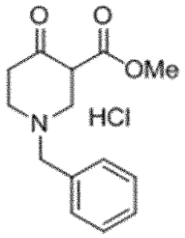
CLAIMS

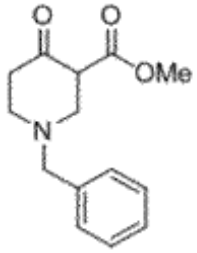
1. A di-hydrochloride salt of an anticancer agent, obtained by or obtainable by a method comprising the following steps:

Step 1: neutralising N-Benzyl-3-carbomethoxy-4-piperidone hydrochloride (compound (3))



(3)

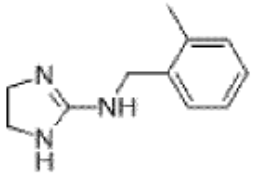
with a base to form N-Benzyl-3-carbomethoxy-4-piperidone free base (compound (4))



(4)

;

Step 2: reacting compound (4) with compound (5)



(5)

to form an anticancer agent; and

Step 3: forming a di-hydrochloride salt of the anticancer agent formed in Step 2, for use in the treatment of cancer.

2. The di-hydrochloride salt of an anticancer agent for use according to claim 1, wherein in the method

Step 1 comprises neutralizing compound (3) with an inorganic base or an organic base; neutralizing compound (3) with a base in the presence of an alcohol or an organic solvent; or neutralizing compound (3) with a base in the presence of n-butanol and/or ethyl acetate, in

the presence of $NaHCO_3$ and n-butanol, or in the presence of n-butanol and triethyl amine (Et_3N), and/or

Step 2 comprises heating compound (4) with compound (5), for example reflux heating compound (4) and compound (5) in the presence of a solvent, and/or

Step 3 comprises treating the anticancer agent formed in Step 2 with HCI in dioxane, for example with 4N HCI in dioxane.

3. The di-hydrochloride salt of an anticancer agent for use according to claim 1, wherein in the method

Step 1 comprises neutralizing compound (3) in the presence of NaHCO 3 and n-butanol or ethyl acetate;
Step 2 comprises reflux heating compound (4) and compound (5) in the presence of n-butanol; and
Step 3 comprises treating the anticancer agent formed in Step 2 with HCl.

4. The di-hydrochloride salt of an anticancer agent for use according to claim 1, wherein the method further comprises the step of recrystallizing the di-hydrochloride salt of the anticancer agent formed in Step 3.

5. The di-hydrochloride salt of an anticancer agent for use according to claim 1, wherein Steps 1 and 2 comprise the following steps:

adding compound (3) (239.7 g, 0.845 mol, 1.6 equiv) in portions to a stirred 800 mL saturated NaHCO 3 in a 2 L round bottom flask;
adding n-Butanol (500 mL) to the resulting mixture, stirring the mixture for 30 min, and then transferring to a separating funnel;
separating the organic phase, containing compound (4), and transferring it to a 2 L three-neck round bottom flask equipped with mechanical stirring, N 2 inlet, a thermocouple, a condenser and a Dean-Stark trap;
adding compound (5) (100 g, 0.528 mol, 1 equiv) and pyridinium p-toluenesulfonate (PPTS) (6.63 gm 0.026 mol, 5 mol%) to the contents of the flask;
heating the resulting mixture to reflux for 6 hours;

separating water in the reaction mixture into the Dean-Stark trap as necessary;

increasing the refluxing temperature from 93 °C to 118 °C; and

monitoring the reaction progress by HPLC, and stopping the reaction when the peak area of the anticancer agent on HPLC remained constant with the reaction time,

and wherein Step 3 comprises the following steps:

without isolation of the anticancer agent, washing the reaction mixture with 500 mL of water and diluting it with methyl tert-butyl ether (MTBE) (800 mL);

washing the organic phase with water (500 mL × 2) and transferring it to a 3 L three-neck round bottom flask equipped with mechanical stirring, N2 inlet, a thermocouple, a condenser and a Dean-Stark trap;

while agitating the reaction mixture, adding 1 N HCI in dioxane-MTBE solution dropwise (4 N HCI in dioxane: 300 mL, 1.2 mol, 2.27 equiv; MTBE: 1200 mL) until no more solid precipitated out of the reaction mixture upon addition of HCI;

heating the reaction mixture to reflux at 60-65 °C for 2 hours;

separating water into the Dean-Stark trap as necessary;

upon cooling to room temperature, filtering the solid precipitate through a sintered glass funnel and washing it with n-butanol-MTBE (1: 2, 600 mL) and MTBE (600 mL) respectively; and

drying the solid in the vacuum oven at 65°C overnight (16 hours) to afford 200 g yellow solid.

6. The di-hydrochloride salt of an anticancer agent for use according to claim 5, wherein the di-hydrochloride salt of the anticancer agent formed in Step 3 is purified as follows:

adding the yellow solid (200 g) to a 2 L three-neck round bottom flask equipped with mechanical stirring, N2 inlet, a thermocouple and a condenser, followed by ethanol (1000 mL);

heating the mixture to reflux at 78°C for 2 hours;

upon cooling to room temperature, filtering the solid through a sintered glass funnel and washing it with ethanol (200 mL × 3); and

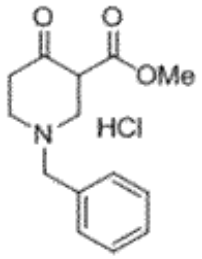
drying the wet solid in the vacuum oven at 85°C for 3 days until the residual solvent met specification;

thereby obtaining 120 g of the di-hydrochloride salt of the anticancer agent as a white solid in a yield of 49%, with 99.7% HPLC purity.

7. The di-hydrochloride salt of an anticancer agent for use according to any of claims 1-6, wherein the treatment of cancer further comprises administering an additional anticancer agent.

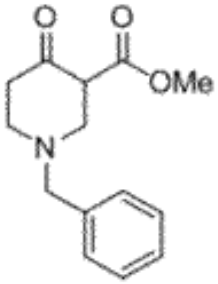
8. A pharmaceutical composition comprising a di-hydrochloride salt of an anticancer agent, obtained by or obtainable by a method comprising the following steps:

Step 1: neutralising N-Benzyl-3-carbomethoxy-4-piperidone hydrochloride (compound (3))



(3)

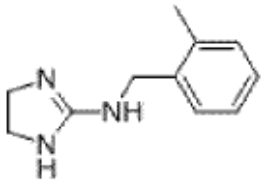
with a base to form N-Benzyl-3-carbomethoxy-4-piperidone free base (compound (4))



(4)

;

Step 2: reacting compound (4) with compound (5)



(5)

to form an anticancer agent; and

Step 3: forming a di-hydrochloride salt of the anticancer agent formed in Step 2,

an additional anticancer agent, and

a pharmaceutically acceptable carrier.

9. The pharmaceutical composition according to claim 8, wherein in the method

Step 1 comprises neutralizing compound (3) with an inorganic base or an organic base; neutralizing compound (3) with a base in the presence of an alcohol or an organic solvent; or neutralizing compound (3) with a base in the presence of n-butanol and/or ethyl acetate, in the presence of $NaHCO_3$ and n-butanol, or in the presence of n-butanol and triethyl amine (Et_3N), and/or
Step 2 comprises heating compound (4) with compound (5), for example reflux heating compound (4) and compound (5) in the presence of a solvent, and/or
Step 3 comprises treating the anticancer agent formed in Step 2 with HCI in dioxane, for example with 4N HCI in dioxane.

10. The pharmaceutical composition according to claim 8, wherein in the method

Step 1 comprises neutralizing compound (3) in the presence of $NaHCO_3$ and n-butanol or ethyl acetate;
Step 2 comprises reflux heating compound (4) and compound (5) in the presence of n-butanol; and
Step 3 comprises treating the anticancer agent formed in Step 2 with HCl.

11. The pharmaceutical composition according to claim 8, wherein the method further comprises the step of recrystallizing the di-hydrochloride salt of the anticancer agent formed in Step 3.

12. The pharmaceutical composition according to claim 8, wherein Steps 1 and 2 comprise the following steps:

adding compound (3) (239.7 g, 0.845 mol, 1.6 equiv) in portions to a stirred 800 mL saturated $NaHCO_3$ in a 2 L round bottom flask;
adding n-Butanol (500 mL) to the resulting mixture, stirring the mixture for 30 min, and then transferring to a separating funnel;
separating the organic phase, containing compound (4), and transferring it to a 2 L three-neck round bottom flask equipped with mechanical stirring, N 2 inlet, a thermocouple, a condenser and a Dean-Stark trap;

adding compound (5) (100 g, 0.528 mol, 1 equiv) and pyridinium p-toluenesulfonate (PPTS) (6.63 gm 0.026 mol, 5 mol%) to the contents of the flask;

heating the resulting mixture to reflux for 6 hours;

separating water in the reaction mixture into the Dean-Stark trap as necessary;

increasing the refluxing temperature from 93 °C to 118 °C; and

monitoring the reaction progress by HPLC, and stopping the reaction when the peak area of the anticancer agent on HPLC remained constant with the reaction time,

and wherein Step 3 comprises the following steps:

without isolation of the anticancer agent, washing the reaction mixture with 500 mL of water and diluting it with methyl tert-butyl ether (MTBE) (800 mL);

washing the organic phase with water (500 mL × 2) and transferring it to a 3 L three-neck round bottom flask equipped with mechanical stirring, N2 inlet, a thermocouple, a condenser and a Dean-Stark trap;

while agitating the reaction mixture, adding 1 N HCI in dioxane-MTBE solution dropwise (4 N HCI in dioxane: 300 mL, 1.2 mol, 2.27 equiv; MTBE: 1200 mL) until no more solid precipitated out of the reaction mixture upon addition of HCI;

heating the reaction mixture to reflux at 60-65 °C for 2 hours;

separating water into the Dean-Stark trap as necessary;

upon cooling to room temperature, filtering the solid precipitate through a sintered glass funnel and washing it with n-butanol-MTBE (1: 2, 600 mL) and MTBE (600 mL) respectively; and

drying the solid in the vacuum oven at 65°C overnight (16 hours) to afford 200 g yellow solid.

13. The pharmaceutical composition according to claim 12, wherein the di-hydrochloride salt of the anticancer agent formed in Step 3 is purified as follows:

adding the yellow solid (200 g) to a 2 L three-neck round bottom flask equipped with mechanical stirring, N2 inlet, a thermocouple and a condenser, followed by ethanol (1000 mL);

heating the mixture to reflux at 78°C for 2 hours;

upon cooling to room temperature, filtering the solid through a sintered glass funnel and washing it with ethanol (200 mL × 3); and

drying the wet solid in the vacuum oven at 85°C for 3 days until the residual solvent met specification;

thereby obtaining 120 g of the di-hydrochloride salt of the anticancer agent as a white solid in a yield of 49%, with 99.7% HPLC purity.

14. The pharmaceutical composition of any of claims 8-13, for use as a medicament.

15. The pharmaceutical composition of any of claims 8-13, for use in the treatment of cancer.