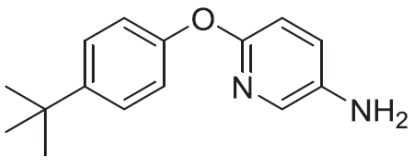
CLAIMS

1. A crystalline form of a monohydrochloride salt of the compound of formula (Ia)



Formula (Ia)

wherein the crystalline form is characterized by having an X-ray powder diffractogram which has one or more peaks chosen from peaks (° 2θ) at 7.3°±0.2°, 11.1°±0.2°, 14.6°±0.2°, 18.7°±0.2°, 21.4°±0.2°, 23.3°±0.2°, 23.8°±0.2°, 25.9°±0.2°, 27.4°±0.2°, and 30.7°±0.2°.

2. Use of the monohydrochloride salt of claim 1 in the manufacture of a medicament for the treatment of cancer in a patient in need thereof, wherein the monohydrochloride salt is to be administered to a patient in need thereof.

3. The monohydrochloride salt of claim 1, wherein the salt is anhydrous.

4. The monohydrochloride salt of claim 1, characterized by having a melting point with an onset of 170.9 °C and peaking at 173.4 °C.

5. The monohydrochloride salt of claim 1, characterized by having a melting point of 173 °C.

6. The monohydrochloride salt of claim 1, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in FIG. 1.

7. The monohydrochloride salt of claim 1, having a purity of 99.9% pure as determined by HPLC.

8. The monohydrochloride salt of claim 1, wherein the salt is in a crystalline form.

9. The monohydrochloride salt of claim 8, characterized by an X-ray powder diffraction (XRPD) pattern substantially as set forth in FIG. 3.

10. The monohydrochloride salt of claim 8, characterized by having an X-ray powder diffractogram which has one or more peaks chosen from peaks (° 2θ) as set forth in FIG. 3, wherein the one or more peaks have a Cps intensity greater than 100.

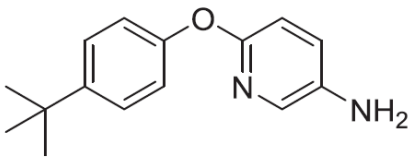
11. The monohydrochloride salt of claim 8, wherein the one or more peaks (° 2θ) have a Cps intensity greater than 100 are selected from about 7.3°, about 14.6°, about 21.4°, about 27.4°, about 25.9°, about 30.7°, about 22.0°, about 33.8°, about 23.3°, about 23.8° and about 28.7°.

12. A pharmaceutical formulation comprising the monohydrochloride salt of claim 1 and an excipient.

13. Use of the monohydrochloride salt of claim 1 or a pharmaceutical formulation thereof in the manufacture of a medicament for the treatment of a notch dependent cancer, wherein the monohydrochloride salt or pharmaceutical formulation is to be administered.

14. A monohydrochloride salt of claim 1 or a pharmaceutical formulation thereof for use as a medicament.

15. A process for making a crystalline form of monohydrochloride salt of the compound of formula (Ia) according to claim 1

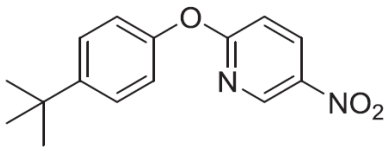


Formula (Ia)

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the process comprising:

reducing a compound of formula (IIa) with hydrogen in the presence of a palladium catalyst and a solvent wherein the solvent is a polar, aprotic solvent or a C3-C10 alcohol



Formula (IIa)

to form said compound of formula (Ia), further comprising reacting the compound of formula (Ia) with less than about 1.5 molar equivalents of hydrochloric acid to form the monohydrochloride salt of said compound of formula (Ia).

16. The process according to claim 15, wherein said palladium catalyst is palladium on activated charcoal.

17. The process according to claim 15, wherein said palladium catalyst is present in an amount of less than 7 mol%.

18. The process according claim 15, wherein the solvent is selected from 2-propanol, acetone, 2-butanone, 3-methyl-2-butanone, cyclohexanone, acetonitrile, chlorobenzene, methylene chloride, chloroform, trichloroethane, ethylene chloride, benzaldehyde, sulfolane, ethyl acetate, propyl acetate, amyl acetate, dimethylsulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide, diethylcarbonate, propylene carbonate, ethylene carbonate, methyl ethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone and mixtures thereof.

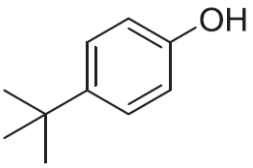
19. The process according to claim 15, wherein said solvent is ethyl acetate.

20. The process according to claim 15, further comprising contacting the compound of formula (Ia) with activated charcoal.

21. The process according to claim 15, further comprising crystallizing said compound of formula (Ia).

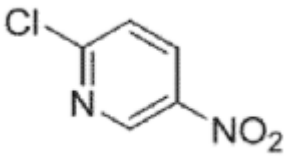
22. The process according to claim 15, further comprising crystallizing said monohydrochloride salt.

23. The process according to claim 15, wherein said compound of formula (II) is obtained by a process comprising reacting a compound of formula (IIIa)



Formula (IIIa)

with a compound of formula (IVa)



Formula (IVa)

wherein Cl is a leaving group; and

optionally

further comprising the step of crystallizing said starting material of formula (IIa).