in dichloromethane (DCM) under nitrogen at room temperature to obtain a mixed solution, adding *N,N'*-dicyclohexylcarbodiimide (DCC) dropwise to the mixed solution to form a mixture, filtering the mixture after completion of the reaction, and evaporating a solvent under reduced pressure and purifying to provide rotigotine behenate; or dissolving behenic anhydride and rotigotine in anhydrous tetrahydrofuran (THF) under nitrogen, adding a catalytic amount of triethylamine to obtain a mixture, heating the mixture in oil bath, and evaporating a solvent under reduced pressure after completion of the reaction, and subsequently adding dichloromethane (DCM), followed by washing with sodium hydrogencarbonate solution, evaporating a solvent under reduced pressure and purifying to provide rotigotine behenate.

14. A method for preparing the crystal form I according to any one of claims 2 to 7, comprising: dissolving rotigotine behenate in an organic solvent, cooling and crystallizing, filtering, washing to provide the crystal form I of otigotine behenate , wherein the organic solvent is one or more selected from the group consisting of ethyl acetate, ethanol, methanol, cyclohexane, *n*-hexane, petroleum ether, tetrahydrofuran, acetone and *n*-heptane.

15. The method of claim 14, wherein the method comprises after the thermal dissolution of rotigotine behenate in ethyl acetate, adding methanol, cooling and crystallizing, followed by filtering and washing with an appropriate amount of methanol.

16. A method for preparing the crystal form Ⅱ according to any one of claims 8 to 11, comprising: placing rotigotine behenate in a mixed solvent of tetrahydrofuran and methanol, and stirring in the suspension at 40 °C to provide the crystal form Ⅱ of rotigotine behenate.

17. A pharmaceutical composition comprising an effective amount of any one or combination of the rotigotine behenate according to claim 1, , the crystal form I according to any one of claims 2-7, and the crystal form Ⅱ according to any one of claims 8-11.

18. The pharmaceutical composition according to claim 17, wherein the pharmaceutical composition is administered in a parenteral form.

19. Use of any one or combination of the rotigotine behenate according to claim 1, the crystal form I according to any one of claims 2-7, and the crystal form II according to any one of claims 8-11 in the preparation of a medicament for treating a disease associated with dopamine receptor.

20. The use according to claim 19, wherein the disease associated with dopamine receptor is Parkinson's disease.