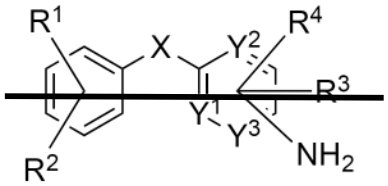
CLAIMS

1. A process for making a compound of formula (I)



Formula (I)

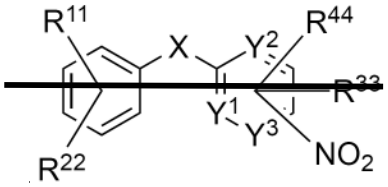
wherein X is selected from O and NH; and

wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and

wherein R^1 and R^2 are each independently selected from H, C1-C10 alkyl and C3-C12 cycloalkyl; and

wherein R^3 and R^4 are each independently selected from H, halogen and C1-C10 alkyl, comprising:

reducing a compound of formula (II) 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 (II)

wherein X is selected from O and NH; and

wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and

wherein R^{11} and R^{22} are each independently selected from H, C1-C10 alkyl, and C3-C12 cycloalkyl; and

wherein R^{33} and R^{44} are each independently selected from H, halogen and C1-C10 alkyl;

to form said compound of formula (I).

2. The process according to claim 1, wherein said palladium catalyst is palladium on activated charcoal.

3. The process according to claim 1 or 2, wherein said palladium catalyst is present in an amount of less than 7 mol%.

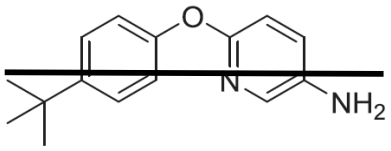
4. The process according to any one of claims 1 to 3, wherein the solvent is selected from 2-propanol, acetone, 2-butanone, 3-methyl-2-butanone, cyclohexanone, acetonitrile, chlorobenzene, methylene chloride, chloroform, trichloroethane, ethylene chloride, benzaldehyde, sulfolane, ethyl acetate, propyl 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.

5. The process according to any one of claims 1 to 3, wherein said solvent is ethyl acetate.

6. The process according to any one of claims 1 to 5, further comprising contacting the compound of formula (I) with activated charcoal.

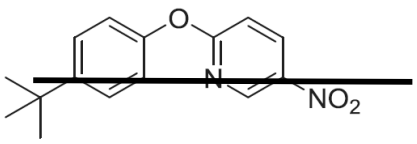
7. The process according to any one of claims 1 to 6, further comprising crystallizing said compound of formula (I).

8. The process according to any one of claims 1 to 7, wherein said compound of formula (I) is 6-(4-(*tert*-butyl)phenoxy)pyridin-3-amine (formula (Ia)); and



Formula (Ia)

wherein said compound of formula (II) is 2-(4-(*tert*-butyl)phenoxy)-5-nitropyridine (Formula (IIa)).



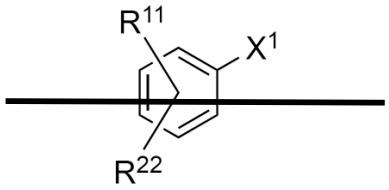
Formula (IIa)

9. The process according to any one of claims 1 to 8, further comprising reacting the compound of formula (I) or (Ia) with hydrochloric acid to form a hydrochloride salt of said compound of formula (I) or (Ia).

10. The process according to any one of claims 1 to 8, further comprising reacting the compound of formula (I) or (Ia) with less than about 1.5 molar equivalents of hydrochloric acid to form the monohydrochloride salt of said compound of formula (I) or (Ia).

11. The process according to claim 11, further comprising crystallizing said monohydrochloride salt.

12. The process according to any one of claims 1 to 11, wherein said compound of formula (II) is obtained by a process comprising reacting a compound of formula (III)

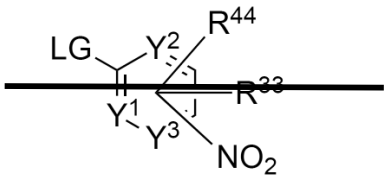


Formula (III)

wherein X^1 is selected from OH and NH_2; and

wherein R^{11} and R^{22} are each independently selected from H, C1-C10 alkyl, and C3-C12 cycloalkyl

with a compound of formula (IV)



Formula (IV)

wherein LG is a leaving group and

wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and

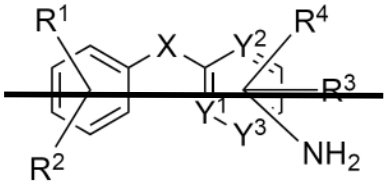
wherein R^{33} and R^{44} are each independently selected from H, halogen and C1-C10 alkyl;

in the presence of a base to form a compound of formula (II)

wherein X is O or NH; and

wherein R^{11} and R^{22} are as defined for the compound of formula (III); and
wherein R^{33}, R^{44}, Y^1, Y^2 and Y^3 are as defined for the compound of formula (IV); and optionally
further comprising crystallizing said starting material of formula (II).

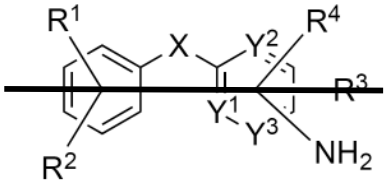
13. A process for making a hydrochloride salt of the compound of formula (I)



Formula (I)

wherein X is selected from O and NH; and
wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and
wherein R^1 and R^2 are each independently selected from H, C1-C10 alkyl and C3-C12 cycloalkyl and
wherein R^3 and R^4 are each independently selected from H, halogen and C1-C10 alkyl
comprising reacting said compound of formula (I) with hydrochloric acid to form a hydrochloride salt of said compound of formula (I).

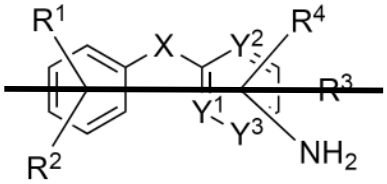
14. A process for making a monohydrochloride salt of the compound of formula (I)



Formula (I)

wherein X is selected from O and NH; and
wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and
wherein R^1 and R^2 are each independently selected from H, C1-C10 alkyl and C3-C12 cycloalkyl and
wherein R^3 and R^4 are each independently selected from H, halogen and C1-C10 alkyl
comprising reacting said compound of formula (I) with less than 1.5 molar equivalents of hydrochloric acid, to form the monohydrochloride salt of said compound of formula (I).

15. A hydrochloride salt of the compound of formula (I)



Formula (I)

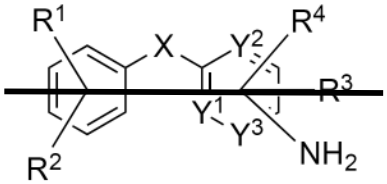
wherein X is selected from O and NH; and

wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and

wherein R^1 and R^2 are each independently selected from H, C1-C10 alkyl and C3-C12 cycloalkyl and

wherein R^3 and R^4 are each independently selected from H, halogen and C1-C10 alkyl.

16. A monohydrochloride salt of the compound of formula (I)



Formula (I)

wherein X is selected from O and NH; and

wherein Y^1, Y^2 and Y^3 are each independently selected from N and CH; and

wherein R^1 and R^2 are each independently selected from H, C1-C10 alkyl and C3-C12 cycloalkyl and

wherein R^3 and R^4 are each independently selected from H, halogen and C1-C10 alkyl.

17. The process according to claim 13 or the hydrochloride salt according to claim 15, wherein said hydrochloride salt is 6-(4-(*tert*-butyl)phenoxy)pyridin-3-amine hydrochloride.

18. The process according to claim 14 or the monohydrochloride salt according to claim 16, wherein said monohydrochloride salt is 6-(4-(*tert*-butyl)phenoxy)pyridin-3-amine monohydrochloride.

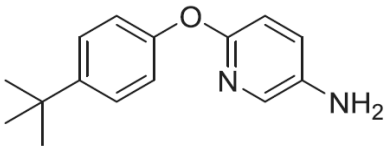
19. The hydrochloride salt according to claim 15 or 17 for use as a medicament.

~~20. The monohydrochloride salt according to claim 16 or 18 for use as a medicament.~~

~~21. The hydrochloride salt according to claim 15 or 17 for use in a method of treatment and/or prevention of cancer.~~

~~22. The monohydrochloride salt according to claim 16 or 18 for use in a method of treatment and/or prevention of cancer.~~

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.

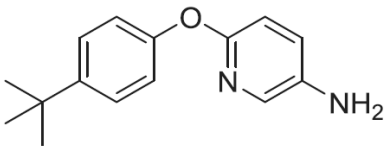
11. The monohydrochloride salt of claim 8, wherein the one or more peaks (° 2θ) have a Cps intensity greater than 100 are selected from about 7.3°, about 14.6°, about 21.4°, about 27.4°, about 25.9°, about 30.7°, about 22.0°, about 33.8°, about 23.3°, about 23.8° and about 28.7°.

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

13. Use of the monohydrochloride salt of claim 1 or ~~administering~~ a pharmaceutical formulation ~~of claim~~ 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

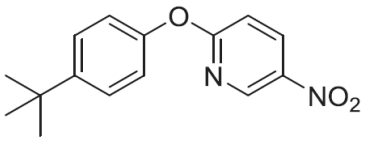


Formula (Ia)

,

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.

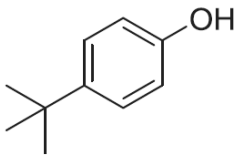
19. The process according to claim 15, wherein said solvent is ethyl acetate.

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).

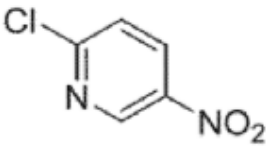
22. The process according to claim 15, further comprising crystallizing said monohydrochloride salt.

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).