SALT OF COMPOUND FOR DEGRADING BTK, CRYSTAL FORM THEREOF, AND USE THEREOF IN MEDICINE

Technical Field

The present invention relates to the field of medicine, and specifically relates to a crystal form of a salt of a compound for degrading BTK, preparation therefor, and an application thereof.

Background Art

Bruton's tyrosine kinase (BTK), a member of the Tec family of non-receptor protein tyrosine kinases, is a key regulator in the B cell antigen receptor (BCR) signalling pathway, and is distributed in the lymphatic system, hematopoietic system and blood system. BTK mutations may activate downstream signalling pathways in tumour cell proliferation, differentiation, angiogenesis, etc., which may lead to X-linked agammaglobulinemia, non-Hodgkin’s lymphoma (NHL) and many B-cell malignancies, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma, and diffuse large B-cell lymphoma. As mainly expressed in B cells and myeloid cells, BTK is a target with relatively high targeting ability and safety.

PROTAC (proteolysis targeting chimera) molecules are a class of dual function compounds which are capable of binding to both targeted proteins and E3 ubiquitin ligases. This class of compounds can induce recognition of targeted proteins by proteasomes in a cell to cause the degradation of the targeted protein, which can effectively reduce the contents of the targeted proteins in the cell. By introducing a ligand capable of binding to various targeted proteins into the PROTAC molecules, it is possible to apply the PROTAC technology to the treatment of various diseases, and this technology has attracted extensive attention in recent years.

Summary of the Invention

An object of the present invention is to provide a compound with a novel structure and a good pharmaceutical effect for degrading BTK, a pharmaceutical composition thereof and the use thereof in the anti-tumour field. The compound for degrading BTK of the present invention has good stability (including chemical stability and crystal form stability), is convenient for oral administration, and has relatively good solubility and bioavailability.

An object of the present invention is to provide a pharmaceutical salt of a compound with a novel structure and a good pharmaceutical effect for degrading BTK or crystals of the compound for degrading BTK and the pharmaceutical salt thereof, a pharmaceutical composition thereof and the use thereof in the anti-tumour field.

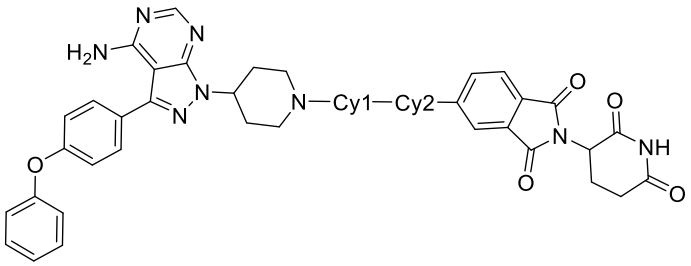
The crystals of the present invention are easy to be processed, crystallized and treated, has good stability, is convenient for oral administration, and has relatively good solubility and bioavailability.

Another object of the present invention is to provide a method for preparing the compound for degrading BTK and/or the crystal.

Another object of the present invention is to provide a pharmaceutical composition containing the compound for degrading BTK and/or the crystal.

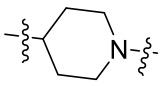
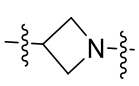
Yet another object of the present invention is to provide an application of the compound for degrading BTK and/or the crystal.

The present invention provides a pharmaceutical salt of a compound as shown in formula (I),



(I).

In some embodiments, Cy1 or Cy2 is each independently selected from piperidyl or azacyclobutyl.

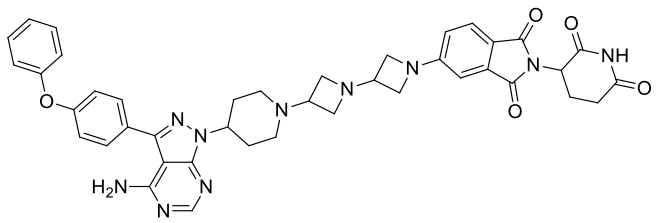
In some embodiments, Cy1 or Cy2 is each independently selected from  or .

In some embodiments, the pharmaceutical salt of the compound as shown in formula (I) is selected from maleate, fumarate, halogen acid salt (preferably hydrobromide and hydrochloride), sulfate, phosphate, L-tartrate, citrate, L-malate, hippurate, D-glucuronate, glycollate, mucate, succinate, lactate, orotate, pamoate, glycinate, alanine salt, arginine salt, cinnamate, benzoate, benzenesulfonate, p-toluenesulfonate, acetate, propionate, valerianate, triphenyl acetate, L-proline salt, ferulate, 2-hydroxyethanesulfonate, mandelate, nitrate, mesylate, malonate, gentisate, salicylate, oxalate or glutarate.

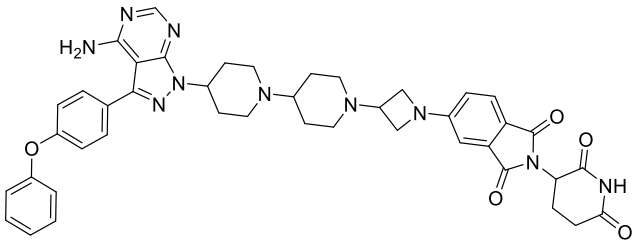
In some embodiments, the halogen acid salt is hydrobromide or hydrochloride.

In some embodiments, the molar ratios of the compound (free base) as shown in formula (I) to different acids are about 1 : 1, 1 : 1.5, 1 : 2, 1 : 2.5 or 1 : 3.

The present invention further provides a pharmaceutical salt of the compound as shown in formula (Ia) or (Ib) below,



(Ia)



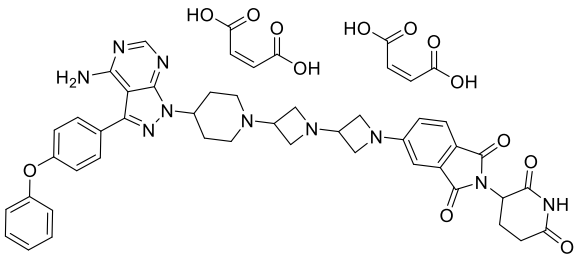
(Ib).

In some embodiments, the pharmaceutical salt of the compound as shown in formula (Ia) or (Ib) is selected from maleate, fumarate, halogen acid salt (preferably hydrobromide and hydrochloride), sulfate, phosphate, L-tartrate, citrate, L-malate, hippurate, D-glucuronate, glycollate, mucate, succinate, lactate, orotate, pamoate, glycinate, alanine salt, arginine salt, cinnamate, benzoate, benzenesulfonate, p-toluenesulfonate, acetate, propionate, valerianate, triphenyl acetate, L-proline salt, ferulate, 2-hydroxyethanesulfonate, mandelate, nitrate, mesylate, malonate, gentisate, salicylate, oxalate or glutarate, preferably maleate, fumarate, L-tartrate, citrate, L-malate, salicylate or oxalate.

In some embodiments, the pharmaceutical salt of the compound as shown in formula (Ia) is selected from maleate, and the molar ratio of the compound as shown in formula (Ia) to the maleate is about 1 : 1, 1 : 1.5, 1 : 2, 1 : 2.5 or 1 : 3.

In some embodiments, the pharmaceutical salt of the compound as shown in formula (I) has a structure as shown in formula (II).

The present invention further provides a compound as shown in formula (II) below,


(II).

The present invention further provides a crystal form I of the compound as shown in formula (II), wherein the crystal form I has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.96° ± 0.2°, 9.30° ± 0.2°, 11.86° ± 0.2°, 15.80° ± 0.2°, 21.75° ± 0.2° and 23.93° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form I of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 3.98° ± 0.2°, 7.65° ± 0.2°, 10.87° ± 0.2°, 16.88° ± 0.2°, 17.89° ± 0.2° and 26.21° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form I of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 15.29° ± 0.2°, 17.33° ± 0.2°, 18.55° ± 0.2°, 19.21° ± 0.2°, 19.91° ± 0.2° and 22.41° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form I of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 4.72° ± 0.2°, 9.58° ± 0.2°, 9.92° ± 0.2°, 12.85° ± 0.2°, 13.37° ± 0.2°, 13.75° ± 0.2°, 14.45° ± 0.2°, 27.37° ± 0.2°, 28.43° ± 0.2°, 30.27° ± 0.2°, 31.51° ± 0.2° and 34.21° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form I of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 28.

In some embodiments, the crystal form I of the compound as shown in formula (II) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 29 or a thermogravimetric analysis curve as shown in Figure 30.

The present invention further provides an amorphous form of the compound as shown in formula (II), which, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern substantially as shown in Figure 31.

In some embodiments, the amorphous form of the compound as shown in formula (II) of the present invention has a differential scanning calorimetry (DSC)

curve as shown in Figure 32 or a thermogravimetric analysis curve as shown in Figure 33.

The present invention further provides a crystal form II of the compound as shown in formula (II), wherein the crystal form II has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 3.98° ± 0.2°, 6.35° ± 0.2°, 8.10° ± 0.2°, 9.66° ± 0.2°, 12.21° ± 0.2°, 15.79° ± 0.2°, 16.75° ± 0.2° and 19.39° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form II of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 12.78° ± 0.2°, 16.33° ± 0.2°, 17.13° ± 0.2°, 17.41° ± 0.2°, 20.45° ± 0.2°, 21.43° ± 0.2°, 23.23° ± 0.2°, 24.65° ± 0.2° and 25.75° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form II of the compound as shown in formula (II) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 34.

In some embodiments, the crystal form II of the compound as shown in formula (II) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 35 or a thermogravimetric analysis curve as shown in Figure 36.

The present invention further provides an amorphous form of the compound as shown in formula (Ia), which, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern substantially as shown in Figure 1.

In some embodiments, the amorphous form of the compound as shown in formula (Ia) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 2 or a thermogravimetric analysis curve as shown in Figure 3.

The present invention further provides a crystal form I of the compound as shown in formula (Ia), wherein the crystal form I has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 8.32° ± 0.2°, 15.69° ± 0.2°, 16.41° ± 0.2°, 17.57° ± 0.2°, 18.89° ± 0.2° and 19.75° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form I of the compound as shown in formula (Ia) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 10.94° ± 0.2°, 11.90° ± 0.2°, 13.30° ± 0.2°, 14.39°

± 0.2°, 16.67° ± 0.2°, 17.24° ± 0.2°, 18.00° ± 0.2°, 21.25° ± 0.2°, 22.27° ± 0.2°, 23.85° ± 0.2° and 26.45° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form I of the compound as shown in formula (Ia) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 4.

In some embodiments, the crystal form I of the compound as shown in formula (Ia) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 5 or a thermogravimetric analysis curve as shown in Figure 6.

The present invention further provides a crystal form II of the compound as shown in formula (Ia), wherein the crystal form II has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 4.98° ± 0.2°, 7.86° ± 0.2°, 13.72° ± 0.2°, 17.65° ± 0.2° and 20.01° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form II of the compound as shown in formula (Ia) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 5.48° ± 0.2°, 13.43° ± 0.2°, 14.93° ± 0.2°, 15.90° ± 0.2°, 16.57° ± 0.2°, 16.95° ± 0.2°, 21.29° ± 0.2°, 22.05° ± 0.2°, 24.97° ± 0.2° and 25.77° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form II of the compound as shown in formula (Ia) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 7.

In some embodiments, the crystal form II of the compound as shown in formula (Ia) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 8 or a thermogravimetric analysis curve as shown in Figure 9.

The present invention further provides a crystal form III of the compound as shown in formula (Ia), wherein the crystal form III has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.02° ± 0.2°, 8.04° ± 0.2°, 16.91° ± 0.2°, 17.23° ± 0.2°, 18.19° ± 0.2°, 19.41° ± 0.2° and 20.03° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form III of the compound as shown in formula (Ia) has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 12.36° ± 0.2°, 14.60° ± 0.2°, 15.03° ± 0.2°, 15.73° ± 0.2°, 20.57° ± 0.2°, 21.31° ± 0.2° and 25.45° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form III of the compound as shown in formula (Ia) has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.19° ± 0.2°, 16.32° ± 0.2°, 18.75° ± 0.2°, 19.73° ± 0.2°, 21.91° ± 0.2°, 22.41° ± 0.2°, 23.48° ± 0.2°, 23.95° ± 0.2° and 26.33° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form III of the compound as shown in formula (Ia) has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 10.34° ± 0.2°, 24.85° ± 0.2°, 26.93° ± 0.2°, 27.57° ± 0.2°, 28.41° ± 0.2°, 29.59° ± 0.2°, 30.19° ± 0.2°, 31.77° ± 0.2°, 33.13° ± 0.2° and 35.75° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form III of the compound as shown in formula (Ia) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 10.

In some embodiments, the crystal form III of the compound as shown in formula (Ia) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 11 or a thermogravimetric analysis curve as shown in Figure 12.

The present invention further provides a crystal form I of the compound as shown in formula (Ib), wherein the crystal form I has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 4.38° ± 0.2°, 8.66° ± 0.2°, 13.06° ± 0.2°, 14.34° ± 0.2°, 18.18° ± 0.2°, 20.28° ± 0.2° and 21.82° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form I of the compound as shown in formula (Ib) has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 11.92° ± 0.2°, 12.74° ± 0.2° and 17.44° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form I of the compound as shown in formula (Ib) has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 9.76° ± 0.2°, 11.26° ± 0.2°, 14.14° ± 0.2°, 17.04° ± 0.2°, 23.23° ± 0.2°, 24.06° ± 0.2°, 25.26° ± 0.2° and 26.42 ± 0.2° 2θ, as determined by using Cu-Kα radiation. In some embodiments, the crystal form I of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 13-1 and/or Figure 13-2.

In some embodiments, the crystal form I of the compound as shown in formula (Ib) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 14 or a thermogravimetric analysis curve as shown in Figure 15.

The present invention further provides a crystal form II of the compound as shown in formula (Ib), wherein the crystal form II has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.12° ± 0.2°, 6.68° ± 0.2°, 16.50° ± 0.2° and 20.18° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form II of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 9.98° ± 0.2°, 13.44° ± 0.2°, 13.86° ± 0.2°, 15.34° ± 0.2°, 22.40° ± 0.2° and 23.12° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form II of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 15.76° ± 0.2°, 20.99° ± 0.2°, 24.14° ± 0.2° and 26.28° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form II of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 16-1 and/or Figure 16-2.

In some embodiments, the crystal form II of the compound as shown in formula (Ib) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 17 or a thermogravimetric analysis curve as shown in Figure 18.

The present invention further provides a crystal form III of the compound as shown in formula (Ib), wherein the crystal form III has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 7.48° ± 0.2°, 12.24° ± 0.2°, 20.50° ± 0.2° and 25.77° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form III of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 15.59° ± 0.2°, 18.74° ± 0.2° and 23.85° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

More preferably, the crystal form III of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 14.95° ± 0.2°, 16.18° ± 0.2°, 16.70° ± 0.2°, 19.00° ± 0.2° and 21.39° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form III of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 19-1 and/or Figure 19-2.

In some embodiments, the crystal form III of the compound as shown in formula (Ib) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 20 or a thermogravimetric analysis curve as shown in Figure 21.

The present invention further provides a crystal form IV of the compound as shown in formula (Ib), wherein the crystal form IV has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 3.92° ± 0.2°, 8.7° ± 0.2°, 15.54° ± 0.2° and 18.22° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

Preferably, the crystal form IV of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 7.76° ± 0.2°, 10.48° ± 0.2°, 12.46° ± 0.2°, 16.79° ± 0.2°, 18.94° ± 0.2° and 19.67° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

In some embodiments, the crystal form IV of the compound as shown in formula (Ib) of the present invention has an X-ray powder diffraction pattern substantially as shown in Figure 22-1 and/or Figure 22-2.

In some embodiments, the crystal form IV of the compound as shown in formula (Ib) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 23 or a thermogravimetric analysis curve as shown in Figure 24.

The present invention further provides an amorphous form of the compound as shown in formula (Ib), which, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern substantially as shown in Figure 25.

In some embodiments, the amorphous form of the compound as shown in formula (Ib) of the present invention has a differential scanning calorimetry (DSC) curve as shown in Figure 26 or a thermogravimetric analysis curve as shown in Figure 27.

The present invention further provides a method for preparing a pharmaceutical salt of a compound as shown in formula (I), wherein the method comprises: a step of allowing the compound as shown in formula (I) and an acid to form a salt.

In some embodiments of the method for preparing the compound as shown in formula (I) of the present invention, the solvent used therein is selected from one or

more of a C_{1-6} halogenated alkane solvent, a C_{2-6} ester solvent, a C_{2-6} ether solvent, a C_{1-6} alcohol solvent or water, preferably one or more of dichloromethane, 1,2-dichloroethane, ethyl acetate, methanol, ethanol, isopropanol, diethyl ether, tetrahydrofuran and water, more preferably one or more of dichloromethane, methanol, ethanol and water.

In some embodiments of the method for preparing the compound as shown in formula (I) of the present invention, the method comprises: a step of allowing the compound as shown in formula (Ia) and an acid to form a salt, wherein the acid is selected from maleic acid, fumaric acid, halogen acid (preferably hydrobromic acid and hydrochloric acid), sulfuric acid, phosphoric acid, L-tartaric acid, citric acid, L-malic acid, hippuric acid, D-glucuronic acid, glycolic acid, mucic acid, succinic acid, lactic acid, orotic acid, pamoic acid, glycine, alanine, arginine, cinnamic acid, benzoic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, valeric acid, triphenylacetic acid, L-proline, ferulic acid, 2-hydroxyethanesulfonic acid, mandelic acid, nitric acid, methanesulfonic acid, malonic acid, gentisic acid, salicylic acid, oxalic acid or glutaric acid.

In some embodiments of the method for preparing the maleate of the compound as shown in formula (I) of the present invention, the method comprises: allowing the compound as shown in formula (Ia) and maleic acid to form a salt, and preparing a compound as shown in formula (II).

The present invention further provides a method for preparing a crystal form of a compound as shown in formula (Ia), (Ib) or (II), wherein the method comprises a step of preparing the compound as shown in formula (II), (Ia) or (Ib) in any crystal form or the compound as shown in formula (II), (Ia) or (Ib) in an amorphous form by means of recrystallization or slurrying, wherein a solvent for the recrystallization or slurrying is selected from one of or a mixed solvent of two or more of a C_{2-6} ester solvent, a C_{2-6} ether solvent, a C_{1-6} alcohol solvent, a C_{1-6} nitrile solvent, an alkane solvent and water. The solvent for the recrystallization or slurrying is preferably one of or a mixed solvent of two or more of ethyl acetate, isopropyl acetate, n-heptane, acetonitrile, tetrahydrofuran, trifluoroethanol, methanol, ethanol and water.

In some embodiments of the method for preparing the crystal form of the compound as shown in formula (Ia), (Ib) or (II) of the present invention, the recrystallization or slurrying is performed at a temperature of 4°C to 100°C, preferably room temperature to 90°C, more preferably 40°C to 90°C.

In some embodiments of the method for preparing the crystal form I of the compound as shown in formula (II) of the present invention, the method comprises steps of mixing the compound as shown in formula (II) with a suitable solvent to form a suspension, heating, stirring and slurrying the mixture, leaving the resulting product to stand for crystallization, and performing filtering and separation, wherein the solvent is preferably ethanol, and the slurrying is performed at a temperature of preferably 90°C.

In some embodiments of the method for preparing the crystal form III of the compound as shown in formula (Ia) of the present invention, the method comprises steps of mixing the compound as shown in formula (Ia) in an amorphous form with a suitable solvent, heating, stirring and slurrying the mixture, and performing filtering and separation, wherein the solvent is preferably an acetonitrile/water mixed solvent, and the slurrying is performed at a temperature of preferably 40°C.

In another aspect, the present invention further provides a pharmaceutical composition, wherein the pharmaceutical composition contains a therapeutically effective amount of the compound or the crystal according to any one of the present invention as described above, and a pharmaceutically acceptable excipient.

In yet another aspect, the present invention further provides use of the pharmaceutical salt of the compound as shown in formula (I) or the crystals of the compounds as shown in formula (Ia), (Ib) and (II) and the pharmaceutical composition in the preparation of a drug for treating and/or preventing tumour.

In yet another aspect, the present invention further provides a method for treating and/or preventing tumour. The method comprises administering a therapeutically effective amount of the pharmaceutical salt of the compound as shown in formula (I) or the crystals of the compounds as shown in formula (Ia), (Ib) and (II) and the pharmaceutical composition.

It can be understood that the expression “preferably, ...has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at ... 2θ” or “more preferably, ...has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at ... 2θ” and other similar expressions of the present invention means that in addition to comprising characteristic diffraction peaks at 2θ positions described above, the X-ray powder diffraction pattern further comprises characteristic diffraction peaks at “2θ positions described below”.

Other patterns substantially the same as the X-ray powder diffraction pattern, DSC pattern or TGA pattern disclosed in the present invention also fall within the scope of the present invention.

Unless stated to the contrary, the terms used in the description and claims have the following meanings.

The "therapeutically effective amount" means an amount that causes a physiological or medical response in a tissue, system or subject and is a desirable amount, including the amount of a compound that is, when administered to a subject to be treated, sufficient to prevent occurrence of one or more symptoms of the disease or condition to be treated or to reduce the symptom(s) to a certain degree.

The "IC_{50}" refers to the half maximal inhibitory concentration, i.e., a concentration where half of the maximum inhibitory effect is achieved.

The "ether solvent" of the present invention refers to a chain compound or a cyclic compound containing an ether bond -O- and having 1 to 10 carbon atoms, and the specific examples thereof include, but are not limited to: tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl tert-butyl ether, isopropyl ether or 1,4-dioxane.

The "alcohol solvent" of the present invention refers to a group derived from "C_{1-6} alkyl" on which one or more hydrogen atoms are substituted with one or more "hydroxyl groups", wherein the "hydroxyl group" and "C_{1-6} alkyl" are as defined above, and the specific examples thereof include, but are not limited to: methanol, ethanol, isopropanol, n-propanol, isopentanol or trifluoroethanol.

The "ester solvent" of the present invention refers to a combination of a lower organic acid containing 1-4 carbon atoms and a lower alcohol containing 1-6 carbon atoms, and the specific examples thereof include, but are not limited to: ethyl acetate, isopropyl acetate or butyl acetate.

The "ketone solvent" of the present invention refers to a compound in which a carbonyl group (-C(O)-) is connected to two hydrocarbon groups. According to the difference of hydrocarbon groups in molecules, ketones can be divided into aliphatic ketone, alicyclic ketone, aromatic ketone, saturated ketone and unsaturated ketone, and the specific examples thereof include, but are not limited to: acetone, acetophenone and 4-methyl-2-pentanone.

The "nitrile solvent" of the present invention refers to a group derived from "C_{1-6} alkyl" on which one or more hydrogen atoms are substituted with one or more

"cyano groups", wherein the "cyano group" and "C_{1-6} alkyl" are as defined above, and the specific examples thereof include, but are not limited to: acetonitrile or propionitrile.

The "halogenated hydrocarbon solvent" of the present invention refers to a group derived from "C_{1-6} alkyl" on which one or more hydrogen atoms are substituted with one or more "halogen atoms", wherein the "halogen atom" and "C_{1-6} alkyl" are as defined above, and the specific examples thereof include, but are not limited to: dichloromethane, 1,2-dichloroethane, chloroform or carbon tetrachloride.

As used in the present invention, "the crystal of the present invention", "the crystal form of the present invention", "the polymorph of the present invention" and the like can be used interchangeably.

The "room temperature" of the present invention generally refers to 4°C to 30°C, preferably 20°C ± 5°C.

The structure of the crystal form of the present invention can be analysed by using various analytical techniques known to those skilled in the art, including but not limited to X-ray powder diffraction (XRD), differential scanning calorimetry (DSC) and/or thermogravimetric analysis (TGA). Thermogravimetric analysis (TGA) is also called as thermogravimetry (TG).

The X-ray powder diffractometer (XRD) used in the present invention is Bruker D8 Advance diffractometer, using Ka radiation (40 Kv, 40 mA) with a copper target wavelength of 1.54 Å, a θ-2θ goniometer, a Mo monochromator, and an Lynxeye detector, using Al_2O_3 as a calibration material, Diffrac Plus XRD Commander as an acquisition software, and MDI Jade 6 as an analysis software; the method parameters involve: a non-reflective sample plate at 24.6 mm diameter x 1.0 mm thickness, manufactured by MTI corporation; a variable-temperature hot stage, manufactured by Shanghai Weitu Instrument Technology Development Co., Ltd., using a copper plate as a sample plate; a detection angle of 3-40° 2θ/3-30° 2θ (hot-stage XRPD); and a step length of 0.02° 2θ.

The differential scanning calorimeter (DSC) used in the present invention is TA Instruments Q200 DSC or DSC 3, operated under nitrogen protection with a gas flow rate of 50 mL/min.

The thermogravimetric analyser (TGA) used in the present invention is TA Instruments Q500 TGA or TGA/DSC 3^+, operated under nitrogen protection with a gas flow rate of 40 mL/min or 50 mL/min.

The “2θ or 2θ angle” of the present invention refers to a diffraction angle, wherein θ is the Bragg angle in the unit of ° or degree, and the error range of the 2θ can be ± 0.3, ± 0.2 or ± 0.1.

It can be understood that the numerical values described and claimed in the present invention are approximate values. Changes in values may be attributed to device calibration, device errors, crystal purity, crystal size, sample size and other factors.

It can be understood that the crystal forms of the present invention are not limited to the characteristic patterns such as XRD, DSC and TGA which are completely identical to those described in the drawings disclosed in the present invention, and any crystal form having a characteristic pattern which is essentially or substantially the same as those described in the drawings falls within the scope of the present invention.

It can be understood that, as is well known in the field of differential scanning calorimetry (DSC), a melting peak height of a DSC curve depends on many factors related to sample preparation and geometric shapes of instruments, and a peak position is relatively insensitive to experiment details. Therefore, in some embodiments, the crystallized compounds of the present invention are characterized in that DSC patterns comprising characteristic peak positions have substantially the same properties as the DSC patterns provided in the drawings of the present invention, with an error tolerance of ± 3°C.

The crystal forms disclosed in the present invention can be prepared by the following common methods for preparing crystal forms:

1. a volatilization experiment, in which a clear solution of a sample is exposed to an atmosphere at various temperatures until the solvent is volatilized and removed;

2. a crystal slurrying experiment, in which a supersaturated solution of a sample (containing an undissolved solid) is stirred in different solvent systems at a certain temperature;

3. an anti-solvent experiment, in which a sample is dissolved in a good solvent, an anti-solvent is added to precipitate a solid, followed by brief stirring and immediate filtration;

4. a cooling crystallization experiment, in which a certain amount of samples is dissolved in a corresponding solvent at a high temperature, and the

mixture is directly stirred at room temperature or a low temperature for crystallization;

5. a polymer template experiment, in which various polymer materials are added to a clear solution of a sample, and the resulting solution is exposed to an atmosphere at room temperature until the solvent is volatilized and removed;

6. a thermal method experiment, in which a sample is treated according to a certain thermal method under crystallization conditions and cooled to room temperature; and

7. a water vapor diffusion experiment, in which a sample is left in a certain humidity environment at room temperature.

Brief Description of the Drawings

Figure 1 is an XRD pattern of an amorphous form of compound 1.

Figure 2 is a DSC pattern of an amorphous form of compound 1.

Figure 3 is a TGA pattern of an amorphous form of compound 1.

Figure 4 is an XRD pattern of a crystal form I of compound 1.

Figure 5 is a DSC pattern of a crystal form I of compound 1.

Figure 6 is a TGA pattern of a crystal form I of compound 1.

Figure 7 is an XRD pattern of a crystal form II of compound 1.

Figure 8 is a DSC pattern of a crystal form II of compound 1.

Figure 9 is a TGA pattern of a crystal form II of compound 1.

Figure 10 is an XRD pattern of a crystal form III of compound 1.

Figure 11 is a DSC pattern of a crystal form III of compound 1.

Figure 12 is a TGA pattern of a crystal form III of compound 1.

Figure 13-1 is an XRD pattern of a crystal form I of compound 2.

Figure 13-2 is an XRD pattern of a crystal form I of compound 2.

Figure 14 is a DSC pattern of a crystal form I of compound 2.

Figure 15 is a TGA pattern of a crystal form I of compound 2.

Figure 16-1 is an XRD pattern of a crystal form II of compound 2.

Figure 16-2 is an XRD pattern of a crystal form II of compound 2.

Figure 17 is a DSC pattern of a crystal form II of compound 2.

Figure 18 is a TGA pattern of a crystal form II of compound 2.

Figure 19-1 is an XRD pattern of a crystal form III of compound 2.

Figure 19-2 is an XRD pattern of a crystal form III of compound 2.

Figure 20 is a DSC pattern of a crystal form III of compound 2.

Figure 21 is a TGA pattern of a crystal form III of compound 2.

Figure 22-1 is an XRD pattern of a crystal form IV of compound 2.

Figure 22-2 is an XRD pattern of a crystal form IV of compound 2.

Figure 23 is a DSC pattern of a crystal form IV of compound 2.

Figure 24 is a TGA pattern of a crystal form IV of compound 2.

Figure 25 is an XRD pattern of an amorphous form of compound 2.

Figure 26 is a DSC pattern of an amorphous form of compound 2.

Figure 27 is a TGA pattern of an amorphous form of compound 2.

Figure 28 is an XRD pattern of a crystal form I of compound 3.

Figure 29 is a DSC pattern of a crystal form I of compound 3.

Figure 30 is a TGA pattern of a crystal form I of compound 3.

Figure 31 is an XRD pattern of an amorphous form of compound 3.

Figure 32 is a DSC pattern of an amorphous form of compound 3.

Figure 33 is a TGA pattern of an amorphous form of compound 3.

Figure 34 is an XRD pattern of a crystal form II of compound 3.

Figure 35 is a DSC pattern of a crystal form II of compound 3.

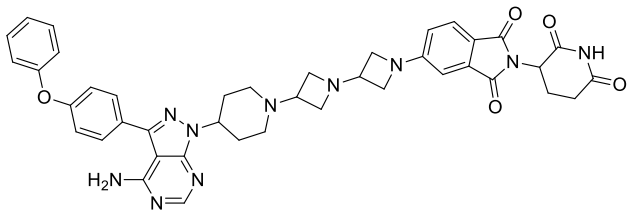
Figure 36 is a TGA pattern of a crystal form II of compound 3.

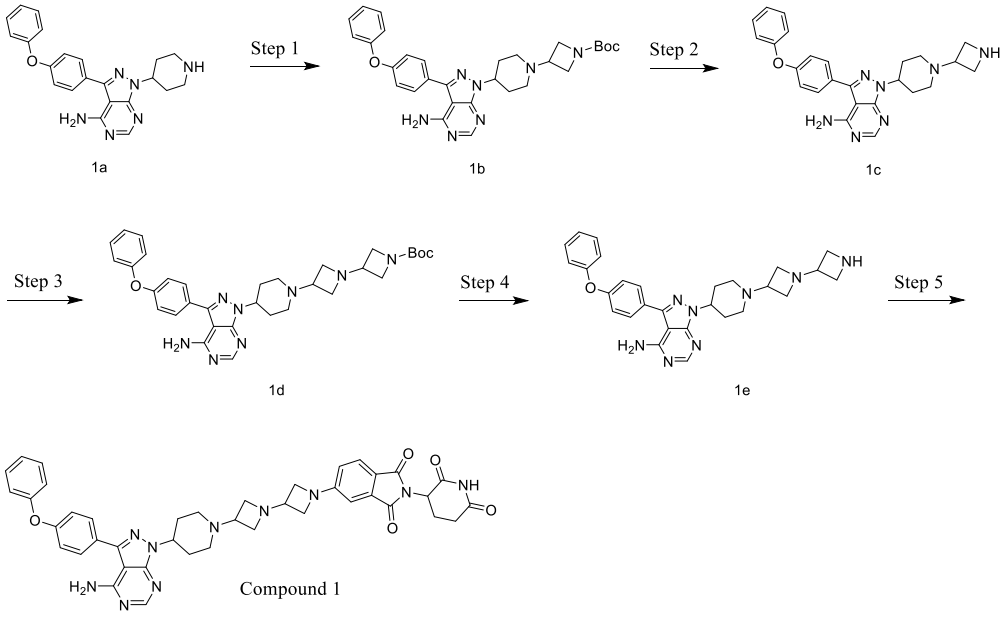
Detailed Description of Embodiments

The implementation process and beneficial effects of the present invention are described in detail below through specific examples, which are intended to help readers better understand the essence and characteristics of the present invention, and are not intended to limit the scope of implementation of the present invention.

Example 1: Preparation of compound 1

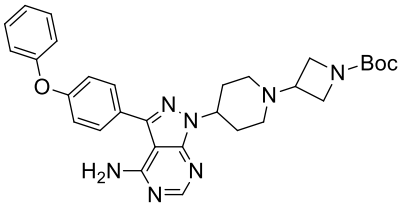
5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (**compound 1, also known as a compound as shown in formula (Ia)**)





Step 1:

tert-butyl 3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidine-1-carboxylate (1b)

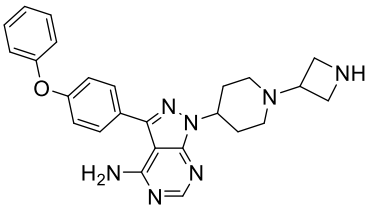


3-(4-phenoxyphenyl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1a) (see *J. Med. Chem.* **2015**, *58*, 9625-9638 for a synthetic method) (11.0 g, 28.5 mmol) was dissolved in 100 mL of 1,2-dichloroethane. Tert-butyl 3-oxoazetidine-1-carboxylate (9.74 g, 56.9 mmol) and glacial acetic acid (3.42 g, 57.0 mmol) were sequentially added. Upon completion of the addition, the reaction was carried out at 65°C for 3 h. The reaction liquid was cooled to room temperature. Sodium triacetoxyborohydride (12.1 g, 57.1 mmol) was added. Upon completion of the addition, the reaction was carried out at room temperature overnight. The pH was adjusted to 9-10 by dropwise adding a saturated sodium bicarbonate solution to the reaction liquid. The resulting solution was concentrated under reduced pressure, and then the crude product was separated and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100 : 0 to 19 : 1) to obtain tert-butyl 3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidine-1-carboxylate (1b) (7.20 g, yield: 47%).

LCMS m/z = 542.3 $[M+1]^+$

Step 2:

1-[1-(azetidin-3-yl)-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1c)

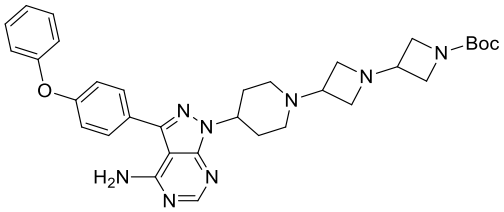


Tert-butyl 3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidine-1-carboxylate (1b) (7.20 g, 13.3 mmol) was dissolved in 15 mL of dichloromethane. 50 mL of 4 N ethyl acetate hydrochloride solution and 10 mL of anhydrous methanol were added. The resulting mixture was stirred at room temperature for 2 h. The reaction liquid was concentrated under reduced pressure, and then 20 mL of dichloromethane was added to the residue. The pH was adjusted to 9-10 by using a saturated sodium bicarbonate solution. Liquid separation was performed. The aqueous layer was extracted (100 mL x 3) with methanol/dichloromethane (v/v = 1 : 10), and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 1-[1-(azetidin-3-yl)-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1c) (5.80 g, yield: 99%).

LCMS m/z = 442.2 $[M+1]^+$

Step 3:

tert-butyl 3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidine-1-carboxylate (1d)



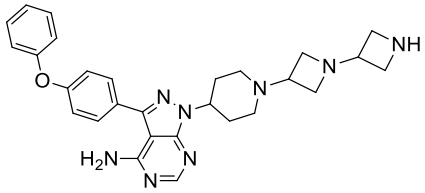
1-[1-(azetidin-3-yl)-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1c) (5.80 g, 13.1 mmol) was dissolved in 25 mL of 1,2-dichloroethane. Tert-butyl 3-oxoazetidine-1-carboxylate (4.50 g, 26.3 mmol) and glacial acetic acid (1.58 g, 26.3 mmol) were sequentially added. Upon completion of the addition, the reaction was carried out at 65°C for 3 h. The reaction liquid was cooled to room temperature. Sodium triacetoxyborohydride (5.57 g, 26.3 mmol) was added. Upon completion of the addition, the reaction was carried out at room

temperature overnight. The pH was adjusted to 9-10 by dropwise adding a saturated sodium bicarbonate solution to the reaction liquid. The resulting solution was concentrated under reduced pressure, and then the crude product was separated and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100 : 0 to 19 : 1) to obtain tert-butyl 3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidine-1-carboxylate (1d) (3.60 g, yield: 46%).

LCMS m/z = 597.3 $[M+1]^+$

Step 4:

1-[1-[1-(azetidin-3-yl)azetidin-3-yl]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1e)

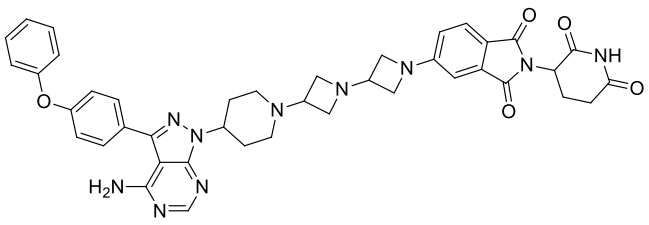


Tert-butyl 3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidine-1-carboxylate (1d) (3.60 g, 6.03 mmol) was dissolved in 5 mL of dichloromethane. 5 mL of trifluoroacetic acid was added. The resulting mixture was stirred at room temperature for 2 h. The reaction liquid was concentrated under reduced pressure, and then 20 mL of dichloromethane was added to the residue. The pH was adjusted to 9-10 by using a saturated sodium bicarbonate solution. Liquid separation was performed. The aqueous layer was extracted with 100 mL of dichloromethane, and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 1-[1-[1-(azetidin-3-yl)azetidin-3-yl]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1e) as a crude product (3.0 g).

LCMS m/z = 497.3 $[M+1]^+$

Step 5:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1)



The above crude product of 1-[1-[1-(azetidin-3-yl)azetidin-3-yl]-4-piperidyl]-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (1e) (3.00 g) was dissolved in 15 mL of dimethylsulfoxide. 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (see WO 2017197056 for a synthetic method) (2.00 g, 7.25 mmol) and diisopropylethylamine (3.90 g, 30.2 mmol) were sequentially added. Upon completion of the addition, the reaction was carried out at 90°C for 2 h. The reaction liquid was cooled to room temperature, and 10 mL of water was slowly added dropwise. Filtration was performed. The filter cake was dissolved in 50 mL of dichloromethane, and then washed with 15 mL of saturated sodium chloride solution. Liquid separation was performed. The organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure, and then the crude product was separated and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100 : 0 to 19 : 1), and the purified product solution obtained by column chromatography was directly concentrated under reduced pressure to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (2.90 g, the two-step yield calculated from compound 1d: 64%),

which is an amorphous form (yellow solid) of compound 1 as analysed by XRD, DSC and TGA. Reference was made to Figures 1, 2 and 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.39 (s, 1H), 7.72-7.57 (m, 3H), 7.45-7.32 (m, 2H), 7.21-7.11 (m, 3H), 7.10-7.04 (m, 2H), 6.78 (d, 1H), 6.52 (dd, 1H), 5.81 (brs, 2H), 4.92 (dd, 1H), 4.87-4.71 (m, 1H), 4.08-3.99 (m, 2H), 3.94-3.83 (m, 2H), 3.76-3.65 (m, 1H), 3.64-3.49 (m, 2H), 3.20-3.04 (m, 3H), 3.00-2.64 (m, 5H), 2.52-2.34 (m, 2H), 2.18-1.89 (m, 5H).

LCMS m/z = 377.3 $[M/2 + 1]^+$

Example 2: Preparation of crystal form I of compound 1

8 mL of ethyl acetate was added to the amorphous form (40 mg) of compound 1 prepared in example 1 to obtain a clear solution. The solution was exposed to an atmosphere at 40°C and volatilized to obtain a crystal form I (yellow solid) of

compound 1. The crystal form I of compound 1 was characterized by XRD, DSC and TGA. Reference was made to Figures 4, 5 and 6.

Example 3: Preparation of crystal form II of compound 1

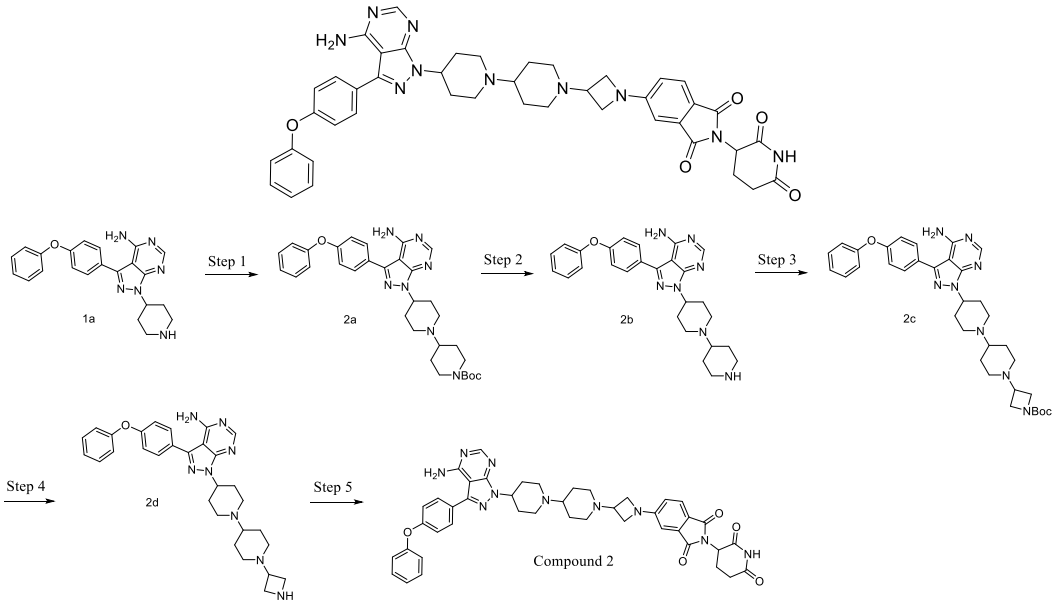
6 mL of ethanol was added to the amorphous form (200 mg) of compound 1 prepared in example 1. Crystal slurrying was performed at room temperature for 3 days. Centrifugation was performed, and then the solid was dried under vacuum overnight at room temperature to obtain a crystal form II (yellow solid) of compound 1. The crystal form II of compound 1 was characterized by XRD, DSC and TGA. Reference was made to Figures 7, 8 and 9.

Example 4: Preparation of crystal form III of compound 1

6 mL of acetonitrile and 6 mL of water were added to the amorphous form (400 mg) of compound 1 prepared in example 1. The resulting solution was stirred at 40°C for 72 h, and suction filtration was performed. The filter cake was collected and dried under vacuum overnight at 40°C to obtain a crystal form III (yellow solid) of compound 1. The crystal form III of compound 1 was characterized by XRD, DSC and TGA. Reference was made to Figures 10, 11 and 12.

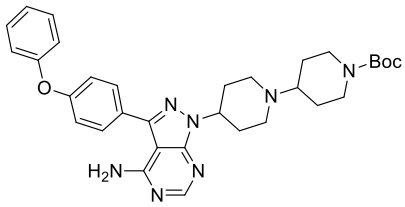
Example 5: Preparation of compound 2

5-(3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **(compound 2, which also known as a compound as shown in formula (Ib))**



Step 1:

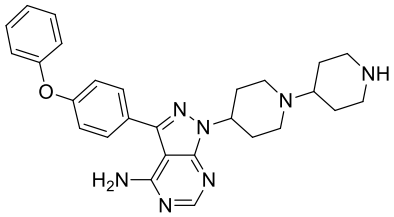
tert-butyl 4-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]piperidine-1-carboxylate (2a)



3-(4-phenoxyphenyl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (1a) (see J. Med. Chem. 2015, 58, 9625-9638 for a synthetic method) (10.42 g, 26.97 mmol) was dissolved in 200 mL of 1,2-dichloroethane. Tert-butyl 4-oxopiperidine-1-carboxylate (13.43 g, 67.42 mmol) and glacial acetic acid (4.2 g, 67.42 mmol) were sequentially added. The resulting solution was heated to 65°C, stirred for 2 h and cooled to room temperature, and sodium triacetoxyborohydride (34.29 g, 161.79 mmol) was added. The reaction was carried out under stirring at room temperature for 16 h. After TLC showed the reaction was completed, the reaction liquid was left to stand. 50 mL of 2 M aqueous solution of sodium hydroxide was added. The pH was adjusted to 8-9 by using a saturated sodium bicarbonate solution. The resulting mixture was allowed to stand for layer separation. The aqueous phase was extracted with dichloromethane (200 mL x 3), and the organic phases were combined, washed once with a saturated brine (300 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (200-300 mesh silica gel, dichloromethane/methanol (v/v) = 100/1 to 15/1) to obtain tert-butyl 4-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]piperidine-1-carboxylate (2a) (10.72 g, yield: 70%).

Step 2:

3-(4-phenoxyphenyl)-1-[1-(4-piperidyl)-4-piperidyl]pyrazolo[3,4-d]pyrimidin-4-amine (2b)

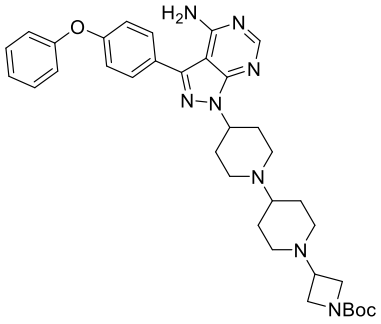


Tert-butyl 4-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]piperidine-1-carboxylate (2a) (45 g, 92.48 mmol) was added to a reaction flask. 410 mL of dichloromethane was added and dissolved under stirring, and then 80 mL of trifluoroacetic acid was added. The reaction was carried out under stirring at room temperature overnight. After the reaction was completed, the

reaction liquid was concentrated under reduced pressure to obtain an oil. 500 mL of dichloromethane was added. The pH was adjusted to 10 by slowly adding a 2 mol/L sodium hydroxide solution dropwise under stirring. Liquid separation was performed. The aqueous phase was extracted with dichloromethane (400 mL x 3), and the organic phases were combined. The organic layer was washed with a 15% aqueous solution of sodium chloride (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain 3-(4-phenoxyphenyl)-1-[1-(4-piperidyl)-4-piperidyl]pyrazolo[3,4-d]pyrimidin-4-amine (2b) (29.3 g, yield: 82%).

Step 3:

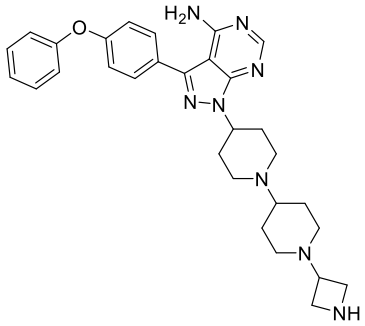
tert-butyl 3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidine-1-carboxylate (2c)



3-(4-phenoxyphenyl)-1-[1-(4-piperidyl)-4-piperidyl]pyrazolo[3,4-d]pyrimidin-4-amine (2b) (29.3 g, 0.076 mol) was added to 1,2-dichloroethane (0.5 L). 1-Boc-3-azetidinone (37.7 g, 0.189 mol), acetic acid (11.4 g, 0.189 mol) and anhydrous sodium sulfate (30 g) were sequentially added. Upon completion of the addition, sodium triacetoxyborohydride (96.3 g, 0.45 mol) was slowly added. The reaction was carried out under stirring at room temperature for 2 h. The reaction liquid was poured into a 2 L plastic beaker. Ice was added, and the pH was adjusted to 12-13 by using a 2M aqueous solution of sodium hydroxide. The resulting mixture was allowed to stand for layer separation. The aqueous phase was extracted with dichloromethane (400 mL x 3), and the organic phases were combined, washed with a saturated brine (600 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product. The crude product was purified by column chromatography (200-300 mesh silica gel, dichloromethane/methanol (v/v) = 100/0 to 12/1) to obtain tert-butyl 3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidine-1-carboxylate (2c) (35 g, yield: 81%).

Step 4:

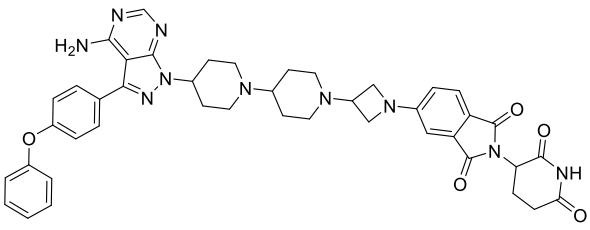
1-(1'-(azetidin-3-yl)-[1,4'-bipiperidin]-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (2d)



Tert-butyl 3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidine-1-carboxylate (2c) (25 g, 0.04 mmol) was added to a reaction flask. 125 mL of dichloromethane was added, and 50 mL of trifluoroacetic acid was slowly added dropwise. Upon completion of the addition, the reaction was carried out under stirring at room temperature for 2 h. After the reaction was completed, the reaction liquid was concentrated under reduced pressure to obtain an oil. 200 mL of methyl tert-butyl ether was added under stirring, with a white solid gradually precipitated. Stirring was performed for crystallization at room temperature for 1 h. The resulting product was filtered and concentrated under reduced pressure to obtain 1-(1'-(azetidin-3-yl)-[1,4'-bipiperidin]-4-yl)-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine trifluoroacetate (2d) (50 g, yield: 99%).

Step 5:

5-(3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione **(**compound 2**)**



2-(2,6-dioxopiperidin-3-yl)-5-fluoroisoindoline-1,3-dione (see WO 2017197056 for a synthetic method) (10.3 g, 0.037 mmol), N,N'-diisopropylethylamine (40 g, 0.31 mmol) and dimethylsulfoxide (0.2 L) were sequentially added to 1-(1'-(azetidin-3-yl)-[1,4'-bipiperidin]-4-yl)-3-(4-

phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine trifluoroacetate (2d) (48 g, 0.031 mmol). The reaction was carried out under stirring at 120°C for 3 h. The reaction liquid was cooled to room temperature with ice water, and water (0.2 L) was added to the reaction liquid under stirring, with a large amount of solids precipitated. The resulting mixture was continuously stirred for 30 min, filtered and dried with suction. The filter cake was dissolved in 0.5 L of dichloromethane under stirring, washed with concentrated ammonia water (200 mL x 3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the residue was separated and purified by silica gel column chromatography (dichloromethane/methanol (v/v) = 100/0 to 94/6) to collect the product. Ethyl acetate (0.28 L) was added to the above product obtained by column chromatography. The resulting mixture was slurried under stirring for 20 h and filtered. The filter cake was dried under vacuum at 45°C for 92 h to obtain 5-(3-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-[1,4'-bipiperidin]-1'-yl)azetidin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (compound 2) (17 g, yield: 72%),

which is a crystal form I (yellow solid) of compound 2 as analysed by XRD, DSC and TGA. Reference was made to Figures 13-1, 13-2, 14 and 15.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (brs, 1H), 8.39 (s, 1H), 7.67-7.60 (m, 3H), 7.42-7.34 (m, 2H), 7.19-7.10 (m, 3H), 7.10-7.04 (m, 2H), 6.78 (d, 1H), 6.51 (dd, 1H), 5.89 (brs, 2H), 4.96-4.88 (m, 1H), 4.83-4.70 (m, 1H), 4.14-4.04 (m, 2H), 3.92-3.84 (m, 2H), 3.39-3.30 (m, 1H), 3.18-3.04 (m, 2H), 3.00-2.91 (m, 2H), 2.90-2.65 (m, 3H), 2.56-2.32 (m, 5H), 2.16-2.01 (m, 3H), 2.01-1.84 (m, 4H), 1.73-1.59 (m, 2H).

LC-MS m/z = 781.4 $[M+1]^+$.

Example 6: Preparation of crystal form II of compound 2

2.8 mL of tetrahydrofuran and 1.4 mL of water were added to the crystal form I (210 mg) of compound 2. The resulting mixture was heated and stirred at 60°C to obtain a clear solution. The solution was stirred at 4°C overnight, with a solid precipitated. Suction filtration was performed under reduced pressure. The resulting product was dried under vacuum at room temperature for about 3 h to obtain a crystal form II (yellow solid) of compound 2. The crystal form II of compound 2 was characterized by XRD, DSC and TGA. Reference was made to Figures 16-1, 16-2, 17 and 18.

Example 7: Preparation of crystal form III of compound 2

14 mL of water and 1.4 mL of tetrahydrofuran were added to the crystal form I (210 mg) of compound 2. Crystal slurrying was performed at 4°C for 3 days. The resulting product was filtered with suction to dryness under reduced pressure to obtain a crystal form III (yellow solid) of compound 2. The crystal form III of compound 2 was characterized by XRD, DSC and TGA. Reference was made to Figures 19-1, 19-2, 20 and 21.

Example 8: Preparation of crystal form IV of compound 2

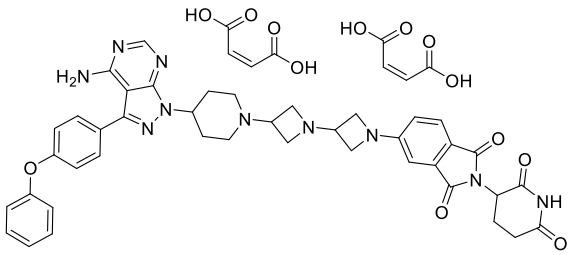
1 mL of isopropyl acetate and 1 mL of n-heptane were added to the crystal form I (30 mg) of compound 2. Crystal slurrying was performed at room temperature for 3 days. Centrifugation was performed, and then the sample was dried under vacuum at room temperature for about 5 h to obtain a crystal form IV (yellow solid) of compound 2. The crystal form IV of compound 2 was characterized by XRD, DSC and TGA. Reference was made to Figures 22-1, 22-2, 23 and 24.

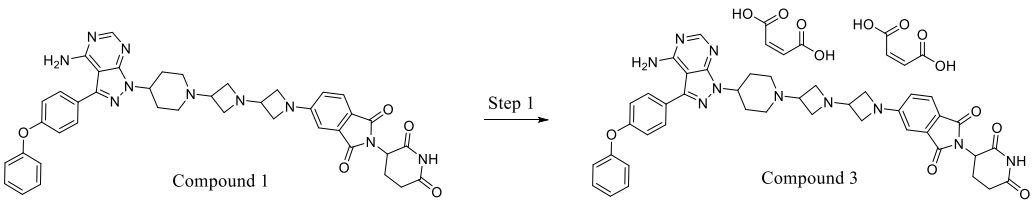
Example 9: Preparation of amorphous form of compound 2

5 mL of dichloromethane was added to the crystal form I (400 mg) of compound 2. The resulting mixture was heated to obtain a clear solution. Filtration was performed. The filtrate was concentrated to dryness under reduced pressure at 40°C to obtain an amorphous form (yellow solid) of compound 2. The amorphous form of compound 2 was characterized by XRD, DSC and TGA. Reference was made to Figures 25, 26 and 27.

Example 10: Preparation of compound 3

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione dimaleate (**compound 3, also known as a compound as shown in formula (II)**)





Dichloromethane (10 mL) was added to 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (1.0 g, 1.33 mmol). The mixture was stirred at room temperature until a clear solution was obtained. A solution of maleic acid (0.309 g, 2.66 mmol) in methanol (1 mL) was added dropwise, during which a solid was gradually precipitated. The resulting mixture was continuously stirred at room temperature for 3 h, and then suction filtration was performed under reduced pressure. The filter cake was washed with 10 mL of dichloromethane, collected and then concentrated under reduced pressure at 40°C to remove the residual solvent, so as to obtain 0.96 g of a crude product. 20 mL of ethanol was added to the above crude product. The resulting mixture was heated at 90°C and slurried under stirring for 0.5 h. The suspension was cooled to room temperature for crystallization for 2 h. Suction filtration was performed under reduced pressure. The filter cake was washed with 10 mL of ethanol, collected and then concentrated under reduced pressure at 40°C to remove the residual solvent, so as to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)]pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione dimaleate (compound 3) (0.62 g, yield: 47%),

which is a crystal form I (yellow solid) of compound 3 as analysed by XRD, DSC and TGA. Reference was made to Figures 28, 29 and 30.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.27 (s, 1H), 7.72-7.63 (m, 3H), 7.48-7.41 (m, 2H), 7.24-7.09 (m, 5H), 6.86 (d, 1H), 6.72 (dd, 1H), 6.15 (s, 4H), 5.06 (dd, 1H), 5.01-4.86 (m, 1H), 4.24-4.12 (m, 2H), 4.11-3.93 (m, 3H), 3.92-3.79 (m, 2H), 3.77-3.59 (m, 3H), 3.37-3.22 (m, 2H), 2.98-2.68 (m, 3H), 2.65-2.51 (m, 2H), 2.46-2.31 (m, 2H), 2.18-2.06 (m, 2H), 2.06-1.96 (m, 1H).

Example 11: Preparation of amorphous form of compound 3

50 mL of trifluoroethanol and 50 mL of dichloromethane were sequentially added to compound 3 (300 mg) (crystal form I) to obtain a clear solution. The solution was concentrated to dryness under reduced pressure at 40°C to obtain an amorphous form (yellow solid) of compound 3,

which is an amorphous form of compound 3 as analysed by XRD, DSC and TGA. Reference was made to Figures 31, 32 and 33.

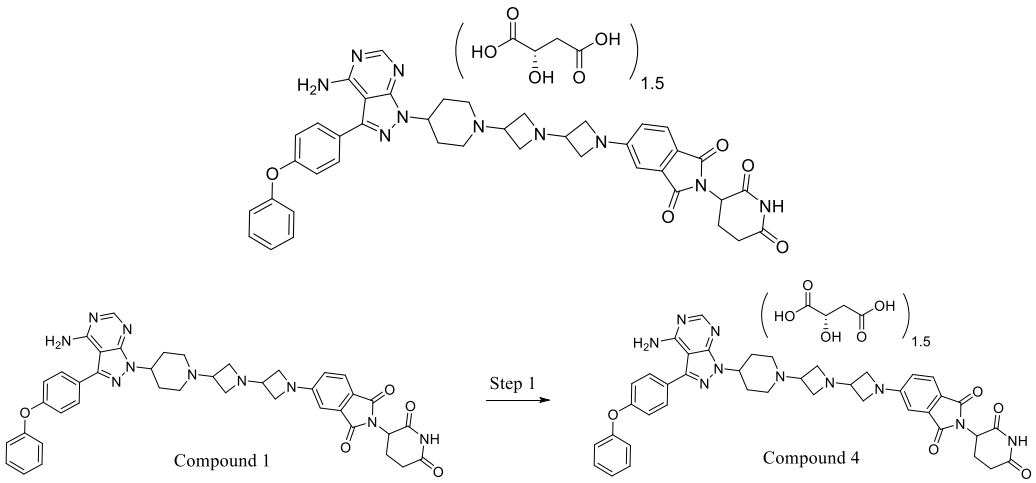
Example 12: Preparation of crystal form II of compound 3

6.0 mL of methanol and 4.0 mL of water were added to compound 3 (150 mg) (crystal form I). The resulting mixture was placed in a water bath at 70°C to obtain a clear solution. The solution was stirred at 4°C overnight, with a solid precipitated. Suction filtration was performed under reduced pressure. The resulting product was dried under vacuum at room temperature overnight to obtain a crystal form II (yellow solid) of compound 3,

which is a crystal form II of compound 3 as analysed by XRD, DSC and TGA. Reference was made to Figures 34, 35 and 36.

Example 13:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione L-malate (**compound 4**)



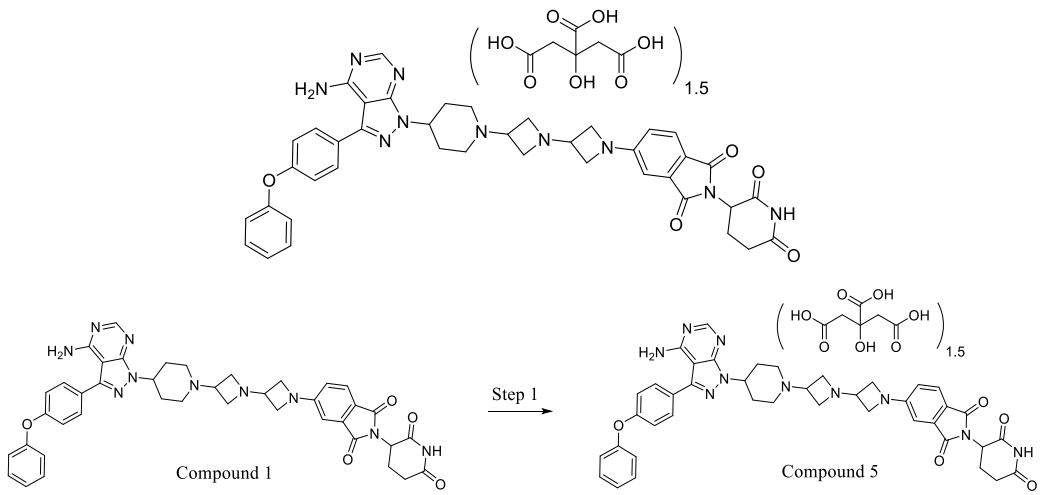
Dichloromethane (8 mL) was added to 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.40 g, 0.531 mmol). The mixture was stirred at room temperature until a clear solution was obtained. A solution of L-malic acid (0.28 g, 2.09 mmol) in methanol (0.5 mL) was added dropwise, during which a viscous solid was gradually precipitated. The resulting mixture was continuously stirred at room temperature for 2 h, and then concentrated under reduced pressure at 40°C. Ethanol (10 mL) was added to the residue. The resulting mixture was heated to 90°C, stirred for 1 h, then cooled to room temperature and stirred for 2 h. Suction filtration was performed. The filter

cake was dried under vacuum at 50°C for 18 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione L-malate (compound 4) (yellow solid) (0.41 g, yield: 81%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.24 (s, 1H), 7.70-7.61 (m, 3H), 7.48-7.40 (m, 2H), 7.23-7.08 (m, 5H), 6.80 (d, 1H), 6.67 (dd, 1H), 5.05 (dd, 1H), 4.77-4.64 (m, 1H), 4.21 (dd, 1.5H), 4.11-4.02 (m, 2H), 3.88-3.80 (m, 2H), 3.76-3.66 (m, 1H), 3.55-3.46 (m, 2H), 3.16-3.04 (m, 3H), 3.00-2.80 (m, 3H), 2.65-2.52 (m, 3H), 2.49-2.38 (m, 2H), 2.31-2.07 (m, 4H), 2.06-1.89 (m, 3H).

Example 14:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione citrate (**compound 5**)



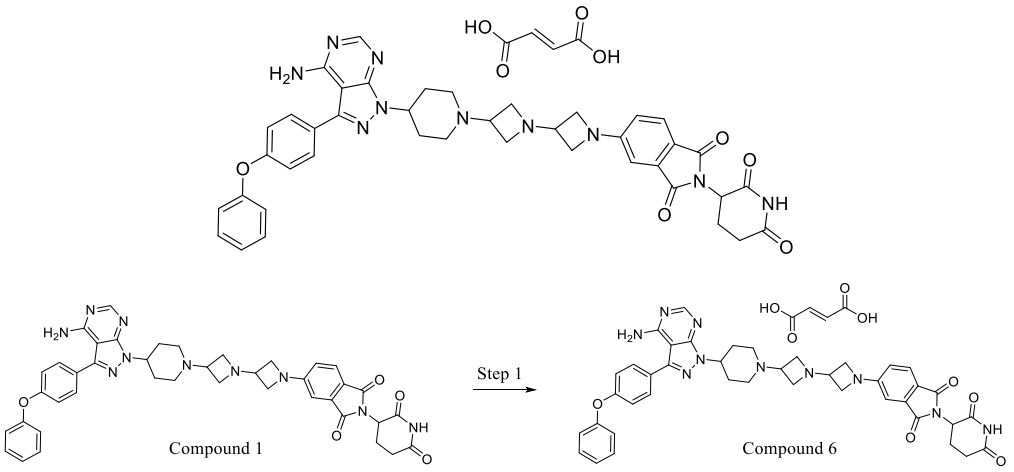
Dichloromethane (8 mL) was added to 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.40 g, 0.531 mmol). The mixture was stirred at room temperature until a clear solution was obtained. A solution of citric acid monohydrate (0.45 g, 2.14 mmol) in methanol (0.7 mL) was added dropwise, during which a viscous solid was gradually precipitated. The resulting mixture was continuously stirred at room temperature for 2 h, and then concentrated under reduced pressure at 40°C. Ethanol (10 mL) was added to the residue. The resulting mixture was heated to 90°C, stirred for 1 h, then cooled to room temperature and stirred for 2 h. Suction filtration was performed. The filter cake was dried under vacuum at 50°C for 18 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-

1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione citrate (compound 5) (yellow solid) (0.48 g, yield: 87%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.25 (s, 1H), 7.70-7.63 (m, 3H), 7.48-7.40 (m, 2H), 7.23-7.09 (m, 5H), 6.82 (d, 1H), 6.68 (dd, 1H), 5.06 (dd, 1H), 4.83-4.71 (m, 1H), 4.15-4.04 (m, 2H), 3.91-3.74 (m, 3H), 3.64-3.53 (m, 2H), 3.33-3.20 (m, 3H), 3.09-2.96 (m, 2H), 2.94-2.82 (m, 1H), 2.79-2.53 (m, 8H), 2.40-2.20 (m, 4H), 2.07-1.91 (m, 3H).

Example 15:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione fumarate (**compound 6**)



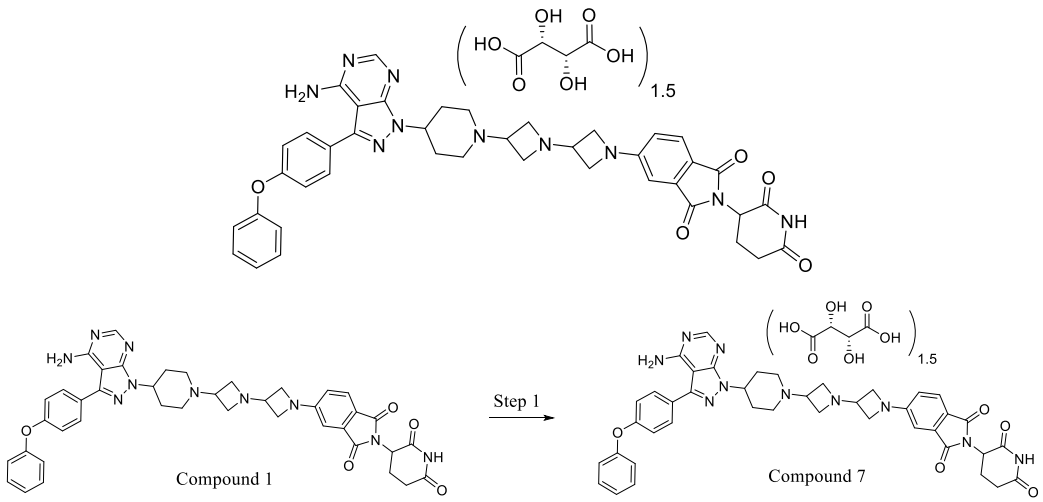
5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.500 g, 0.664 mmol) was dissolved in dichloromethane (5 mL). Anhydrous methanol (1.25 mL) and fumaric acid (0.616 g, 5.31 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 7 h and then filtered. The filter cake was collected, and anhydrous ethanol (15 mL) was added to the filter cake. The resulting product was heated to 80°C, stirred for 2 h, cooled to room temperature and filtered. The filter cake was dried under vacuum at 50°C for 16 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione fumarate (compound 6) (yellow solid) (0.400 g, yield: 69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.23 (s, 1H), 7.70-7.60 (m, 3H), 7.47-7.40 (m, 2H), 7.23-7.09 (m, 5H), 6.79 (d, 1H), 6.66 (dd, 1H), 6.62 (s, 2H),

5.05 (dd, 1H), 4.74-4.62 (m, 1H), 4.09-4.01 (m, 2H), 3.86-3.78 (m, 2H), 3.71-3.62 (m, 1H), 3.50-3.40 (m, 2H), 3.08-2.97 (m, 3H), 2.94-2.82 (m, 3H), 2.64-2.46 (m, 2H), 2.29-2.14 (m, 2H), 2.12-1.86 (m, 5H).

Example 16:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione L-tartrate (**compound 7**)

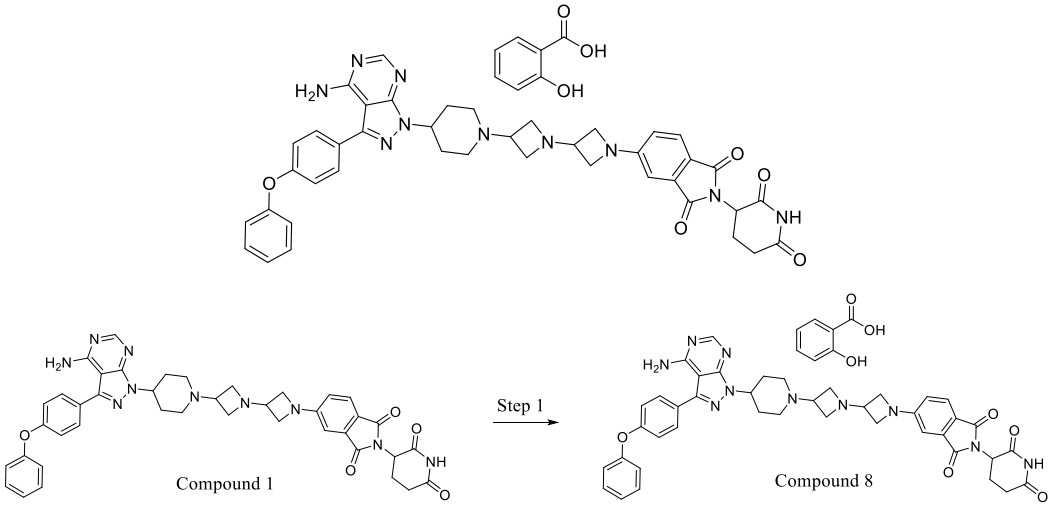


5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.500 g, 0.664 mmol) was dissolved in dichloromethane (5 mL). Anhydrous methanol (0.75 ml) and L-tartaric acid (0.399 g, 2.66 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 4 h and then filtered. The filter cake was collected, and anhydrous ethanol (15 mL) was added to the filter cake. The resulting product was heated to 80°C, stirred for 2 h, cooled to room temperature and filtered. The filter cake was dried under vacuum at 50°C for 16 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione L-tartrate (compound 7) (yellow solid) (0.510 g, yield: 79%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.24 (s, 1H), 7.70-7.61 (m, 3H), 7.48-7.40 (m, 2H), 7.23-7.09 (m, 5H), 6.80 (d, 1H), 6.67 (dd, 1H), 5.06 (dd, 1H), 4.78-4.65 (m, 1H), 4.28 (s, 3H), 4.11-4.02 (m, 2H), 3.88-3.79 (m, 2H), 3.76-3.66 (m, 1H), 3.56-3.40 (m, 2H), 3.18-3.04 (m, 3H), 2.98-2.80 (m, 3H), 2.65-2.46 (m, 2H), 2.35-1.87 (m, 7H).

Example 17:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione salicylate (**compound 8**)



10 mL of an ethanol/water (v/v = 4 : 1) mixed solvent was added to 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.400 g, 0.531 mmol). The mixture was heated to 80°C until complete dissolution. Salicylic acid (0.293 g, 2.12 mmol) was added. The resulting mixture was continuously stirred at 80°C until a clear solution was obtained. The solution was cooled to 60°C, stirred for 1 h, then cooled to room temperature and stirred for 2 h for crystallization. Suction filtration was performed. The filter cake was collected, and 10 mL of an ethanol/water (v/v = 4/1) mixed solvent was added to the filter cake. The resulting product was heated to 80°C, stirred until the solid was dissolved, then cooled to room temperature and stirred for 2 h for crystallization. Filtration was performed. The filter cake was collected and dried under vacuum at 50°C for 16 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione salicylate (compound 8) (yellow solid) (0.140 g, yield: 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.24 (s, 1H), 7.78-7.59 (m, 4H), 7.48-7.40 (m, 2H), 7.39-7.31 (m, 1H), 7.24-7.08 (m, 5H), 6.85-6.74 (m, 3H), 6.65 (dd, 1H), 5.06 (dd, 1H), 4.87-4.73 (m, 1H), 4.15-4.04 (m, 2H), 3.95-3.77 (m,

3H), 3.70-3.58 (m, 2H), 3.41-3.28 (m, 3H), 3.14-3.01 (m, 2H), 2.95-2.81 (m, 1H), 2.65-2.46 (m, 2H), 2.45-2.22 (m, 4H), 2.07-1.94 (m, 3H).

Example 18:

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione oxalate (**compound 9**)

5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (compound 1) (0.500 g, 0.664 mmol) was dissolved in dichloromethane (10 mL). A solution of oxalic acid dihydrate (0.335 g, 2.66 mmol) in methanol (2 mL) was slowly added dropwise. The resulting mixture was stirred at room temperature for 4 h and then filtered. The filter cake was collected, and anhydrous ethanol (12 mL) was added to the filter cake. The resulting product was heated to 80°C, stirred for 2 h, and cooled to room temperature. Filtration was performed. The filter cake was collected and dried under vacuum at 50°C for 16 h to obtain 5-[3-[3-[4-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidyl]azetidin-1-yl]azetidin-1-yl]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione oxalate (compound 9) (yellow solid) (0.480 g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 8.26 (s, 1H), 7.71-7.62 (m, 3H), 7.49-7.39 (m, 2H), 7.24-7.09 (m, 5H), 6.84 (d, 1H), 6.70 (dd, 1H), 5.06 (dd, 1H), 4.95-4.83 (m, 1H), 4.21-4.09 (m, 2H), 4.06-3.91 (m, 3H), 3.88-3.74 (m, 2H), 3.70-3.55 (m, 3H), 3.30-3.16 (m, 2H), 2.96-2.81 (m, 1H), 2.74-2.46 (m, 4H), 2.44-2.28 (m, 2H), 2.15-1.94 (m, 3H).

Test example

1. XRD tests of compounds 1, 2 and 3

The compounds of the present invention were subjected to X-ray powder diffraction tests according to the following methods. The test parameters of the amorphous form and crystal forms I, II and III of compound 1 were as shown in Table 1-1, the test parameters of the crystal forms I, II, III and IV and amorphous form of compound 2 were as shown in Table 1-1, and the test parameters of the crystal forms I and II and amorphous form of compound 3 were as shown in Table 1-2. The test results were as shown in Figures 1, 4, 7, 10, 13-1, 13-2, 16-1, 16-2, 19-1, 19-2, 22-1, 22-2, 25, 28, 31 and 34.

Table 1-1 Test parameters of XRD

Device name	**X-ray powder diffractometer (XRPD) and hot-stage XRPD**		
Instrument	Model	Bruker D8 Advance Diffractometer	
	Number	LY-01-034	
	Technical indicator	Kα radiation (40 kV, 40 mA) with a copper target wavelength of 1.54 Å, a θ-2θ goniometer, a Mo monochromator and a Lynxeye detector	
	Acquisition software	Diffrac Plus XRD Commander	
	Calibration material	Corundum (Al_2O_3)	
	Analysis software	MDI Jade	
Accessory	Non-reflective sample plate	Specification	24.6 mm diameter × 1.0 mm thickness
		Manufacturer	MTI corporation
	Variable-temperature hot stage	Manufacturer	Shanghai Weitu Instrument Technology Development Co., Ltd.
		Material of sample plate	Copper plate
Parameter	Detection angle	3-40° 2θ/3-30° 2θ (hot-stage XRPD)	
	Step length	0.02° 2θ	
	Speed	0.2 $s.step^{-1}$	
	Sample size to be detected	> 2 mg	
	Note	Unless otherwise specified, samples are not subjected to grinding before detection	

Table 1-2 Test parameters of XRD

Device name	**X-ray powder diffractometer (XRPD) and hot-stage XRPD**	
Instrument	Model	Bruker D8 Advance Diffractometer
	Number	LY-01-034
	Technical indicator	Kα radiation (40 kV, 40 mA) with a copper target wavelength of 1.54 Å, a θ-2θ goniometer, nickel filtration, and a Lynxeye detector

	Acquisition software	Diffrac Plus XRD Commander	
	Calibration material	Corundum (Al_2O_3)	
	Analysis software	MDI Jade	
Accessory	Non-reflective sample plate	Specification	24.6 mm diameter × 1.0 mm thickness
		Manufacturer	MTI corporation
	Variable-temperature hot stage	Manufacturer	Shanghai Weitu Instrument Technology Development Co., Ltd.
		Material of sample plate	Copper plate
Parameter	Detection angle	3-40° 2θ/3-30° 2θ (hot-stage XRPD)	
	Step length	0.02° 2θ	
	Speed	0.2 $s.step^{-1}$	
	Sample size to be detected	> 2 mg	
	Note	Unless otherwise specified, samples are not subjected to grinding before detection	

2. DSC tests of compounds 1, 2 and 3

DSC patterns were collected on TA Instruments Q200 DSC and DSC 3 differential scanning calorimeters. The test parameters of compound 1 and compound 2 were as shown in Table 2-1, and the test parameters of compound 3 were as shown in Table 2-2. The test results were as shown in Figures 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32 and 35.

Table 2-1 Test parameters of DSC

Instrument	Model	TA Instruments Q200 DSC
	Number	LY-01-002
	Control software	Thermal Advantage
	Analysis software	Universal Analysis
	Sample tray	Aluminium crucible (with a cover, but without perforation)
Parameter	Sample size to be detected	0.5 mg to 5 mg
	Protective gas	Nitrogen gas
	Gas flow rate	50 mL/min

	Commonly used detection method	Equilibrate at 0°C Ramp 10°C/min to 250°C/290°C

Table 2-2 Test parameters of DSC

Instrument	Model	DSC 3
	Number	LY-01-166
	Control software	STARe
	Analysis software	STARe
	Sample tray	Aluminium crucible (with a cover and with perforation)
Parameter	Sample size to be detected	1 mg to 10 mg
	Protective gas	Nitrogen gas
	Gas flow rate	50 mL/min
	Commonly used detection method	Equilibrate at 0°C Ramp 10°C/min to 250°C

3. TGA tests of compounds 1, 2 and 3

TGA patterns were collected on TA Instruments Q500 TGA and TGA/DSC 3^+ thermogravimetric analysers. The test parameters of compound 1 and compound 2 were as shown in Table 3-1, and the test parameters of compound 3 were as shown in Table 3-2. The test results were as shown in Figures 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36.

Table 3-1 Test parameters of TGA

Instrument	Model	TA Instruments Q500 TGA
	Number	LY-01-003
	Control software	Thermal Advantage
	Analysis software	Universal Analysis
	Sample tray	Platinum crucible
Parameter	Sample size to be detected	1 mg to 10 mg
	Protective gas	Nitrogen gas
	Gas flow rate	40 mL/min
	Commonly used detection method	Hi-Res sensitivity 3.0; Ramp 10.00°C/min, res 5.0 to 150.00°C; Ramp 10.00°C/min to 350°C

Table 3-2 Test parameters of TGA

Instrument	Model	TGA/DSC 3^+
	Number	LY-01-167
	Control software	STARe
	Analysis software	STARe
	Sample tray	Ceramic crucible
Parameter	Sample size to be detected	1 mg to 10 mg
	Protective gas	Nitrogen gas
	Gas flow rate	50 mL/min
	Commonly used detection method	Hi-Res sensitivity 3.0; Ramp 10.00°C/min, res 5.0 to 150.00°C; Ramp 10.00°C/min to 350°C

4. Specific peak value characterization results of XRD tests of compounds 1, 2 and 3

The X-ray powder diffraction (XRD) pattern of the crystal form I of compound 1 was as shown in Figure 4. Specific peak values were as shown in Table 4.

Table 4

2-Theta	d	BG	Height	I%	Area	I%	FWHM
8.323	10.6149	669	2324	57.2	23926	50.1	0.175
10.245	8.6272	577	140	3.4	647	1.4	0.079
10.942	8.0791	577	1554	38.3	23713	49.6	0.26
11.903	7.4289	553	673	16.6	6101	12.8	0.154
13.304	6.6497	524	891	21.9	9265	19.4	0.177
14.386	6.1517	523	511	12.6	7603	15.9	0.253
15.686	5.6449	732	1715	42.2	18578	38.9	0.184
16.407	5.3984	702	1404	34.6	25605	53.6	0.31
16.667	5.3147	716	715	17.6	15844	33.1	0.377
17.243	5.1383	672	224	5.5	3107	6.5	0.236
17.568	5.0441	675	1408	34.7	17676	37	0.214
18.003	4.9232	679	363	8.9	3830	8	0.179
18.888	4.6944	881	4062	100	42818	89.6	0.179
19.747	4.492	828	2841	69.9	47795	100	0.286
20.187	4.3951	707	438	10.8	11036	23.1	0.429
21.249	4.1779	577	650	16	9218	19.3	0.241
21.62	4.107	586	80	2	671	1.4	0.143

22.271	3.9884	581	2283	56.2	26904	56.3	0.2
23.849	3.7279	538	1167	28.7	25991	54.4	0.379
24.83	3.5829	488	190	4.7	3040	6.4	0.272
25.269	3.5216	470	514	12.7	8436	17.7	0.279
26.45	3.367	435	1518	37.4	26092	54.6	0.292
27.123	3.2849	435	83	2	3142	6.6	0.644
27.589	3.2305	415	68	1.7	856	1.8	0.214
28.285	3.1525	372	148	3.6	2321	4.9	0.267
29.45	3.0304	327	71	1.7	586	1.2	0.14
30.111	2.9654	318	323	8	5231	10.9	0.275
31.07	2.8761	314	141	3.5	2229	4.7	0.269
31.649	2.8247	292	74	1.8	1424	3	0.327
32.01	2.7937	262	76	1.9	1421	3	0.318
33.694	2.6578	254	369	9.1	7891	16.5	0.364
35.169	2.5496	227	121	3	1866	3.9	0.262
36.154	2.4824	214	76	1.9	953	2	0.213
36.997	2.4277	210	59	1.5	1205	2.5	0.347
37.625	2.3887	208	61	1.5	499	1	0.139

The X-ray powder diffraction (XRD) pattern of the crystal form II of compound 1 was as shown in Figure 7. Specific peak values were as shown in Table 5.

Table 5

2-Theta	**d**	**BG**	**Height**	**I%**	**Area**	**I%**	**FWHM**
4.979	17.7336	1214	8900	100	87065	100	0.166
5.479	16.117	1135	3492	39.2	36750	42.2	0.179
7.859	11.2407	735	3518	39.5	33929	39	0.164
10.944	8.078	583	613	6.9	10168	11.7	0.282
11.407	7.7507	583	586	6.6	6779	7.8	0.197
11.945	7.4028	581	109	1.2	584	0.7	0.091
12.685	6.9724	605	145	1.6	1192	1.4	0.14
13.425	6.5899	630	2024	22.7	44754	51.4	0.376
13.724	6.4472	644	3852	43.3	56786	65.2	0.251
14.247	6.2115	730	180	2	645	0.7	0.061
14.927	5.9302	663	2359	26.5	29085	33.4	0.21
15.204	5.8227	656	751	8.4	11837	13.6	0.268
15.902	5.5686	768	850	9.6	8216	9.4	0.164
16.565	5.347	823	2445	27.5	34850	40	0.242

16.946	5.2279	812	1197	13.4	12636	14.5	0.18
17.646	5.0221	776	4534	50.9	46966	53.9	0.176
18.751	4.7283	577	152	1.7	2342	2.7	0.262
19.589	4.528	634	325	3.7	8890	10.2	0.465
20.007	4.4344	590	2610	29.3	40346	46.3	0.263
20.603	4.3074	680	324	3.6	2205	2.5	0.116
21.288	4.1704	607	942	10.6	33012	37.9	0.596
22.047	4.0285	586	1705	19.2	45071	51.8	0.45
23.049	3.8555	437	175	2	3277	3.8	0.318
23.988	3.7067	400	68	0.8	1079	1.2	0.27
24.969	3.5633	475	789	8.9	16036	18.4	0.346
25.768	3.4545	593	981	11	12591	14.5	0.218
27.332	3.2603	385	224	2.5	8099	9.3	0.615
27.651	3.2234	383	406	4.6	13554	15.6	0.568
27.989	3.1852	395	294	3.3	7071	8.1	0.409
28.693	3.1087	352	229	2.6	2724	3.1	0.202
29.629	3.0126	331	87	1	796	0.9	0.156
30.154	2.9613	335	85	1	1152	1.3	0.23
30.557	2.9231	323	66	0.7	1460	1.7	0.376
32.223	2.7757	251	62	0.7	764	0.9	0.21
32.708	2.7356	262	136	1.5	1641	1.9	0.205
33.458	2.676	250	94	1.1	2578	3	0.466
33.91	2.6414	235	107	1.2	2828	3.2	0.449
37.353	2.4054	200	77	0.9	1822	2.1	0.402

The X-ray powder diffraction (XRD) pattern of the crystal form III of compound 1 was as shown in Figure 10. Specific peak values were as shown in Table 6.

Table 6

2-Theta	d	BG	Height	I%	Area	I%	FWHM
5.017	17.5993	1189	3030	47.7	49913	97.5	0.28
5.181	17.0438	1156	2438	38.4	23296	45.5	0.153
8.042	10.9853	743	6351	100	51190	100	0.137
10.042	8.8012	578	180	2.8	1655	3.2	0.156
10.343	8.5457	565	686	10.8	6708	13.1	0.166
10.993	8.0414	556	114	1.8	776	1.5	0.116
12.362	7.1542	526	1039	16.4	9628	18.8	0.158

13.352	6.6256	500	90	1.4	757	1.5	0.143
14.602	6.0613	575	1704	26.8	10243	20	0.102
15.026	5.8911	605	1725	27.2	17629	34.4	0.174
15.563	5.6891	687	1078	17	8808	17.2	0.139
15.725	5.631	723	1908	30	12761	24.9	0.114
16.322	5.4262	873	676	10.6	2780	5.4	0.07
16.588	5.3398	817	512	8.1	3731	7.3	0.124
16.905	5.2404	692	3370	53.1	29024	56.7	0.146
17.228	5.1427	714	5157	81.2	50079	97.8	0.165
17.446	5.0791	740	866	13.6	19679	38.4	0.386
18.189	4.8733	593	3405	53.6	23288	45.5	0.116
18.746	4.7296	592	526	8.3	5266	10.3	0.17
19.405	4.5704	854	4526	71.3	29764	58.1	0.112
19.728	4.4964	901	976	15.4	7699	15	0.134
20.029	4.4295	603	3291	51.8	32507	63.5	0.168
20.345	4.3614	1045	645	10.2	2976	5.8	0.074
20.568	4.3146	901	2278	35.9	30207	59	0.226
21.311	4.1659	559	2693	42.4	19069	37.3	0.12
21.505	4.1287	538	980	15.4	11540	22.5	0.188
21.907	4.0538	507	467	7.4	4704	9.2	0.171
22.41	3.9639	452	435	6.8	3508	6.9	0.137
22.846	3.8893	432	148	2.3	931	1.8	0.107
23.026	3.8593	428	252	4	2573	5	0.174
23.484	3.7851	416	508	8	5576	10.9	0.187
23.953	3.7121	402	659	10.4	4741	9.3	0.122
24.195	3.6754	392	228	3.6	3468	6.8	0.259
24.412	3.6432	383	292	4.6	2984	5.8	0.174
24.847	3.5805	366	364	5.7	3496	6.8	0.163
25.249	3.5243	352	514	8.1	9114	17.8	0.302
25.449	3.497	345	857	13.5	10768	21	0.214
26.03	3.4203	336	84	1.3	491	1	0.099
26.328	3.3823	327	637	10	6787	13.3	0.181
26.934	3.3076	331	361	5.7	3068	6	0.145
27.568	3.2329	296	443	7	3894	7.6	0.149
28.409	3.1391	264	326	5.1	4278	8.4	0.223
29.176	3.0583	257	165	2.6	1458	2.8	0.15
29.587	3.0167	258	242	3.8	4832	9.4	0.34

29.79	2.9967	242	180	2.8	2773	5.4	0.262
30.191	2.9577	250	250	3.9	2737	5.3	0.186
31.171	2.8669	233	162	2.6	1331	2.6	0.14
31.772	2.814	239	249	3.9	3365	6.6	0.23
32.049	2.7904	238	255	4	3324	6.5	0.222
32.472	2.755	226	102	1.6	1597	3.1	0.266
33.135	2.7014	220	210	3.3	2073	4	0.168
34.068	2.6295	215	100	1.6	1059	2.1	0.18
34.416	2.6037	207	161	2.5	2267	4.4	0.239
35.754	2.5092	219	196	3.1	3196	6.2	0.277
36.747	2.4437	225	87	1.4	868	1.7	0.17
37.101	2.4212	195	57	0.9	511	1	0.152
37.938	2.3697	178	113	1.8	1350	2.6	0.203

The X-ray powder diffraction (XRD) patterns of the crystal form I of compound 2 were as shown in Figures 13-1 and 13-2. Specific peak values were as shown in Table 7.

Table 7

2-Theta	**d**	**Height**	**I%**	**Area**	**I%**
4.377	20.1693	1741	100	17639	100
8.023	11.0103	66	3.8	737	4.2
8.663	10.1993	1030	59.2	14242	80.7
9.762	9.0531	151	8.7	1098	6.2
10.845	8.1509	100	5.7	593	3.4
11.262	7.8502	133	7.6	1213	6.9
11.922	7.4173	252	14.5	2371	13.4
12.742	6.9415	577	33.1	8200	46.5
13.061	6.7727	843	48.4	11391	64.6
14.144	6.2565	188	10.8	6934	39.3
14.343	6.1704	453	26	8216	46.6
14.897	5.942	74	4.3	207	1.2
15.31	5.7827	64	3.7	1110	6.3
15.605	5.6738	85	4.9	1941	11
16.319	5.4272	75	4.3	623	3.5
17.041	5.1988	141	8.1	1246	7.1
17.442	5.0802	219	12.6	3443	19.5
18.18	4.8756	347	19.9	6360	36.1

19.524	4.543	72	4.1	599	3.4
20.282	4.3748	490	28.1	10772	61.1
21.823	4.0692	559	32.1	14868	84.3
23.23	3.8258	87	5	814	4.6
24.061	3.6955	106	6.1	1320	7.5
25.262	3.5226	136	7.8	2239	12.7
26.423	3.3703	86	4.9	2148	12.2
26.799	3.324	54	3.1	1126	6.4
29.503	3.0251	55	3.2	813	4.6
39.228	2.2947	35	2	337	1.9

The X-ray powder diffraction (XRD) patterns of the crystal form II of compound 2 were as shown in Figures 16-1 and 16-2. Specific peak values were as shown in Table 8.

Table 8

2-Theta	**d**	**Height**	**I%**	**Area**	**I%**
5.116	17.2585	514	41.8	6102	41.8
6.682	13.218	1230	100	14607	100
9.986	8.8505	169	13.7	2115	14.5
11.036	8.0108	45	3.7	636	4.4
13.441	6.5823	232	18.9	3725	25.5
13.863	6.3829	206	16.7	2553	17.5
15.341	5.7711	201	16.3	3304	22.6
15.762	5.6176	148	12	2952	20.2
16.503	5.3673	424	34.5	5827	39.9
18.976	4.6729	63	5.1	650	4.4
20.182	4.3963	575	46.7	10939	74.9
20.988	4.2293	97	7.9	980	6.7
21.255	4.1766	62	5	612	4.2
22.399	3.966	204	16.6	2155	14.8
23.121	3.8436	242	19.7	5358	36.7
24.14	3.6837	82	6.7	1954	13.4
24.54	3.6245	41	3.3	538	3.7
26.281	3.3883	110	8.9	3092	21.2
26.595	3.3489	56	4.6	2211	15.1
27.321	3.2616	47	3.8	814	5.6
27.574	3.2322	40	3.3	815	5.6

28.283	3.1528	56	4.6	864	5.9
28.538	3.1252	42	3.4	879	6
30.409	2.937	35	2.8	381	2.6
31.342	2.8517	40	3.3	512	3.5

The X-ray powder diffraction (XRD) patterns of the crystal form III of compound 2 were as shown in Figures 19-1 and 19-2. Specific peak values were as shown in Table 9.

Table 9

2-Theta	**d**	**Height**	**I%**	**Area**	**I%**
3.996	22.0947	148	5.8	847	4.8
7.475	11.816	2550	100	17651	100
9.313	9.4881	75	2.9	564	3.2
11.431	7.7343	54	2.1	362	2.1
11.776	7.5089	191	7.5	1545	8.8
12.242	7.2237	770	30.2	5762	32.6
13.322	6.6406	156	6.1	1162	6.6
14.511	6.099	49	1.9	348	2
14.948	5.9219	213	8.4	1091	6.2
15.585	5.6813	298	11.7	3871	21.9
16.176	5.4749	272	10.7	3225	18.3
16.437	5.3885	159	6.2	738	4.2
16.701	5.3038	157	6.2	736	4.2
17.687	5.0105	106	4.2	1521	8.6
18.742	4.7307	373	14.6	5292	30
19.001	4.6668	264	10.4	2993	17
20.246	4.3825	107	4.2	919	5.2
21.385	4.1517	151	5.9	3600	20.4
21.624	4.1062	104	4.1	3292	18.7
21.845	4.0652	122	4.8	2466	14
22.503	3.9478	997	39.1	9765	55.3
22.842	3.89	123	4.8	2515	14.2
23.102	3.8468	91	3.6	855	4.8
23.845	3.7286	343	13.5	3284	18.6
24.331	3.6552	93	3.6	2279	12.9
25.038	3.5536	47	1.8	201	1.1
25.765	3.4549	452	17.7	4944	28
27.825	3.2036	128	5	2406	13.6
29.364	3.0391	87	3.4	1335	7.6

The X-ray powder diffraction (XRD) patterns of the crystal form IV of compound 2 were as shown in Figures 22-1 and 22-2. Specific peak values were as shown in Table 10.

Table 10

2-Theta	d	Height	I%	Area	I%
3.918	22.5314	331	60.2	3600	38.7
7.762	11.3801	146	26.5	1419	15.3
8.7	10.1553	550	100	9302	100
10.136	8.7195	66	12	1716	18.4
10.481	8.4337	145	26.4	3370	36.2
12.048	7.3398	54	9.8	1454	15.6
12.46	7.0979	190	34.5	2852	30.7
13.914	6.3592	56	10.2	1100	11.8
15.542	5.6967	224	40.7	3615	38.9
16.785	5.2777	139	25.3	1469	15.8
17.508	5.0613	87	15.8	1830	19.7
18.221	4.8649	205	37.3	4139	44.5
18.943	4.681	143	26	1862	20
19.665	4.5107	183	33.3	3792	40.8
23.639	3.7605	72	13.1	1363	14.7

5

The X-ray powder diffraction (XRD) pattern of the crystal form I of compound 3 was as shown in Figure 28. Specific peak values were as shown in Table 11.

Table 11

2-Theta	d	Height	I%	Area	I%
3.982	22.171	1341	24.9	12956	26.1
4.717	18.7191	212	3.9	2332	4.7
5.961	14.8149	4110	76.2	48450	97.5
6.183	14.2819	1080	20	12242	24.6
7.645	11.5541	633	11.7	5532	11.1
9.302	9.4998	1257	23.3	16176	32.5
9.578	9.2265	467	8.7	5600	11.3
9.921	8.908	451	8.4	4411	8.9
10.866	8.1354	693	12.8	7712	15.5
11.161	7.9208	192	3.6	3691	7.4
11.861	7.4553	5395	100	49258	99.1

2-Theta	d	Height	I%	Area	I%
12.605	7.0167	432	8	3167	6.4
12.845	6.8859	442	8.2	3326	6.7
13.366	6.6189	322	6	2465	5
13.745	6.4371	508	9.4	5537	11.1
14.447	6.1259	368	6.8	3491	7
15.004	5.8997	179	3.3	1285	2.6
15.287	5.7912	467	8.7	5870	11.8
15.804	5.603	1491	27.6	16385	33
16.202	5.466	113	2.1	714	1.4
16.604	5.3347	641	11.9	5691	11.4
16.884	5.2468	1193	22.1	11488	23.1
17.325	5.1144	1072	19.9	8684	17.5
17.885	4.9554	855	15.8	8847	17.8
18.246	4.8581	841	15.6	12818	25.8
18.546	4.7802	958	17.8	13140	26.4
19.207	4.6171	402	7.5	5519	11.1
19.91	4.4558	862	16	30956	62.3
20.167	4.3995	899	16.7	12343	24.8
20.444	4.3406	1060	19.6	13328	26.8
21.326	4.163	238	4.4	1531	3.1
21.749	4.0829	2558	47.4	27358	55
22.166	4.0071	978	18.1	24665	49.6
22.409	3.9642	1003	18.6	17207	34.6
22.749	3.9056	204	3.8	1848	3.7
23.927	3.716	3166	58.7	49712	100
24.616	3.6136	188	3.5	1593	3.2
25.306	3.5165	248	4.6	2013	4
25.77	3.4542	542	10	3586	7.2
26.21	3.3973	1085	20.1	18055	36.3
26.707	3.3351	244	4.5	1638	3.3
27.369	3.2559	361	6.7	5116	10.3
27.689	3.2191	723	13.4	12127	24.4
27.952	3.1894	477	8.8	12761	25.7
28.431	3.1367	353	6.5	4167	8.4
28.988	3.0777	175	3.2	3531	7.1
29.195	3.0563	219	4.1	3535	7.1

2-Theta	d	Height	I%	Area	I%
29.77	2.9986	428	7.9	10655	21.4
30.269	2.9503	531	9.8	5579	11.2
30.826	2.8983	75	1.4	212	0.4
31.13	2.8706	104	1.9	2031	4.1
31.512	2.8367	581	10.8	12473	25.1
32.586	2.7456	91	1.7	800	1.6
34.209	2.619	218	4	2492	5
34.912	2.5678	86	1.6	1384	2.8

The X-ray powder diffraction (XRD) pattern of the crystal form II of compound 3 was as shown in Figure 34. Specific peak values were as shown in Table 12.

Table 12

2-Theta	d	Height	I%	Area	I%
3.982	22.1703	4212	100	73527	100
6.345	13.9191	1726	41	19664	26.7
8.103	10.9026	1208	28.7	12546	17.1
9.661	9.1473	1086	25.8	13129	17.9
10.473	8.4399	95	2.3	436	0.6
12.205	7.246	4062	96.4	48626	66.1
12.784	6.9191	901	21.4	12703	17.3
14.882	5.9481	245	5.8	1714	2.3
15.346	5.7689	208	4.9	964	1.3
15.785	5.6096	1143	27.1	11201	15.2
16.325	5.4252	959	22.8	5761	7.8
16.747	5.2895	1406	33.4	23883	32.5
17.127	5.1728	1068	25.4	30246	41.1
17.407	5.0904	704	16.7	22768	31
18.446	4.806	226	5.4	1473	2
18.948	4.6797	183	4.3	3450	4.7
19.388	4.5746	1225	29.1	22320	30.4
20.449	4.3394	665	15.8	8048	10.9
21.427	4.1435	383	9.1	5700	7.8
22.308	3.9819	91	2.2	1544	2.1
23.227	3.8264	1225	29.1	26339	35.8
23.547	3.7751	532	12.6	17218	23.4
24.649	3.6088	768	18.2	10917	14.8
25.749	3.457	698	16.6	17885	24.3
26.77	3.3274	160	3.8	2917	4

2-Theta	d	Height	I%	Area	I%
27.091	3.2887	322	7.6	7139	9.7
27.608	3.2283	194	4.6	1590	2.2
28.31	3.1498	582	13.8	12038	16.4
28.871	3.0899	210	5	6754	9.2
29.433	3.0322	143	3.4	2317	3.2
31.015	2.881	139	3.3	1867	2.5
31.69	2.8211	95	2.3	1678	2.3
33.072	2.7064	145	3.4	3709	5
33.45	2.6767	90	2.1	1869	2.5

5. Chemical stability data of compound 1 and pharmaceutical salt thereof

Samples were taken and tested at high temperature (40°C) and under high humidity (RH 92.5%) respectively. The purity (represented by a percentage) was detected by HPLC. The experimental results were as shown in Table 16.

With regard to methods for preparing test solutions and conditions for detecting purity by HPLC, reference was made to Tables 13, 14 and 15.

Table 13 Preparation method 1 for test solution

Diluent	Acetonitrile : methanol = 1 : 1
Blank solution	Acetonitrile : methanol = 1 : 1
Test solution	An appropriate amount of test samples was weighed precisely and dissolved and diluted with a diluent to prepare a test solution, which contains about 0.5 mg of the test samples per 1 mL.

Table 14 Preparation method 2 for test solution

Diluent	Aqueous solution containing 0.05% TFA: MeOH = 8 : 2
Blank solution	Aqueous solution containing 0.05% TFA: MeOH = 8 : 2
Test solution	An appropriate amount of test samples was weighed precisely and dissolved and diluted with a diluent to prepare a test solution, which contains about 0.5 mg of the test samples per 1 mL.

Table 15 Conditions for detecting purity by HPLC

Instrument	LC-20AT (Shimadzu)
Chromatographic column	Agilent Eclipse plus C18, 4.6 mm × 150 mm, 3.5 μm

Mobile phase	A: 0.02 mol/L sodium dihydrogen phosphate solution (the pH was adjusted to 2.5 with phosphoric acid) B: Acetonitrile
Detection wavelength	220 nm
Flow rate	1.0 mL/min
Column temperature	30°C
Injection volume	10 μL
Operation time	45 min
Elution procedure	Time (min) / Mobile phase A (%) / Mobile phase B (%) 0 / 80 / 20 15 / 70 / 30 35 / 65 / 35 40 / 10 / 90 40.10 / 80 / 20 45 / 80 / 20

Table 16 Chemical stability of various salts and crystal forms of compound 1 under different conditions

(the content was determined by HPLC)

Condition / Name	Preparation method for test solution	0 day	40°C 30 days	92.5% RH 30 days
Amorphous form of compound 1	Preparation method 1	98.88%	98.85%	98.82%
Crystal form III of compound 1	Preparation method 1	99.41%	99.28%	99.30%
Crystal form I of compound 3	Preparation method 1	99.85%	99.74%	99.76%
Compound 5	Preparation method 1	98.44%	N/A	98.05%
Compound 9	Preparation method 2	98.67%	N/A	98.28%

Conclusion: the amorphous form and crystal form III of compound 1 and the pharmaceutical salts (e.g., crystal form I of compound 3, compound 5 and compound 9) of compound 1 had relatively good chemical stability.

6. Stability data of crystal form of compounds 1 and 3

6.1. Stability of crystal form of compound 1 and compound 3. See table 17.

Table 17 Stability of crystal form of compound 1 and compound 3

Crystal form before transformation	Transformation condition	Crystal form after transformation
Amorphous form of compound 1	High humidity (97% RH), room temperature, for 30 days	Amorphous form of compound 1
Crystal form I of compound 1	Hermetically sealed, room temperature, for 30 days	Crystal form I of compound 1
Crystal form II of compound 1	Hermetically sealed, room temperature, for 30 days	Crystal form II of compound 1
Crystal form III of compound 1	Hermetically sealed, room temperature, for 30 days	Crystal form III of compound 1
Crystal form I of compound 3	Hermetically sealed, room temperature, for 30 days	Crystal form I of compound 3
Amorphous form of compound 3	Exposed to an atmosphere, high humidity (25°C ± 2°C, 85% RH ± 10% RH), for 10 days	Amorphous form of compound 3
Crystal form II of compound 3	Hermetically sealed, for 20 days	Crystal form II of compound 3

Conclusion: the amorphous form and crystal forms I, II and III of compound 1 and the amorphous form and crystal forms I and II of compound 3 had relatively good stability.

6.2. Competitive experiments of crystal forms I, II and III of compound 1 were performed at room temperature to investigate the stability of the crystal forms in isopropyl acetate and a water/acetonitrile (v/v = 1 : 1) solvent, and Competitive experiments of the crystal forms I and II of compound 3 were performed at room temperature to investigate the stability of the crystal forms in an ethanol/water (v/v = 1 : 1) solvent and an acetone/water (v/v = 1 : 1) solvent. See Table 18 for details.

Table 18 Crystal slurrying competition experiment of crystal forms of compound 1 and compound 3

Crystal form	Experimental condition	Experimental XRD result
Mixed sample of crystal forms I, II and III of	Competing for crystal slurrying in isopropyl acetate for 2 days	Crystal form III of compound 1

compound 1 in equal weights	Competing for crystal slurrying in water/acetonitrile (v/v = 1 : 1) for 2 days	Crystal form III of compound 1
Mixed sample of crystal forms I and II of compound 3 in equal weights	Competing for crystal slurrying in ethanol/water (v/v = 1 : 1) for 3 days	Crystal form I of compound 3
	Competing for crystal slurrying in acetone/water (v/v = 1 : 1) for 3 days	Crystal form I of compound 3

It can be seen from the above crystal slurrying competition experiments of the crystal forms of compound 1 that the crystal form III was the most stable crystal form of compound 1 at room temperature. It can be seen from the above crystal slurrying competition experiments of the crystal forms of compound 3 that the crystal form I was the most stable crystal form of compound 3 at room temperature.

7. Solubility data in water at 25°C

Table 19 Solubility of various pharmaceutical salts of compound 1 in water at 25°C

Name	Amorphous form of compound 1	Crystal form I of compound 3	Compound 4	Compound 5	Compound 7	Compound 9
Solubility in water at 25°C	0.009 mg/mL	0.172 mg/mL	0.158 mg/mL	0.166 mg/mL	0.143 mg/mL	0.346 mg/mL

Conclusion: compound 1 and the pharmaceutical salts thereof had a certain level of solubility in water at 25°C. The solubility of the pharmaceutical salts of compound 1 (such as the crystal form I of compound 3, compound 4, compound 5, compound 7 and compound 9) was significantly improved as compared with the solubility of compound 1, by more than about 15 times.

8. Detection of BTK degradation in Mino cells

The Mino human mantle cell lymphoma cell line was purchased from ATCC and cultured under conditions of RPMI-1640 + 15% FBS + 1% double antibody in a 37°C, 5% CO_2 incubator. Cells were plated in a 6-well plate, with 5×10^5 cells/well. After plating, compounds at different concentrations were added and cultured in a 37°C, 5% CO_2 incubator for 48 h. After culturing, the cells were collected. The cells were lysed on ice for 15 minutes by adding RIPA lysis buffer (Beyotime, Cat. P0013B) and centrifuged at 12000 rpm at 4°C for 10 minutes. The

protein sample of the supernatant was collected, subjected to protein quantification by using a BCA kit (Beyotime, Cat. P0009) and then diluted to 0.25 mg/mL. The expressions of BTK (CST, Cat. 8547S) and the internal reference β-actin (CST, Cat. 3700S) were detected using a fully automated western blot quantitative analyser (Proteinsimple) with a kit (Protein simple, Cat. SM-W004). The expression level of BTK relative to the internal reference was calculated by using Compass software, and the DC_{50} value was calculated by using Origen9.2 software according to formula (1). Specifically, the $BTK_{administration}$ denoted the expression level of BTK in administration groups at different doses, and the $BTK_{vehicle}$ denoted the expression level of BTK in the vehicle control group.

$$BTK\%=BTK_{administration}/BTK_{vehicle} \times 100 \quad \text{formula (1)}$$

Table 20 DC_{50} values for BTK degradation in Mino cells

Serial No.	Compound No.	DC_{50} (nM)
1	Compound 2	22.9
2	Compound 1	10.9

Conclusion: compound 1 and compound 2 had a significant degradation effect on BTK in Mino cells.

9. Detection of BTK protein degradation in spleen of mice

Female ICR mice, 6-8 weeks old, were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd., and the experiment was started after 3 days of adaptation. After 3 consecutive days of intragastric administration of compounds at different doses, the spleens of mice were taken. The spleen cells were collected, lysed on ice for 15 min by adding RIPA lysis buffer (Beyotime, Cat. P0013B), and then centrifuged at 12000 rpm at 4°C for 10 min. The protein sample of the supernatant was collected, subjected to protein quantification by using a BCA kit (Beyotime, Cat. P0009) and then diluted to 0.25 mg/mL. The expressions of BTK (CST, Cat. 8547S) and the internal reference β-actin (CST, Cat. 3700S) were detected by using a fully automated western blot quantitative analyser (Proteinsimple). The expression level of BTK relative to the internal reference was calculated by using Compass software, and the DD_{50} value was calculated by using Origen9.2 software according to formula (2). Specifically, the $BTK_{administration}$ denoted the expression level of BTK in administration groups at different doses, and the $BTK_{vehicle}$ denoted the expression level of BTK in the vehicle control group.

$$BTK\% = BTK_{administration}/BTK_{vehicle} \times 100\% \quad \text{formula (2)}$$

Table 21 DD_{50} values of compounds for BTK protein degradation in spleens of mice

Serial No.	Compound No.	DD_{50} (mg/kg)
1	Compound 2	3.8
2	Compound 1	3.8

Conclusion: compound 1 and compound 2 had a significant degradation effect on BTK proteins in spleens of mice.

10. *In vitro* kinase detection

Kinases BTK wt (Carna, Cat. No 08-180) and BTK C481S (Carna, Cat. No 08-547) were prepared into a 2.5× kinase solution, and substrates FAM-P2 (GL Biochem, Cat. No. 112394) and ATP ((Sigma, Cat. No. A7699-1G) were prepared into a 2.5× substrate solution, respectively. 5 μL of compounds at different concentrations were added to a 384-well plate.10 μL of 2.5× kinase solution was added, and the resulting mixture was incubated at room temperature for 10 min. 10 μL of 2.5× substrate solution was added, and the mixture was incubated at 28°C for an appropriate period of time. The reaction was stopped by adding 30 μL of stop buffer, and the detection was carried out by using Caliper EZ reader2. The IC_{50} value was calculated by using XLFit excel add-in version 5.4.0.8 software. The calculation formula of the inhibition rate was shown in formula (3), wherein max denoted the readout of the DMSO control, min denoted the readout of the negative control, and conversion denoted the readout of the compound

Inhibition rate % = (max-conversion)/(max-min) * 100%. formula (3)

The results were as shown in Table 22:

Table 22 IC_{50} value on BTK wt/C481S kinase inhibition

Serial No.	Compound No.	BTK C481S IC_{50} (nM)	BTK wt IC_{50} (nM)
1	Compound 1	8	6.3

Conclusion: compound 1 had a significant inhibitory effect on BTK wt/C481S kinase.

11. Pharmacokinetic test of dogs

Experimental objective: in this experiment, a single dose of each test compound was administered to Beagle dogs intravenously and intragastrically, the concentrations of the test compounds in plasma of dogs were measured, and the

pharmacokinetic characteristics and bioavailability of the test compounds in dogs were evaluated.

Experimental animal: male Beagle dogs (about 8-11 kg, 0.5-1 weeks old, 6 dogs/compound), purchased from Beijing Marshall Biotechnology Co. Ltd.

Experimental method: as shown in Table 23, on the day of the experiment, 6 Beagle dogs were randomly according to their body weight. The animals were fasted but with water available for 14 to 18 hours one day before administration, and were fed 4 hours after administration.

Table 23

Group	Quantity	Administration information						
	Male	Test compound	Administration dosage* (mg/kg)	Administration concentration (mg/mL)	Administration volume (mL/kg)	Collected samples	Mode of administration	Vehicle
G1	3	Compound of the present invention	1	1	1	Plasma	Intravenously	5% DMSO + 5% Solutol + 90% Saline
G2	3	Compound of the present invention	10	2	5	Plasma	Intragastrically	0.5% MC

*Dosage is calculated based on free base.

Sampling: before and after administration, 1.0 ml of blood was taken from jugular veins, and placed in an EDTAK2 centrifuge tube. Centrifugation was carried out at 5000 rpm at 4°C for 10 min, and the plasma was collected.

Time points for plasma collection in G1&G2 groups: 0, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h and 24 h.

Before analysis and detection, all samples were stored at -80°C. The samples were detected by using HPLC-MS/MS.

Table 24 Pharmacokinetic parameters of compounds in plasma of dogs

Test compounds	Mode of administration*	AUC_{0-t} (pg/ml·h)	Having bioavailability or not
Amorphous form of compound 1	i.g. (10 mg/kg)	26900 ± 3300	Yes

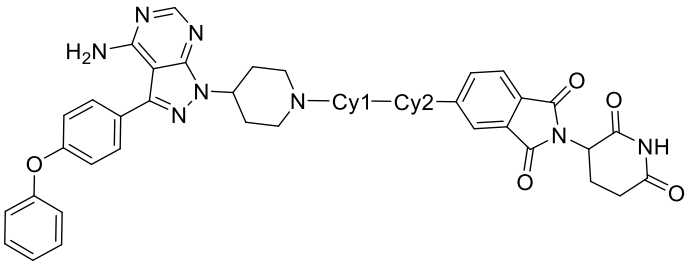
Crystal form I of compound 3	i.g. (10 mg/kg)	75100 ± 50000	Yes
Compound 5	i.g. (10 mg/kg)	59500 ± 21000	Yes
Compound 7	i.g. (10 mg/kg)	95500 ± 65000	Yes
Compound 9	i.g. (10 mg/kg)	79400 ± 20000	Yes

*Note: i.g. (intragastrical) administration,

Conclusion: compound 1 and pharmaceutical salts thereof had a certain level of oral bioavailability in dogs. Oral exposure amounts of the crystal form I of compound 3, compound 5, compound 7 and compound 9 were significantly increased as compared with the oral exposure amount of compound 1, by more than 2 times.

CLAIMS

1. A pharmaceutical salt of a compound as shown in formula (I),



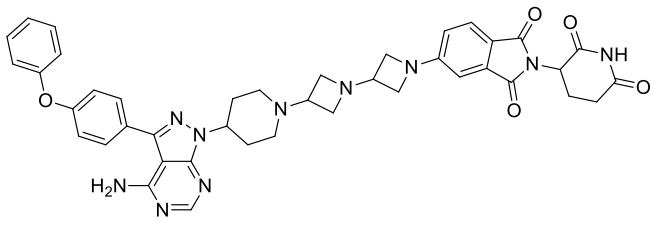
(I)

wherein

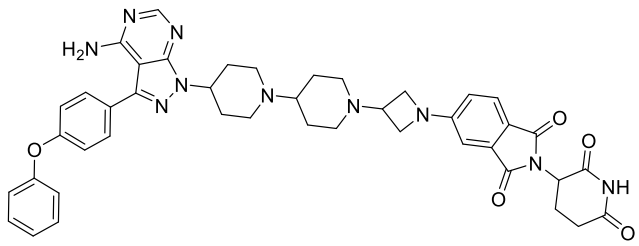
Cy1 or Cy2 is each independently selected from piperidyl or azacyclobutyl; and

the pharmaceutical salt is selected from maleate, fumarate, halogen acid salt (preferably hydrobromide and hydrochloride), sulfate, phosphate, L-tartrate, citrate, L-malate, hippurate, D-glucuronate, glycollate, mucate, succinate, lactate, orotate, pamoate, glycinate, alanine salt, arginine salt, cinnamate, benzoate, benzenesulfonate, p-toluenesulfonate, acetate, propionate, valerianate, triphenyl acetate, L-proline salt, ferulate, 2-hydroxyethanesulfonate, mandelate, nitrate, mesylate, malonate, gentisate, salicylate, oxalate or glutarate.

2. The pharmaceutical salt according to claim 1, wherein the compound as shown in formula (I) is selected from a compound as shown in formula (Ia) or (Ib),



(Ia)



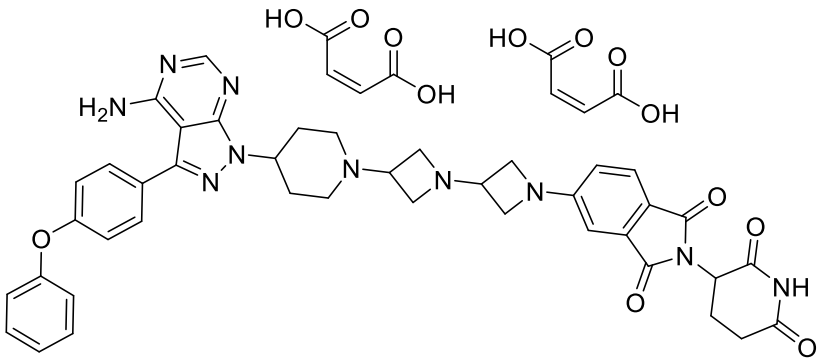
(Ib)

and the pharmaceutical salt is selected from maleate, fumarate, halogen acid salt (preferably hydrobromide and hydrochloride), sulfate, phosphate, L-tartrate, citrate, L-malate, hippurate, D-glucuronate, glycollate, mucate, succinate, lactate, orotate, pamoate, glycinate, alanine salt, arginine salt, cinnamate, benzoate,

benzenesulfonate, p-toluenesulfonate, acetate, propionate, valerianate, triphenyl acetate, L-proline salt, ferulate, 2-hydroxyethanesulfonate, mandelate, nitrate, mesylate, malonate, gentisate, salicylate, oxalate or glutarate.

3. The pharmaceutical salt according to claim 2, wherein the pharmaceutical salt is selected from maleate, fumarate, L-tartrate, citrate, L-malate, salicylate or oxalate.

4. The pharmaceutical salt according to claim 1, wherein the pharmaceutical salt of the compound as shown in formula (I) is selected from a compound as shown in formula (II),


(II).

5. A crystal form I of the compound as shown in formula (II), wherein the crystal form I has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.96° ± 0.2°, 9.30° ± 0.2°, 11.86° ± 0.2°, 15.80° ± 0.2°, 21.75° ± 0.2° and 23.93° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

6. The crystal form I of the compound as shown in formula (II) according to claim 5, wherein the crystal form I has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 3.98° ± 0.2°, 7.65° ± 0.2°, 10.87° ± 0.2°, 16.88° ± 0.2°, 17.89° ± 0.2° and 26.21° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

7. The crystal form I of the compound as shown in formula (II) according to claim 6, wherein the crystal form I has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 15.29° ± 0.2°, 17.33° ± 0.2°, 18.55° ±

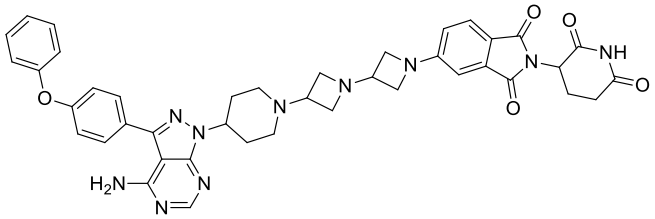
0.2°, 19.21° ± 0.2°, 19.91° ± 0.2° and 22.41° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

8. The crystal form I of the compound as shown in formula (II) according to claim 7, wherein the crystal form I has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 4.72° ± 0.2°, 9.58° ± 0.2°, 9.92° ± 0.2°, 12.85° ± 0.2°, 13.37° ± 0.2°, 13.75° ± 0.2°, 14.45° ± 0.2°, 27.37° ± 0.2°, 28.43° ± 0.2°, 30.27° ± 0.2°, 31.51° ± 0.2° and 34.21° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

9. The crystal form I of the compound as shown in formula (II) according to claim 8, wherein the crystal form I, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern as shown in Figure 28.

10. The crystal form I of the compound as shown in formula (II) according to claim 8, characterized in that the crystal form I has a differential scanning calorimetry curve as shown in Figure 29 or a thermogravimetric analysis curve as shown in Figure 30.

11. A crystal form III of the compound as shown in formula (Ia), wherein the crystal form III has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 5.02° ± 0.2°, 8.04° ± 0.2°, 16.91° ± 0.2°, 17.23° ± 0.2°, 18.19° ± 0.2°, 19.41° ± 0.2° and 20.03° ± 0.2° 2θ, as determined by using Cu-Kα radiation,



(Ia).

12. The crystal form III of the compound as shown in formula (Ia) according to claim 11, wherein the crystal form III has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 12.36° ± 0.2°, 14.60° ± 0.2°, 15.03° ± 0.2°, 15.73° ± 0.2°, 20.57° ± 0.2°, 21.31° ± 0.2° and 25.45° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

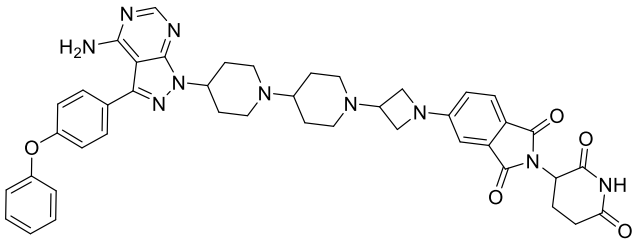
13. The crystal form III of the compound as shown in formula (Ia) according to claim 12, wherein the crystal form III has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 5.19° ± 0.2°, 16.32° ± 0.2°, 18.75° ± 0.2°, 19.73° ± 0.2°, 21.91° ± 0.2°, 22.41° ± 0.2°, 23.48° ± 0.2°, 23.95° ± 0.2° and 26.33° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

14. The crystal form III of the compound as shown in formula (Ia) according to claim 13, wherein the crystal form III has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 10.34° ± 0.2°, 24.85° ± 0.2°, 26.93° ± 0.2°, 27.57° ± 0.2°, 28.41° ± 0.2°, 29.59° ± 0.2°, 30.19° ± 0.2°, 31.77° ± 0.2°, 33.13° ± 0.2° and 35.75° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

15. The crystal form III of the compound as shown in formula (Ia) according to claim 14, wherein the crystal form III, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern as shown in Figure 10.

16. The crystal form III of the compound as shown in formula (Ia) according to claim 14, characterized in that the crystal form III has a differential scanning calorimetry curve as shown in Figure 11 or a thermogravimetric analysis curve as shown in Figure 12.

17. A crystal form I of the compound as shown in formula (Ib), wherein the crystal form I has an X-ray powder diffraction pattern comprising characteristic diffraction peaks at 4.38° ± 0.2°, 8.66° ± 0.2°, 13.06° ± 0.2°, 14.34° ± 0.2°, 18.18° ± 0.2°, 20.28° ± 0.2° and 21.82° ± 0.2° 2θ, as determined by using Cu-Kα radiation,



(Ib).

18. The crystal form I of the compound as shown in formula (Ib) according to claim 17, wherein the crystal form I has an X-ray powder diffraction pattern

further comprising characteristic diffraction peaks at 11.92° ± 0.2°, 12.74° ± 0.2° and 17.44° ± 0.2° 2θ, as determined by using Cu-Kα radiation.

19. The crystal form I of the compound as shown in formula (Ib) according to claim 18, wherein the crystal form I has an X-ray powder diffraction pattern further comprising characteristic diffraction peaks at 9.76° ± 0.2°, 11.26° ± 0.2°, 14.14° ± 0.2°, 17.04° ± 0.2°, 23.23° ± 0.2°, 24.06 ± 0.2°, 25.26° ± 0.2° and 26.42 ± 0.2° 2θ, as determined by using Cu-Kα radiation.

20. The crystal form I of the compound as shown in formula (Ib) according to claim 19, wherein the crystal form I, as determined by using Cu-Kα radiation, has an X-ray powder diffraction pattern substantially as shown in Figure 13-1 and/or Figure 13-2.

21. The crystal form I of the compound as shown in formula (Ib) according to claim 19, characterized in that the crystal form I has a differential scanning calorimetry (DSC) curve as shown in Figure 14 or a thermogravimetric analysis curve as shown in Figure 15.

22. A method for preparing the pharmaceutical salt according to claim 1, wherein the method comprises: a step of allowing the compound as shown in formula (I) and an acid to form a salt.

23. The method according to claim 22, wherein a solvent used therein is selected from one or more of a C_{1-6} halogenated alkane solvent, a C_{2-6} ester solvent, a C_{2-6} ether solvent, a C_{1-6} alcohol solvent or water.

24. The method according to claim 23, wherein the solvent used therein is selected from one or more of dichloromethane, 1,2-dichloroethane, ethyl acetate, methanol, ethanol, isopropanol, diethyl ether, tetrahydrofuran and water.

25. The method according to claim 24, wherein the solvent used therein is selected from one or more of dichloromethane, methanol, ethanol and water.

26. The method according to claim 23, wherein the method comprises: preparing the compound as shown in formula (II) by using the compound as shown in formula (Ia) and maleic acid as raw materials.

27. A method for preparing the crystal form of the compound as shown in formula (Ia), (Ib) or (II), wherein the method comprises a step of preparing the compound as shown in formula (II), (Ia) or (Ib) in any crystal form or the compound as shown in formula (II), (Ia) or (Ib) in an amorphous form by means of recrystallization or slurrying, wherein a solvent for the recrystallization or slurrying is selected from one of or a mixed solvent of two or more of a C_{2-6} ester solvent, a C_{2-6} ether solvent, a C_{1-6} alcohol solvent, a C_{1-6} nitrile solvent, an alkane solvent and water.

28. The method according to claim 27, wherein the solvent for the recrystallization or slurrying is selected from one of or a mixed solvent of two or more of ethyl acetate, isopropyl acetate, n-heptane, acetonitrile, tetrahydrofuran, trifluoroethanol, methanol, ethanol and water.

29. The method according to claim 27, wherein the recrystallization or slurrying is performed at a temperature of 4°C to 100°C, preferably room temperature to 90°C, more preferably 40°C to 90°C.

30. The method according to claim 29, wherein the crystal form is the crystal form I of the compound as shown in formula (II), and the method comprises steps of mixing the compound as shown in formula (II) with a suitable solvent to form a suspension, heating, stirring and slurrying the mixture, leaving the resulting product to stand for crystallization, and performing filtering and separation, wherein the solvent is selected from ethanol.

31. The method according to claim 29, wherein the crystal form is the crystal form III of the compound as shown in formula (Ia), and the method comprises a step of mixing the compound as shown in formula (Ia) in an amorphous form with a suitable solvent, heating, stirring and slurrying the mixture, and performing

filtering and separation, wherein the solvent is selected from an acetonitrile/water mixed solvent.

32. A pharmaceutical composition, wherein the pharmaceutical composition contains a therapeutically effective amount of the pharmaceutical salt of the compound according to any one of claims 1 to 4 or the crystal form according to any one of claims 5 to 21, and a pharmaceutically acceptable excipient.

33. Use of the pharmaceutical salt of the compound according to any one of claims 1 to 4, the crystal form according to claim 5, 11 or 17 or the pharmaceutical composition according to claim 32 in the preparation of a drug for treating and/or preventing tumour or cancer.