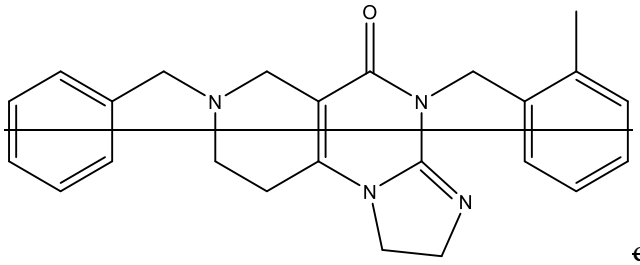
## CLAIMS

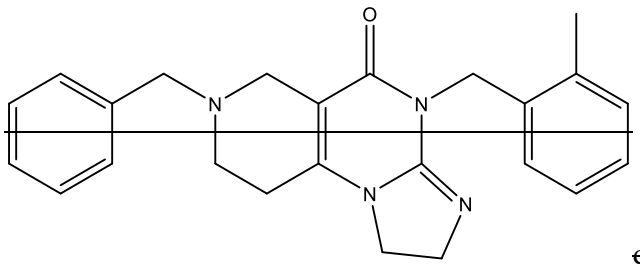
1. Use of Compound (2):



di-HCl

in the manufacture of a medicament for the treatment of one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, spinal cord tumors, central nervous system atypical teratoid tumors, central nervous system atypical rhabdoid tumors, leptomeningeal disease, central nervous system embryonal tumors, central nervous system lymphoma, chordoma, craniopharyngioma, embryonal tumors of central nervous system, ependymoblastoma, ependymoma, extracranial germ cell tumors, extragonadal germ cell tumors, germ cell tumors, glioma, primary central nervous system lymphoma, medulloblastoma, medulloepithelioma, neuroblastoma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma, supratentorial primitive neuroectodermal tumors, pituitary tumors, and primary central nervous system lymphoma.

2. Use of Compound (2):



di-HCl

in the manufacture of a pharmaceutical composition for the treatment of one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, spinal cord tumors, central nervous system atypical teratoid tumors, central nervous system

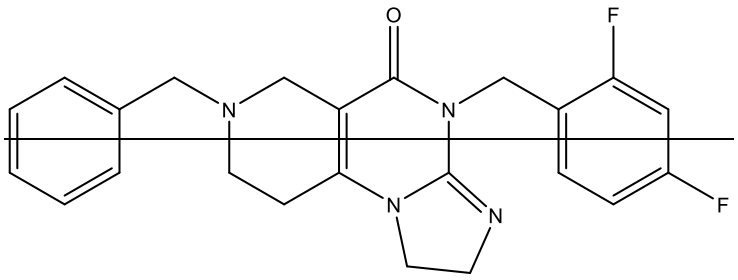
~~atypical rhabdoid tumors, leptomeningeal disease, central nervous system embryonal tumors, central nervous system lymphoma, chordoma, craniopharyngioma, embryonal tumors of central nervous system, ependymoblastoma, ependymoma, extracranial germ cell tumors, extragonadal germ cell tumors, germ cell tumors, glioma, primary central nervous system lymphoma, medulloblastoma, medulloepithelioma, neuroblastoma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma, supratentorial primitive neuroectodermal tumors, pituitary tumors, and primary central nervous system lymphoma.~~

~~3. The use of claims 1 or 2, wherein the treatment is for one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, craniopharyngioma, ependymoblastoma, glioma, and medulloblastoma,~~

~~4. The use of any one of claims 1 to 3, wherein the treatment is for an adult patient.~~

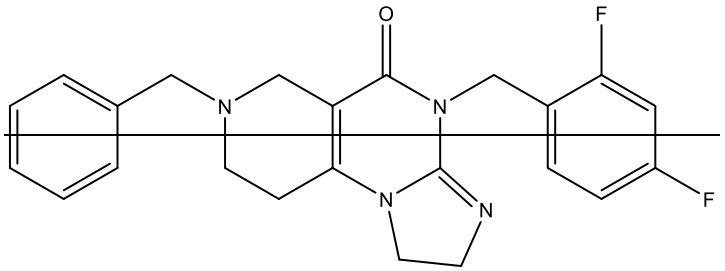
~~5. The use of any one of claims 1 to 3, wherein the treatment is for a pediatric patient.~~

~~6. Use of Compound (18):~~




~~or a salt thereof in the manufacture of a medicament for the treatment of one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, spinal cord tumors, central nervous system atypical teratoid tumors, central nervous system atypical rhabdoid tumors, leptomeningeal disease, central nervous system embryonal tumors, central nervous system lymphoma, chordoma, craniopharyngioma, embryonal tumors of central nervous system, ependymoblastoma, ependymoma, extracranial germ cell tumors, extragonadal germ cell tumors, germ cell tumors, glioma, primary central nervous system lymphoma, medulloblastoma, medulloepithelioma, neuroblastoma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma, supratentorial primitive neuroectodermal tumors, pituitary tumors, and primary central nervous system lymphoma.~~

7. Use of Compound (18):



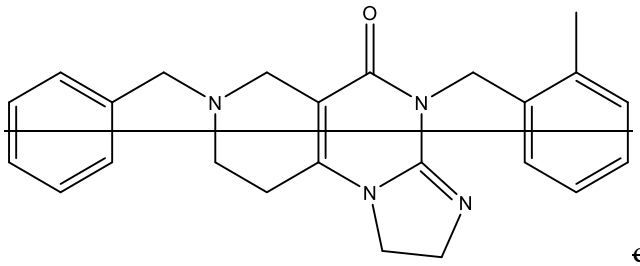

or a salt thereof in the manufacture of a pharmaceutical composition for the treatment of one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, spinal cord tumors, central nervous system atypical teratoid tumors, central nervous system atypical rhabdoid tumors, leptomeningeal disease, central nervous system embryonal tumors, central nervous system lymphoma, chordoma, craniopharyngioma, embryonal tumors of central nervous system, ependymoblastoma, ependymoma, extracranial germ cell tumors, extragonadal germ cell tumors, germ cell tumors, glioma, primary central nervous system lymphoma, medulloblastoma, medulloepithelioma, neuroblastoma, pineal parenchymal tumors of intermediate differentiation, pineoblastoma, supratentorial primitive neuroectodermal tumors, pituitary tumors, and primary central nervous system lymphoma.

8. The use of claims 6 or 7, wherein the treatment is for one or more of brain cancer, glioblastoma, astrocytoma, atypical teratoid tumors, rhabdoid tumors, brain tumors, craniopharyngioma, ependymoblastoma, glioma, and medulloblastoma,

9. The use of any one of claims 6 to 8, wherein the treatment is for an adult patient.

10. The use of any one of claims 6 to 8, wherein the treatment is for a pediatric patient.

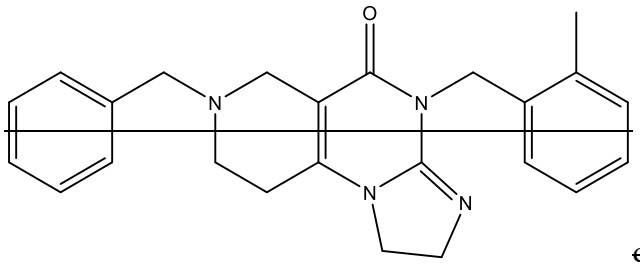
11. Use of Compound (2):




di HCl

~~in the manufacture of a medicament for the treatment of a brain tumor.~~

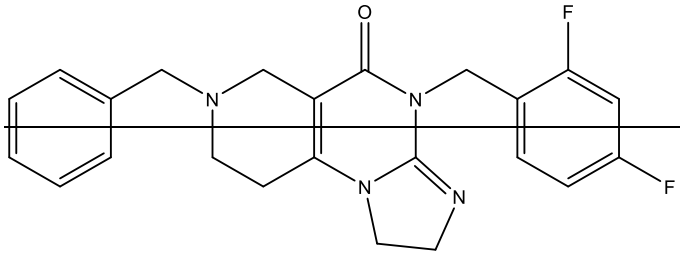
~~12. Use of Compound (2):~~



~~di HCl~~

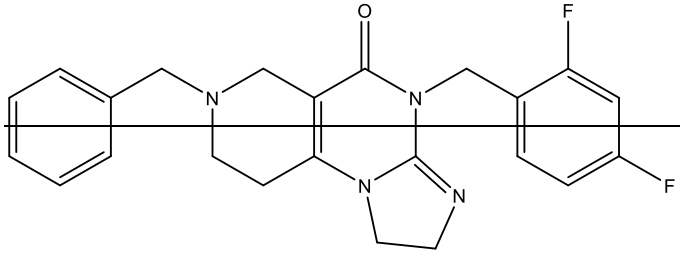
~~in the manufacture of a pharmaceutical composition for treatment of a brain tumor.~~

~~13. Use of Compound (18):~~



~~or a salt thereof in the manufacture of a medicament for the treatment of a brain tumor.~~

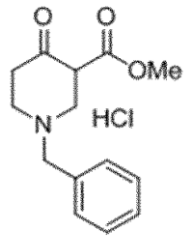
~~14. Use of Compound (18):~~



~~or a salt thereof in the manufacture of a pharmaceutical composition for the treatment of a brain tumor.~~

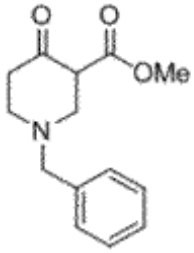
1. A di-hydrochloride salt of an anticancer agent, obtained by or obtainable by a method comprising the following steps:

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




(3)

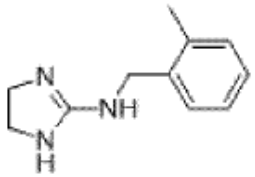
with a base to form N-Benzyl-3-carbomethoxy-4-piperidone free base (compound (4))




(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

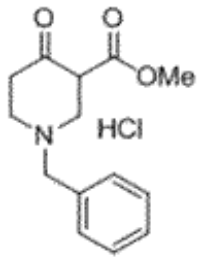
drying the wet solid in the vacuum oven at 85°C for 3 days until the residual solvent met specification;

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.

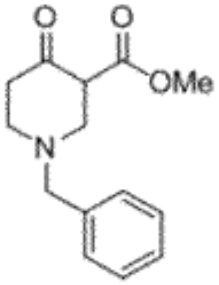
8. A pharmaceutical composition comprising a di-hydrochloride salt of an anticancer agent, obtained by or obtainable by a method comprising the following steps:

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




(3)

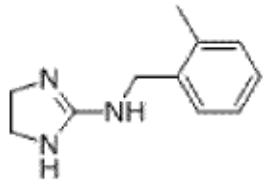
with a base to form N-Benzyl-3-carbomethoxy-4-piperidone free base (compound (4))




(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.