PHARMACEUTICALLY ACCEPTABLE SALT AND CRYSTALLINE FORM OF GLP-1 RECEPTOR AGONIST AND PREPARATION METHOD THEREFOR

[0001] The present application claims the priority of China Patent Application 2021115845744 filed on December 23, 2021. This Chinese patent application is incorporated herein by reference in its entirety.

TECHNICAL FIELD

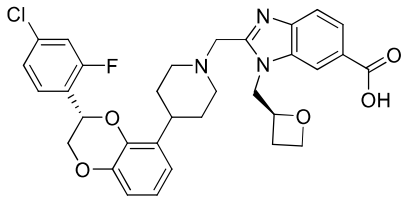
[0002] The present disclosure belongs to the field of medicines, and relates to a pharmaceutically acceptable salt and a crystalline form of a GLP-1 receptor agonist and a preparation method therefor.

BACKGROUND

[0003] Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by L-cells in the lower digestive tract. GLP-1 plays a corresponding role by binding to its ubiquitous specific receptor. Organs in which GLP-1 receptor is now clearly present include islet cells, gastrointestinal, pulmonary, brain, kidney, hypothalamus and cardiovascular systems, and GLP-1 receptor may also be present in liver, adipose tissues and skeletal muscle. GLP-1 not only acts on β cells to promote insulin secretion, but also acts on α cells to inhibit glucagon secretion. There is generally no significant difference in serum GLP-1 levels in patients with normal glucose tolerance, impaired glucose tolerance, and type II diabetes. However, there is a deficiency of the response of β cells to GLP-1 after eating, and under certain conditions, the response is significantly enhanced after continuous infusion of GLP-1. Since the duration of action of human GLP-1 is very short ($t1/2 < 1.5$ minutes via intravenous injection), human GLP-1 is not suitable for clinical treatment of diabetes.

[0004] Peptidic GLP-1 receptor agonists (e.g., liraglutide and exenatide) have effects on improving blood glucose level in type II diabetic patients by lowering fasting and postprandial glucose. However, since the peptidic GLP-1 has poor oral bioavailability and is inconvenient to take, small molecule agonists of GLP-1 receptors with good oral bioavailability are highly desirable.

[0005] 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid is a novel GLP-1 receptor agonist (the structural formula is as follows, PCT/CN2021/115915),



I .

[0006] Half of the new molecular entities approved by the US Food and Drug Administration (FDA) are pharmaceutical salts. Since the first salt form was approved in 1939, salt drugs have been on a growing trajectory. In addition, salt formation can improve some undesirable physical, chemical or biological properties of drugs. It is of great significance to develop salts that are more excellent in physical and chemical properties or pharmaceutical properties than 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0007] In addition, in view of the importance of solid drug crystal forms and their stability in clinical treatment, it is also of great significance to study the polymorphism of a pharmaceutically acceptable salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid in depth for developing drugs suitable for industrial production and with good biological activity.

CONTENT OF THE PRESENT INVENTION

[0008] The present disclosure provides a pharmaceutically acceptable salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0009] In some embodiments, the pharmaceutically acceptable salt is selected from a tromethamine salt, an ammonium salt, a potassium salt, an arginine salt, a sodium salt, a meglumine salt, an ethanolamine salt, a p-toluenesulfonate salt, a tartrate salt, a sulfate salt, a

malate salt, and a hydrochloride salt.

[0010] In some other embodiments, the chemical ratio of the compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid to an alkali molecule (a cation) is 1 : 0.5 to 1 : 3, including 1 : 0.5, 1 : 1, 1 : 2, or 1 : 3.

[0011] In some embodiments, the chemical ratio of the compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid to an alkali molecule is 1 : 1 or 1 : 2.

[0012] In some other embodiments, the chemical ratio of the compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid to an acid molecule (an acid radical) is 1 : 0.5 to 1 : 3, including 1 : 0.5, 1 : 1, 1 : 2, or 1 : 3.

[0013] In some embodiments, the chemical ratio of the compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid to an acid molecule is 1 : 1 or 1 : 2.

[0014] In another aspect, the present disclosure further provides a method for preparing the above-mentioned pharmaceutically acceptable salt, the method comprising a step of salt formation between compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid and an acid, or a step of salt formation between compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid and an alkali.

[0015] In some embodiments, a solvent used in the salt formation reaction is selected from at least one of methanol, 2-butanone, ethyl acetate, 1,4-dioxane, methyl isobutyl ketone, methyl tert-butyl ether, dichloromethane, ethanol, isopropanol, tetrahydrofuran, dimethyl sulfoxide, acetone, acetonitrile, toluene, isopropyl acetate, and water.

[0016] In some other embodiments, the volume (μl) of the solvent used in the salt formation reaction may be 1-200 times the mass (mg) of the above-mentioned compound, and in non-limiting embodiments, may be 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80,

85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, or 200. In some embodiments, the preparation method described in the present disclosure further comprises the step of centrifugation, washing, or drying.

[0017] In one aspect, the present disclosure provides an amorphous form of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, and an X-ray powder diffraction pattern expressed with diffraction angle 2θ has no obvious characteristic peaks.

[0018] In some embodiments, the amorphous form of the tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 1.

[0019] In another aspect, the present disclosure further provides crystal form A of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0020] In some embodiments, the crystal form A of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.850, 13.789, 16.148, and 22.138.

[0021] In some embodiments, the crystal form A of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.850, 9.982, 13.789, 16.148, and 22.138.

[0022] In some embodiments, the crystal form A of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.850, 9.982, 12.697, 13.789, 15.763, 16.148, 18.016, 19.016, and 22.138.

[0023] In some embodiments, the crystal form A of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.850, 8.051, 9.982, 12.697, 13.789, 14.704, 14.990, 15.763, 16.148, 18.016, 19.016, 20.109, 22.138, 25.712, and 27.909.

[0024] In some embodiments, the crystal form A of the tromethamine salt has an X-ray

powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 2.

[0025] In another aspect, the present disclosure further provides crystal form B of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0026] In some embodiments, the crystal form B of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 8.144, 10.511, 12.290, 20.632, and 21.699.

[0027] In some embodiments, the crystal form B of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 8.144, 10.511, 12.290, 13.996, 14.665, 20.632, 21.699, and 24.74.

[0028] In some embodiments, the crystal form B of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 8.144, 10.511, 12.290, 13.996, 14.665, 15.607, 16.520, 18.883, 20.632, 21.699, 23.741, 24.743, 26.055, and 27.035.

[0029] In some embodiments, the crystal form B of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 3.

[0030] In another aspect, the present disclosure further provides crystal form C of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0031] In some embodiments, the crystal form C of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.551, 9.269, 13.175, and 16.906.

[0032] In some embodiments, the crystal form C of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.551, 9.269, 13.175, 14.802, 15.864, 16.906, 18.776, 20.430, and 25.496.

[0033] In some embodiments, the crystal form C of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.551, 8.392, 9.269, 13.175, 14.802, 15.864, 16.906, 18.776, 20.430, 22.211, 22.922,

23.574, 25.496, and 26.290.

[0034] In some embodiments, the crystal form C of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 4.

[0035] In another aspect, the present disclosure further provides crystal form D of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0036] In some embodiments, the crystal form D of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.281, 10.292, 13.322, and 21.390.

[0037] In some embodiments, the crystal form D of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.281, 9.912, 10.292, 10.961, 13.322, 21.390, 22.215, 23.979, 25.029, and 25.846.

[0038] In some embodiments, the crystal form D of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.281, 9.912, 10.292, 10.961, 11.613, 13.322, 15.351, 18.283, 19.214, 21.390, 22.215, 23.471, 23.979, 25.029, 25.846, 27.918, and 30.121.

[0039] In some embodiments, the crystal form D of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 5.

[0040] In another aspect, the present disclosure further provides crystal form E of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0041] In some embodiments, the crystal form E of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.821, 10.035, 12.653, 13.727, and 14.787.

[0042] In some embodiments, the crystal form E of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.821, 10.035, 12.653, 13.727, 14.787, 16.081, 16.648, 18.571, 20.151, and 22.204.

[0043] In some embodiments, the crystal form E of the tromethamine salt has an X-ray

powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 6.

[0044] In another aspect, the present disclosure further provides a method for preparing the above-mentioned crystal form A, B, C, D, or E, the method comprising (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine and a solvent, and dissolving the mixture by means of stirring or heating, and (b) crystallization.

[0045] In some embodiments, the method for preparing the above-mentioned crystal form A comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine, and a solvent (1), dissolving the mixture by means of stirring or heating, and (b) crystallization, wherein the solvent (1) is selected from one or more of ethanol, ethyl acetate, methyl tert-butyl ether or tetrahydrofuran, isopropanol, methanol, and water.

[0046] In some embodiments, the method for preparing the above-mentioned crystal form B comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine, and 10% water/acetone solvent, and dissolving the mixture by means of stirring or heating, and (b) crystallization.

[0047] In some embodiments, the method for preparing the above-mentioned crystal form C comprises (a) mixing crystal form A of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with one or more solvents of ethanol, acetone, isopropyl acetate, dioxane, and toluene, and (b) crystallizing.

[0048] In some embodiments, the method for preparing the above-mentioned crystal form D comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine and one or more solvents of methanol and isopropanol, dissolving the mixture by means of stirring or heating, and (b) crystallization.

[0049] In some embodiments, the method for preparing the above-mentioned crystal form E comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-

dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine, and acetonitrile solvent, and dissolving the mixture by means of stirring or heating, and (b) crystallization.

[0050] In another aspect, the present disclosure further provides crystal form F of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0051] In some embodiments, the crystal form F of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 7.674, 10.614, 16.400, and 18.645.

[0052] In some embodiments, the crystal form F of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.777, 7.674, 10.614, 11.594, 14.408, 14.882, 16.400, and 18.645.

[0053] In some embodiments, the crystal form F of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 6.777, 7.674, 10.614, 11.594, 13.671, 14.408, 14.882, 16.400, 18.645, 20.849, 21.384, 21.731, 22.108, 24.721, 26.169, and 29.192.

[0054] In some embodiments, the crystal form F of the tromethamine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 7.

[0055] In another aspect, the present disclosure further provides a method for preparing the crystal form F of the tromethamine salt. In some embodiments, the method for preparing the crystal form F of the tromethamine salt comprises a step of (a) placing crystal form A of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid at 80 ^{o}C/0% RH for 96 h or drying same at 167 ^{o}C.

[0056] In another aspect, the present disclosure further provides crystal form α of a potassium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0057] In some embodiments, the crystal form α of the potassium salt has an X-ray powder

diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.564, 11.515, 14.683, 19.607, and 20.391.

[0058] In some embodiments, the crystal form α of the potassium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.564, 11.515, 14.683, 16.058, 18.859, 19.607, 20.391, 22.592, 23.320, and 25.176.

[0059] In some embodiments, the crystal form α of the potassium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.564, 11.515, 14.683, 16.058, 17.033, 18.859, 19.607, 20.391, 21.064, 22.592, 23.320, 24.449, 25.176, 25.933, 27.080, and 27.708.

[0060] In some embodiments, the crystal form α of the potassium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 8.

[0061] The present disclosure further provides a method for preparing the crystal form α of the potassium salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with a solvent (2), and adding a potassium hydroxide solution, and (b) pulping, wherein the solvent (2) is selected from one or more of ethyl acetate or methyl tert-butyl ether.

[0062] In another aspect, the present disclosure further provides crystal form I of a sodium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0063] In some embodiments, the crystal form I of the sodium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.257, 5.806, 6.795, 10.106, 12.203, and 20.693.

[0064] In some embodiments, the crystal form I of the sodium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 9.

[0065] The present disclosure further provides a method for preparing the crystal form I of the sodium salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with a

solvent (3), and adding a sodium hydroxide solution, and (b) pulping, wherein the solvent (3) is selected from one or more of methanol or ethyl acetate.

[0066] In another aspect, the present disclosure further provides crystal form II of a sodium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0067] In some embodiments, the crystal form II of the sodium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.754, 11.731, and 19.730.

[0068] In some embodiments, the crystal form II of the sodium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.574, 9.754, 11.731, 14.856, 16.091, 19.730, and 22.670.

[0069] In some embodiments, the crystal form II of the sodium salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 10.

[0070] The present disclosure further provides a method for preparing the crystal form II of the sodium salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with a solvent (4), and adding a sodium hydroxide solution, and (b) crystallization, wherein the solvent (4) is selected from one or more of acetone or acetonitrile.

[0071] In another aspect, the present disclosure further provides crystal form I of a meglumine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0072] In some embodiments, the crystal form I of the meglumine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.498, 11.013, 14.626, and 17.942.

[0073] In some embodiments, the crystal form I of the meglumine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.498, 8.901, 11.013, 14.626, 17.942, 19.454, 22.668, and 25.696.

[0074] In some embodiments, the crystal form I of the meglumine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.498, 8.314, 8.901, 11.013, 11.891, 12.810, 14.626, 15.683, 15.931, 17.942, 18.748, 19.454, 20.393, 21.419, 22.234, 22.668, 23.391, 24.739, and 25.696.

[0075] In some embodiments, the crystal form I of the meglumine salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 11.

[0076] The present disclosure further provides a method for preparing the crystal form I of the meglumine salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with acetonitrile, and adding meglumine, and (b) crystallization.

[0077] In another aspect, the present disclosure further provides crystal form I of a p-toluenesulfonate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0078] In some embodiments, the crystal form I of the p-toluenesulfonate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.453, 5.884, 8.063, 12.925, 16.071, and 19.778.

[0079] In some embodiments, the crystal form I of the p-toluenesulfonate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.453, 5.884, 8.063, 12.925, 13.825, 15.399, 16.071, 18.231, 19.778, and 21.917.

[0080] In some embodiments, the crystal form I of the p-toluenesulfonate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 5.453, 5.884, 8.063, 12.925, 13.825, 15.399, 16.071, 16.560, 17.066, 18.231, 19.778, 20.861, 21.917, 23.898, and 26.744.

[0081] In some embodiments, the crystal form I of the p-toluenesulfonate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 12.

[0082] The present disclosure further provides a method for preparing the crystal form I of the p-toluenesulfonate salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin

-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with acetonitrile, and adding p-toluenesulfonic acid, and (b) crystallization.

[0083] In one aspect, the present disclosure provides an amorphous form of a tartrate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, and an X-ray powder diffraction pattern expressed with diffraction angle 2θ has no obvious characteristic peaks.

[0084] In another aspect, the present disclosure further provides crystal form I of a tartrate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0085] In some embodiments, the crystal form I of the tartrate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 12.810, 18.824, 21.890, and 24.472.

[0086] In some embodiments, the crystal form I of the tartrate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 12.810, 14.448, 15.604, 18.824, 20.410, 21.890, and 24.472.

[0087] In some embodiments, the crystal form I of the tartrate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.342, 10.132, 10.858, 11.272, 12.810, 14.448, 15.604, 18.824, 20.410, 21.890, 24.472, and 27.880.

[0088] In some embodiments, the crystal form I of the tartrate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 13.

[0089] The present disclosure further provides a method for preparing the crystal form I of the tartrate salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with a solvent (5), and adding L-tartaric acid, and (b) crystallization, wherein the solvent (5) is selected from one or more of ethanol, ethyl acetate, and methyl tert-butyl ether.

[0090] In one aspect, the present disclosure provides an amorphous form of a malate salt of

compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, and an X-ray powder diffraction pattern expressed with diffraction angle 2θ has no obvious characteristic peaks.

[0091] In another aspect, the present disclosure further provides crystal form α of a malate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0092] In some embodiments, the crystal form α of the malate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 10.050, 14.508, 15.693, 18.924, and 20.240.

[0093] In some embodiments, the crystal form α of the malate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 10.050, 10.818, 11.213, 12.871, 14.508, 15.693, 18.924, 20.240, 21.829, and 24.396.

[0094] In some embodiments, the crystal form α of the malate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.364, 10.050, 10.818, 11.213, 12.871, 13.774, 14.508, 15.693, 17.760, 18.924, 20.240, 21.829, 24.396, 26.200, 27.936, and 28.188.

[0095] In some embodiments, the crystal form α of the malate salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 14.

[0096] The present disclosure further provides a method for preparing the crystal form α of the malate salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with a solvent (6), and adding malic acid, and (b) crystallization, wherein the solvent (6) is selected from one or more of ethyl acetate or methyl tert-butyl ether.

[0097] In one aspect, the present disclosure further provides an amorphous form of a hydrochloride salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, and an X-ray powder diffraction pattern expressed with

diffraction angle 2θ has no obvious characteristic peaks.

[0098] In another aspect, the present disclosure further provides crystal form I of a hydrochloride salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid.

[0099] In some embodiments, the crystal form I of the hydrochloride salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.939, 14.333, 14.933, 17.523, 18.480, and 20.134.

[0100] In some embodiments, the crystal form I of the hydrochloride salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.939, 13.123, 13.649, 14.333, 14.933, 16.616, 17.523, 18.480, 19.378, 20.134, 20.988, 26.399, and 26.970.

[0101] In some embodiments, the crystal form I of the hydrochloride salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ in which there are characteristic peaks at 9.939, 12.267, 13.123, 13.649, 14.333, 14.933, 16.616, 17.523, 18.480, 19.378, 20.134, 20.988, 22.377, 23.002, 24.477, 25.322, 26.399, 26.970, 27.609, 30.822, and 33.760.

[0102] In some embodiments, the crystal form I of the hydrochloride salt has an X-ray powder diffraction pattern expressed with diffraction angle 2θ as shown in FIG. 15.

[0103] The present disclosure further provides a method for preparing the crystal form I of the hydrochloride salt. In some embodiments, the method comprises (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid with water, and adding hydrochloric acid, and (b) crystallization.

[0104] The volume (μl) of the solvents (1), (2), (3), (4), (5), and (6) used in the present disclosure may be 1-200 times the mass (mg) of the above-mentioned compound, and in non-limiting embodiments, may be 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 200, or values between any two of the numbers.

[0105] In addition, the method for preparing the above-mentioned crystal forms in the present disclosure further comprises one or more steps of filtration, washing, or drying.

[0106] The present disclosure further provides a pharmaceutical composition, which contains the above-mentioned pharmaceutically acceptable salt or a crystal form thereof, and optionally pharmaceutical auxiliaries selected from pharmaceutically acceptable excipients.

[0107] The present disclosure further provides a method for preparing a pharmaceutical composition, the method comprising a step of mixing the above-mentioned pharmaceutically acceptable salt or a crystal form thereof with a pharmaceutically acceptable excipient.

[0108] The present disclosure further provides the use of the above-mentioned pharmaceutically acceptable salt or crystal form thereof or the above-mentioned composition in the preparation of a medicament for treating or preventing a disease associated with GLP-1 receptor.

[0109] The present disclosure further provides the use of the above-mentioned pharmaceutically acceptable salt or crystal form thereof or the above-mentioned composition in the preparation of a medicament for treating or preventing diabetes.

[0110] The "2θ or angle 2θ" mentioned in the present disclosure refers to a diffraction angle, and θ is a Bragg angle in ° or degrees; and the error range of 2θ for each characteristic peak is ± 0.2 (including the rounding of numbers with more than 1 decimal place), and may be -0.20, -0.19, -0.18, -0.17, -0.16, -0.15, -0.14, -0.13, -0.12, -0.11, -0.10, -0.09, -0.08, -0.07, -0.06, -0.05, -0.04, -0.03, -0.02, -0.01, 0.00, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, or 0.20.

[0111] According to the description of hygroscopic characteristics and the definition of hygroscopic weight gain in "9103 Guidelines for Hygroscopicity of Pharmaceuticals", Chinese Pharmacopoeia, Volume IV, 2015 edition, the following are defined:

[0112] deliquescent: absorbing enough water to form a liquid;

[0113] extremely hygroscopic: having a hygroscopic weight gain of not less than 15%;

[0114] hygroscopic: having a hygroscopic weight gain of less than 15% and not less than 2%;

[0115] slightly hygroscopic: having a hygroscopic weight gain of less than 2% and not less than 0.2%; and

[0116] no or almost no hygroscopicity: having a hygroscopic weight gain of less than 0.2%.

[0117] The "differential scanning calorimetry or DSC" mentioned in the present disclosure refers to measuring the temperature difference and heat flow difference between a sample and

a reference during the process in which the sample is heated or maintained at a constant temperature, so as to characterize all physical and chemical changes related to thermal effects and obtain the phase change information of the sample.

[0118] In the present disclosure, the drying is generally at a temperature of 25 °C to 100 °C, preferably 40 °C to 70 °C, and may be either drying under atmospheric pressure or drying under reduced pressure with the pressure < -0.08 MPa.

[0119] The "excipient" mentioned in the present disclosure includes, but is not limited to, any adjuvant, carrier, glidant, sweetener, diluent, preservative, dye/colorant, flavoring agent, surfactant, wetting agent, dispersant, suspending agent, stabilizer, isotonic agent, or emulsifier that has been approved by the US Food and Drug Administration to be acceptable for human or livestock use.

[0120] The "pulping" mentioned in the present disclosure refers to a method of purification by means of the characteristic that a substance has poor solubility in a solvent while impurities have good solubility in the solvent. Pulping purification may result in discoloration, change the crystal form, or remove a small amount of impurities.

[0121] The starting raw materials used in the method for preparing the crystal forms in the present disclosure can be any form of compounds, and specific forms include, but are not limited to, amorphous form, any crystal form, hydrate, solvate, etc.

[0122] If the content of related substances is measured and calculated data, the numerical values in the present disclosure will inevitably have errors to some extent. Generally, ± 10% is within a reasonable error range. There is a certain degree of error variation in the context where it is used. The error variation does not exceed ± 10%, and may be ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, or ± 1%, preferably ± 5%.

[0123] The compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid (hereinafter referred to as Compound A) in the present disclosure is prepared by referring to a method in PCT/CN2021/115915, the relevant content of which is cited herein for illustration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0124] FIG. 1: an XRPD pattern of an amorphous form of a tromethamine salt.

[0125] FIG. 2: an XRPD pattern of crystal form A of a tromethamine salt.

[0126] FIG. 3: an XRPD pattern of crystal form B of a tromethamine salt.

[0127] FIG. 4: an XRPD pattern of crystal form C of a tromethamine salt.

[0128] FIG. 5: an XRPD pattern of crystal form D of a tromethamine salt.

[0129] FIG. 6: an XRPD pattern of crystal form E of a tromethamine salt.

[0130] FIG. 7: an XRPD pattern of crystal form F of a tromethamine salt.

[0131] FIG. 8: an XRPD pattern of crystal form α of a potassium salt.

[0132] FIG. 9: an XRPD pattern of crystal form I of a sodium salt.

[0133] FIG. 10: an XRPD pattern of crystal form II of a sodium salt.

[0134] FIG. 11: an XRPD pattern of crystal form I of a meglumine salt.

[0135] FIG. 12: an XRPD pattern of crystal form I of a p-toluenesulfonate salt.

[0136] FIG. 13: an XRPD pattern of crystal form I of a tartrate salt.

[0137] FIG. 14: an XRPD pattern of crystal form α of a malate salt.

[0138] FIG. 15: an XRPD pattern of crystal form I of a hydrochloride salt.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0139] The present disclosure will be explained in more detail below in conjunction with examples or experimental examples. The examples or experimental examples in the present disclosure are only used to illustrate the technical solutions of the present disclosure and do not limit the essence and scope of the present disclosure.

[0140] The reagents used in the present disclosure are commercially available.

[0141] Test conditions for instruments used in experiments in the present disclosure:

[0142] 1. Differential Scanning Calorimeter (DSC)

[0143] Instrument model: Mettler Toledo DSC 3+STARe System

[0144] Purge gas: nitrogen; nitrogen purging speed: 50 mL/min

[0145] Heating rate: 10.0 ^{o}C/min

[0146] Temperature range: 25-350 ^{o}C or 25-300 ^{o}C

[0147] 2. X-ray Powder Diffraction (XRPD)

[0148] Instrument model: BRUKER D8 Discover X-ray powder diffractometer

[0149] X-ray: monochromatic Cu-Kα ray (λ = 1.5406)

[0150] Scanning mode: θ/2θ, scanning range (2θ range): 3° to 50°

[0151] Voltage: 40 kV, current: 40 mA

[0152] 3. Thermogravimetric Analysis (TGA)

[0153] Instrument model: Mettler Toledo TGA2

[0154] Purge gas: nitrogen; nitrogen purging speed: 50 mL/min

[0155] Heating rate: 10.0 °C/min

[0156] Temperature range: 30-350 °C

[0157] 4. DVS, i.e., dynamic vapor sorption

[0158] Surface Measurement Systems advantage 2 is used for detection at 25 °C. The humidity is 50%-95%-0%-95%-50% RH. The step is 10%. The criterion is that the mass change dM/dT for each step is less than 0.002%. TMAX is 360 min. Two cycles are carried out.

[0159] 5. The progress of the reaction in the examples is monitored by means of thin layer chromatography (TLC). The developing solvent used in the reaction, the eluent system of column chromatography used in the purification of compounds and the developing solvent system of thin layer chromatography include: A: Dichloromethane/methanol system, B: n-hexane/ethyl acetate system. The silica gel plate for thin layer chromatography is Yantai Huanghai HSGF254 or Qingdao GF254 silica gel plate, the specification of the silica gel plate used for thin layer chromatography (TLC) is 0.15 mm to 0.2 mm, and the specification of the silica gel plate used for separating and purifying products by thin layer chromatography is 0.4 mm to 0.5 mm. For silica gel column chromatography, Yantai Huanghai silica gel 200-300 mesh silica gel is generally used as a carrier.

[0160] 6. The structures of the compounds were determined by nuclear magnetic resonance (NMR) spectroscopy and/or mass spectrometry (MS). NMR shifts (δ) are given in a unit of 10-6 (ppm).

[0161] NMR spectra were measured using a Bruker AVANCE-400 nuclear magnetic resonance instrument, with deuterated dimethyl sulfoxide (DMSO-d6), deuterated chloroform (CDCl3) and deuterated methanol (CD3OD) as solvents and tetramethylsilane (TMS) as an internal standard.

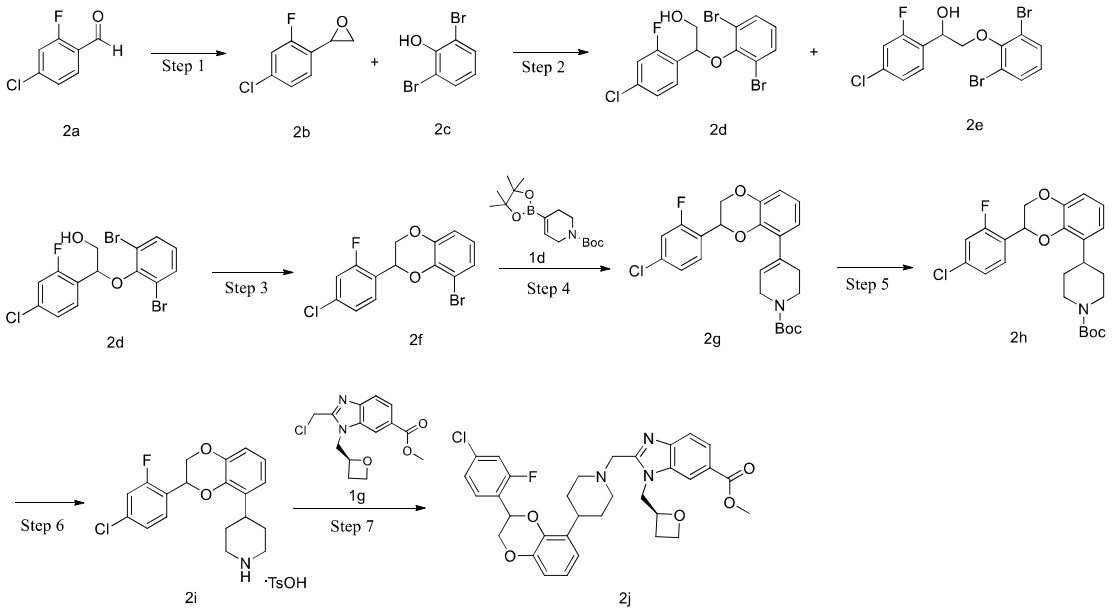
[0162] MS determination was carried out by means of Agilent 1200/1290 DAD-6110/6120

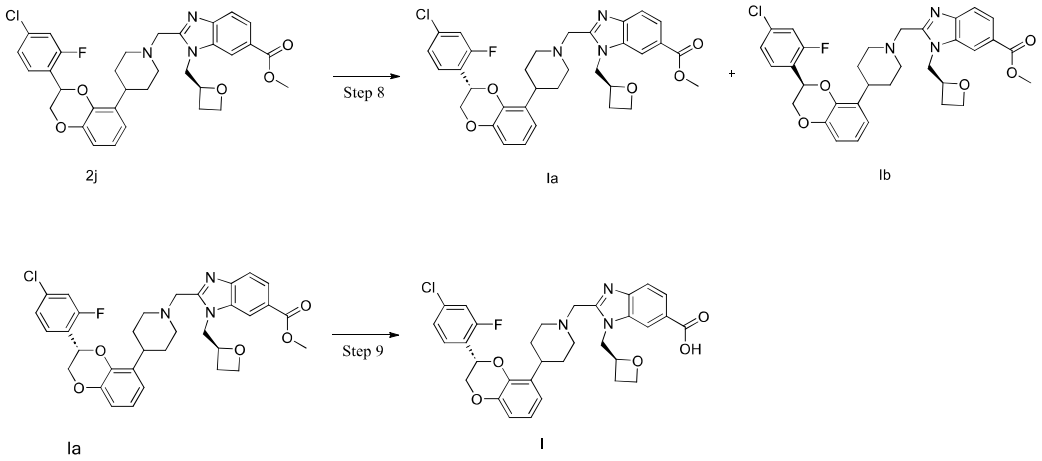
Quadrupole MS liquid chromatography-mass spectrometer (manufacturer: Agilent, MS model: 6110/6120 Quadrupole MS); waters ACQuity UPLC-QD/SQD (manufacturer: waters, MS model: waters ACQuity Qda Detector/waters SQ Detector); and THERMO Ultimate 3000-Q Exactive (manufacturer: THERMO, MS model: THERMO Q Exactive).

[0163] 7. Known starting materials described herein may be synthesized using or according to methods known in the art, or may be purchased from ABCR GmbH & Co. KG, Acros Organics, Aldrich Chemical Company, Accela ChemBio Inc., Chembee Chemicals, and other companies.

[0164] 8. HPLC determination was carried out by means of Agilent 1260DAD high-performance liquid chromatograph (ACE Excel C18 150 × 4.6 mm chromatographic column) and Thermo Dionex Ultimate 3000 high-pressure liquid chromatograph (Waters Xbridge C18 150 × 4.6 mm chromatographic column).

[0165] Example 1: Preparation and Activity Test of Compound A





[0166] Step 1

[0167] 2-(4-Chloro-2-fluorophenyl)oxirane **2b**

[0168] Potassium tert-butoxide (1.70 g, 15.14 mmol, Accela ChemBio (Shanghai) Inc.) was added to tetrahydrofuran (30 mL).Trimethylsulfonium iodide (3.09 g, 15.14 mmol, Adamas Reagent Co., Ltd.) was added under ice bath conditions. The mixture was stirred for 5 min. 4-Chloro-2-fluorobenzaldehyde **2a** (2.0 g, 12.61 mmol, Accela ChemBio (Shanghai) Inc.) was added. The mixture was filtered, diluted with ethyl acetate (80 mL), washed with saturated aqueous ammonium chloride solution (30 mL×2), washed with saturated brine (30 mL×2), dried over anhydrous sodium sulfate and concentrated under reduced pressure to remove the solvent. The resulting residue was purified by silica gel column chromatography with eluent system B to give the title compound **2b** (650 mg, yield: 29.9%).

[0169] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05-7.13 (m, 3H), 4.01-4.15 (m, 1H), 3.17 (dd, 1H), 3.75 (dd, 1H).

[0170] Step 2

[0171] 2-(4-Chloro-2-fluorophenyl)-2-(2,6-dibromophenoxy)ethanol **2d**

[0172] 1-(4-Chloro-2-fluorophenyl)-2-(2,6-dibromophenoxy)ethanol **2e**

[0173] After compound **2b** (520 mg, 3.01 mmol) and 2,6-dibromophenol **2c** (759 mg, 3.01 mmol, TCI (Shanghai) Co., Ltd.) were mixed, sodium methoxide (16 mg, 0.30 mmol, Adamas Reagent Co., Ltd.) was added. The mixture was stirred at 130 ^{o}C. for 2 h. After cooling, the resulting residue was purified by silica gel column chromatography with eluent system B to give the title compound **2d** (210 mg, yield: 16.4%) and compound **2e** (140 mg, yield: 10.9%).

[0174] **2d** MS m/z (ESI):422.9 [M-1].

[0175] **2d** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (t, 1H), 7.63 (d, 2H), 7.40 (dd, 1H), 7.35 (dd, 1H), 7.00 (t, 1H), 5.59 (t, 1H), 5.02 (t, 1H), 3.98-4.03 (m, 1H), 3.81-3.90 (m, 1H).

[0176] **2e** ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (d, 2H), 7.62 (t, 1H), 7.39 (dd, 1H), 7.32 (dd, 1H), 7.02 (t, 1H), 5.82-6.01 (m, 1H), 5.28 (t, 1H), 4.07-4.12 (m, 1H), 3.95-4.00 (m, 1H).

[0177] Step 3

[0178] 8-Bromo-2-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxane **2f**

[0179] Compound **2d** (595 mg, 1.40 mmol) was dissolved in anhydrous toluene (8 mL).S-1,1′-Bi-2-naphthol (159 mg, 0.55 mmol, Accela ChemBio (Shanghai) Inc.), cuprous iodide (52 mg, 0.27 mmol, Sinopharm Chemical Reagent Co., Ltd.) and cesium carbonate (912 mg, 2.80 mmol, Accela ChemBio (Shanghai) Inc.) were successively added. The mixture was heated at reflux and stirred for 18 h, cooled and concentrated under reduced pressure to remove the solvent. The resulting residue was purified by silica gel column chromatography with eluent system B to give the title compound **2f** (380 mg, yield: 78.9%).

[0180] MS m/z (ESI):343.1 [M-1].

[0181] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.57 (dd, 1H), 7.54 (t, 1H), 7.43 (dd, 1H), 7.19 (dd, 1H), 6.98 (dd, 1H), 6.85 (t, 1H), 5.58 (dd, 1H), 4.51 (dd, 1H), 4.20 (dd, 1H).

[0182] Step 4

[0183] tert-Butyl 4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)-5,6-dihydropyridine-1(2H)-carboxylate **2g**

[0184] Compound **2f** (354 mg, 1.03 mmol) and compound **1d** (350 mg, 1.13 mmol, Accela ChemBio (Shanghai) Inc.) were dissolved in 24 mL of a mixed solution of 1,4-dioxane and water (V/V=5 : 1). Sodium carbonate (218 mg, 2.06 mmol), tetrakis(triphenylphosphine)palladium (119 mg, 1.03 mmol) were added. The mixture was stirred at 90 ^{o}C. for 4 h under nitrogen, cooled to room temperature, filtered and concentrated under reduced pressure to remove the solvent. The resulting residue was purified by silica gel column chromatography with eluent system B to give the title compound **2g** (410 mg, yield: 89.2%).

[0185] MS m/z (ESI):390.1 [M-55].

[0186] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, 1H), 7.19-7.23 (m, 1H), 7.15 (dd, 1H), 6.83-6.89 (m, 2H), 6.77-6.81 (m, 1H), 5.76-5.91 (m, 1H), 5.32-5.46 (m, 1H), 5.41 (dd, 1H), 3.99-4.08 (m, 2H), 3.97 (dd, 1H), 3.43-3.69 (m, 2H), 2.40-2.63 (m, 2H), 1.47 (s, 9H).

[0187] Step 5

[0188] tert-Butyl 4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidine -1-carboxylate **2h**

[0189] Compound **2g** (220 mg, 0.49 mmol) was dissolved in ethyl acetate (10 mL) and 1,2-dichlorobenzene (0.5 mL, TCI (Shanghai) Co., Ltd.).10% palladium on carbon (50 mg, 0.47 mmol) was added. Hydrogenation was performed at room temperature for 1 h under one atmosphere of hydrogen. The mixture was filtered and concentrated under reduced pressure to remove the solvent. The resulting residue was purified by silica gel column chromatography with eluent system B to give the title compound **2h** (178 mg, yield: 80.5%).

[0190] MS m/z (ESI):392.1[M-55].

[0191] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, 1H), 7.21-7.24 (m, 1H), 7.16 (dd, 1H), 6.82-6.88 (m, 1H), 6.76-6.81 (m, 2H), 5.35-5.45 (m, 1H), 4.40 (dd, 1H), 4.09-4.33 (m, 2H), 3.96 (dd, 1H), 2.99-3.11 (m, 1H), 2.67-2.90 (m, 2H), 1.72-1.91 (m, 2H), 1.58-1.69 (m, 2H), 1.46 (s, 9H).

[0192] Step 6

[0193] 4-(3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidine 4-methylbenzenesulfonate **2i**

[0194] Compound **2h** (178 mg, 0.40 mmol) was dissolved in ethyl acetate (5 mL). p-Toluenesulfonic acid monohydrate (189 mg, 0.99 mmol) was added. The mixture was stirred at 60 ^{o}C. for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure to give the crude title product **2i** (206 mg).The product was directly used in the next step without being purified.

[0195] MS m/z (ESI):348.1 [M+1].

[0196] Step 7

[0197] Methyl 2-((4-(3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidin -1-yl)methyl)-1-((S)-oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate **2j**

[0198] Compound **1g** (175 mg, 0.59 mmol) and **2i** (206 mg, 0.59 mmol) were dissolved in acetonitrile (10 mL). Potassium carbonate (410 mg, 2.97 mmol) was added. The mixture was stirred at 60 ^{o}C. for 3 h, filtered and concentrated under reduced pressure to remove the solvent. The resulting residue was purified by silica gel column chromatography with eluent

system B to give the title mixture of diastereomers **2j** (207 mg, yield: 57.7%).

[0199] MS m/z (ESI):606.2 [M+1].

[0200] Step 8

[0201] Methyl 2-((4-((R)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate **Ia**

[0202] Methyl 2-((4-((R)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylate **Ib**

[0203] Compound **2j** (830 mg, 1.37 mmol) was resolved by preparative chiral chromatography (resolution conditions: CHIRALPAK IG 250×20 mm, 5 μm (with column protection); mobile phase: hexane/EtOH (0.1% DEA) = 70/30 (V/V), flow rate: 20 mL/min).The corresponding fractions were collected and concentrated under reduced pressure to give the title products (415 mg and 340 mg).

[0204] Single-configuration compound (shorter retention time **Ia**): MS m/z (ESI):606.0 [M+1]. Preparative chiral chromatography: retention time 13.653 min.

[0205] Single-configuration compound (longer retention time **Ib**): MS m/z (ESI):606.0 [M+1]. Preparative chiral chromatography: retention time 16.422 min.

[0206] Step 9

[0207] 2-((4-((S)-3-(4-Chloro-2-fluorophenyl)-2,3-dihydrobenzo[b][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid **I**

[0208] **Ia** (415 mg, 0.68 mmol) was dissolved in 36 mL of a mixed solvent of acetonitrile and water (V : V = 6 : 1). Lithium hydroxide monohydrate (145 mg, 3.46 mmol) was added. The mixture was stirred at 40 °C. for 18 h. The reaction mixture was cooled to room temperature, adjusted to pH 5-6 with aqueous citric acid solution (1 M) and extracted with ethyl acetate (30 mL×3).The organic phase was concentrated under reduced pressure and then purified by high performance liquid chromatography (Gilson281, column: Boston Phlex C18 150×30 mm, 5 μm; mobile phase 1: water (containing 10 mmol/L ammonium bicarbonate); mobile phase 2: acetonitrile; 15 min of gradient elution: 30% to 50%, flow rate: 30 mL/min) to

give the title product **A** (310 mg, yield: 76.46%).

[0209] MS m/z (ESI):592.2 [M+1].

[0210] ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42-12.97 (brs, 1H), 8.20-8.28 (m, 1H), 7.74-7.83 (m, 1H), 7.61 (d, 1H), 7.55-7.58 (m, 1H), 7.48-7.54 (m, 1H), 7.38-7.44 (m, 1H), 6.70-6.90 (m, 3H), 5.40-7.49 (m, 1H), 5.01-5.13 (m, 1H), 4.72-4.84 (m, 1H), 4.59-4.67 (m, 1H), 4.39-4.51 (m, 2H), 4.31-4.38 (m, 1H), 4.04-4.13 (m, 1H), 3.86-3.95 (m, 1H), 3.71-3.79 (m, 1H), 2.91-3.01 (m, 1H), 2.77-2.88 (m, 2H), 2.61-2.72 (m, 1H), 2.33-2.44 (m, 1H), 2.07-2.25 (m, 2H), 1.73-1.81 (m, 1H), 1.63-1.73 (m, 2H), 1.54-1.63 (m, 1H).

[0211] Test Example 1:Evaluation of Agonist Activity Against GLP-1 Receptor

[0212] I. Purpose

[0213] This experiment was intended to test the agonist activity of the compound molecules against the GLP-1 receptor and evaluate the in vitro activity of the molecules according to EC_{50}. The experiment adopted a ONE-Glo™ Luciferase Assay System (Promega, E6110).Under the action of compound molecules, GLP-1R downstream signaling pathways were activated to cause elevated cAMP level. The combination of cAMP and CRE could start the transcription expression of CRE downstream luciferase genes, the luciferase could emit fluorescence when reacting with substrates thereof, and the activity of the compound for agonizing GLP-1 receptors was reflected by measuring fluorescence signals through a ONE-Glo™ reagent.

[0214] II. Method

[0215] Stably-expressed CHO-K1/CRE-luc/GLP-1 receptor cell strains (self-construction of GLP-1 receptor plasmid; CRE-luc plasmid Promega E8471) were constructed. CHO-K1/CRE-luc/GLP-1 receptor cells were digested, and resuspended after centrifugation. Single cell suspension was uniformly mixed, and adjusted to a viable cell density of 2.5×10^5 cells/mL with a cell culture medium (DME/F-12+10% FBS), and the resulting solution was added to a 96-well cell culture plate at 90 μL/well (Corning, #3903). The plate was incubated in an incubator for 16 h (37 ^{o}C., 5% CO_2).

[0216] The compound was dissolved in DMSO to prepare a stock solution with an initial concentration of 20 mM. The starting concentration of the small molecule compound was 0.2 mM, and the compound underwent 3-fold serial dilution for a total of 10 concentration points, with DMSO at the 11th point. To another 96-well plate was added 95 μL of cell culture

medium (DME/F-12+10% FBS), 5 μL of test samples with different concentrations were added to each well, followed by uniform mixing, and then 10 μL of test samples with different concentrations were added to each well, with two duplicate wells set for each sample. The plate was incubated in an incubator for 6 h (37 °C., 5% CO_2). The 96-well cell culture plate was taken out, and 100 μL of ONE-Glo™ reagent was added to each well, followed by incubation at room temperature for 10 min. The plate was placed in a microplate reader (EnVision 2105, PE) for determination of chemiluminescence.

[0217] III. Data Analysis

[0218] Data were processed and analyzed using Microsoft Excel and Graphpad Prism 5. EC_{50} values of the compounds were obtained, and the results are shown in Table 1 below.

[0219] Table 1

Compound	EC_{50} (nM)	Emax%
A	0.74	103.02

[0220] **Example 2: Amorphous form of tromethamine salt of Compound A**

[0221] 15 mg of Compound A was weighed, 0.3 mL of water was added, the mixture was stirred, 3.38 mg of tromethamine was added, and 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the product was an amorphous form of a tromethamine salt, and the XRPD pattern was as shown in FIG. 1.

[0222] **Example 3: Preparation of crystal form A of tromethamine salt of Compound A**

[0223] 10 mg of Compound A was weighed, 200 μl of ethanol was added, the mixture was stirred, and 2.23 mg of tromethamine solid was added, and the mixture was stirred, centrifuged, and dried to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 2, and the positions of the characteristic peaks thereof were as shown in Table 2. The product was designated as crystal form A of the tromethamine salt. The DSC pattern showed that the peak values of endothermic peaks were 163.02 °C and 174.83 °C. The TGA pattern showed that the weight loss at 30-190 °C was 2.38%.

[0224] Table 2

Peak number	2θ value [° or degrees]	d[Å]	Relative intensity %
1	6.850	12.89457	100
2	8.051	10.97333	4.1
3	9.982	8.85433	9.7
4	12.697	6.96639	7.6
5	13.789	6.41715	27.4
6	14.704	6.01968	2.6
7	14.990	5.90531	2.9
8	15.763	5.61761	9.1
9	16.148	5.48451	12.8
10	18.016	4.91975	6.9
11	19.016	4.66326	6.9
12	20.109	4.41207	3.2
13	22.138	4.01217	13.9
14	23.868	3.72507	3.8
15	25.712	3.46204	4.6
16	27.909	3.19426	5.7
17	28.988	3.07781	3.5
18	31.535	2.83478	4.2
19	35.145	2.55140	2.7

[0225] Example 4: Preparation of crystal form A of tromethamine salt of Compound A

[0226] 10 mg of Compound A was weighed, 200 μl of ethyl acetate was added, the mixture was stirred, and 2.23 mg of tromethamine solid was added, and the mixture was stirred, centrifuged, and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form A of the tromethamine salt.

[0227] Example 5: Preparation of crystal form A of tromethamine salt of Compound A

[0228] 10 mg of Compound A was weighed, 200 μl of methyl tert-butyl ether (MTBE) was added, the mixture was stirred, and 2.23 mg of tromethamine solid was added, and the mixture

was stirred, centrifuged, and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form A of the tromethamine salt.

[0229] Example 6: Preparation of crystal form A of tromethamine salt of Compound A

[0230] 10 mg of Compound A was weighed, 200 μl of a mixed solution of tetrahydrofuran/methyl tert-butyl ether (THF : MTBE = 1 : 2) was added, the mixture was stirred, and 2.23 mg of tromethamine solid was added, and the mixture was stirred, centrifuged, and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form A of the tromethamine salt.

[0231] Example 7: Preparation of crystal form A of tromethamine salt of Compound A

[0232] 150 mg of Compound A was weighed, 3 mL of anhydrous ethanol was added, the mixture was heated to 75 °C, a turbid solution of tromethamine (33.7 mg, dissolved in 5 mL of anhydrous ethanol) was dropwise added and dissolved until clear, a small amount of a seed crystal of crystal form A (prepared by referring to the method in Example 3) was added, the mixture was stirred and subjected to crystallization, and the resulting product was cooled to room temperature, stirred, filtered and dried. After detection by X-ray powder diffraction, the product was crystal form A of the tromethamine salt.

[0233] Example 8: Preparation of crystal form B of tromethamine salt of Compound A

[0234] 15 mg of Compound A was weighed, 0.4 mL of 10% water-acetone was added, the mixture was stirred, 3.38 mg of tromethamine was added, and the mixture was dissolved until clear, placed at 4 °C, stirred, precipitated, centrifuged, and dried to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 3, and the positions of the characteristic peaks thereof were as shown in Table 3. The product was designated as crystal form B of the tromethamine salt. The DSC pattern showed that the peak values of endothermic peaks were 128.76 °C and 160.93 °C. The TGA pattern showed that the weight loss at 30-140 °C was 3.39%.

[0235] Table 3

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	8.144	10.84814	100

2	10.511	8.40946	9.2
3	12.290	7.19601	46.5
4	13.996	6.32238	7.9
5	14.665	6.03564	6.4
6	15.607	5.67317	4.9
7	16.520	5.36188	4.2
8	18.883	4.69583	3.9
9	20.632	4.30140	21.9
10	21.699	4.09225	20.7
11	23.741	3.74475	2.6
12	24.743	3.59538	5.5
13	26.055	3.41725	5.4
14	27.035	3.29553	1.4

[0236] Example 9: Preparation of crystal form C of tromethamine salt of Compound A

[0237] 50 mg of a sample of crystal form A of a tromethamine salt of the compound was weighed into 1 mL of methyl tert-butyl ether to form a suspension, the suspension was stirred at room temperature for 72 hours and filtered, and the filter cake was collected and dried in vacuum to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 4, and the positions of the characteristic peaks thereof were as shown in Table 4. The product was designated as crystal form C of the tromethamine salt. The DSC pattern showed that the peak value of an endothermic peak was 158.9 °C. The TGA pattern showed that the weight loss at 30-150 °C was 5.50%.

[0238] Table 4

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	6.551	13.48213	100.0
2	8.392	10.52791	12.1
3	9.269	9.53396	53.4
4	13.175	6.71450	58.2

5	14.802	5.98007	27.8
6	15.864	5.58188	20.8
7	16.906	5.24026	42.6
8	18.776	4.72233	39.7
9	20.430	4.34365	38.0
10	22.211	3.99915	12.8
11	22.922	3.87669	16.0
12	23.574	3.77095	10.6
13	25.496	3.49088	19.9
14	26.290	3.38714	9.9
15	26.770	3.32756	5.9
16	28.208	3.16109	4.7
17	29.846	2.99124	7.1
18	31.404	2.84630	5.2

[0239] Example 10: Preparation of crystal form C of tromethamine salt of Compound A

[0240] 50 mg of a sample of crystal form A of a tromethamine salt of the compound was weighed and added to 1 mL of methyl tert-butyl ether to form a suspension, the suspension was stirred at room temperature for 72 h and filtered, and the filter cake was collected and dried in vacuum to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form C of the tromethamine salt.

[0241] Example 11: Preparation of crystal form D of tromethamine salt of Compound A

[0242] 15 mg of Compound A was weighed, 0.3 mL of methanol was added, the mixture was stirred, 3.38 mg of tromethamine was added, and 3 cycles of heating and cooling from 50 ^{o}C to 5 ^{o}C at 0.8 K/min were carried out, and after centrifugation and drying, a solid was obtained. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 5, and the positions of the characteristic peaks thereof were as shown in Table 5. The product was designated as crystal form D of the tromethamine salt.

[0243] Table 5

Peak number	2θ value [° or degrees]	d[Å]	Relative intensity %
1	5.281	16.72183	54.0
2	9.912	8.91689	35.8
3	10.292	8.58779	60.4
4	10.961	8.06570	29.8
5	11.613	7.61366	17.0
6	13.322	6.64067	100.0
7	15.351	5.76743	17.7
8	17.586	5.03916	7.6
9	18.283	4.84857	17.7
10	19.214	4.61564	18.0
11	19.890	4.46030	5.8
12	21.390	4.15078	58.6
13	22.215	3.99846	32.3
14	23.471	3.78721	8.4
15	23.979	3.70818	28.7
16	25.029	3.55493	21.1
17	25.846	3.44438	24.3
18	26.741	3.33110	7.4
19	27.232	3.27207	6.6
20	27.918	3.19320	11.2
21	29.536	3.02186	5.9
22	30.121	2.96451	13.0
23	30.550	2.92385	7.1
24	32.240	2.77436	0.7

[0244] Example 12: Preparation of crystal form D of tromethamine salt of Compound A

[0245] 1.5 g of Compound A was weighed into 18 mL of isopropanol, heated to 75 °C, an

aqueous solution of tromethamine (308 mg, dissolved in 0.77 mL of water) was added dropwise, 6 mL of isopropanol and 12 mL of methanol were added, the mixture was stirred at 75 °C for half an hour to precipitate a solid, slowly cooled, stirred at room temperature for 16 h, stirred in an ice bath for half an hour, and after filtration, a filter cake core was collected and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form D of the tromethamine salt.

[0246] Example 13: Preparation of crystal form E of tromethamine salt of Compound A

[0247] 60 mg of Compound A was weighed, 1 ml of acetonitrile was added, and 15.7 mg of tromethamine solid was added, the mixture was stirred and crystallized, and after centrifugation and drying, a solid was obtained. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 6, and the positions of the characteristic peaks thereof were as shown in Table 6. The product was designated as crystal form E of the tromethamine salt. The DSC pattern showed that the peak values of endothermic peaks were 127.83 °C and 160.76 °C. The TGA pattern showed that the weight loss at 30-190 °C was 2.13%.

[0248] Table 6

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	6.821	12.94824	100.0
2	10.035	8.80744	12.2
3	12.653	6.99062	12.2
4	13.727	6.44565	24.0
5	14.787	5.98596	13.1
6	16.081	5.50705	11.2
7	16.648	5.32081	11.5
8	18.571	4.77389	9.9
9	19.451	4.56002	7.0
10	20.151	4.40308	11.1
11	20.736	4.28024	4.0
12	22.204	4.00035	10.8
13	25.386	3.50570	1.9

14	27.774	3.20945	5.8
15	29.941	2.98196	4.7

[0249] Example 14: Preparation of crystal form F of tromethamine salt of Compound A

[0250] A sample of crystal form A of the tromethamine salt of Compound A was placed at 80 °C/0% RH for 96 h or dried at 167 °C. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 7, and the positions of the characteristic peaks thereof were as shown in Table 7. The product was designated as crystal form F of the tromethamine salt. The DSC pattern showed that the peak values of endothermic peaks were 159.88 °C and 175.93 °C. The TGA pattern showed that the weight loss at 30-180 °C was 2.91%.

[0251] Table 7

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	6.777	13.03260	15.1
2	7.674	11.51123	100.0
3	10.614	8.32815	27.1
4	11.594	7.62626	13.1
5	13.671	6.47190	5.5
6	14.408	6.14261	9.7
7	14.882	5.94792	18.4
8	16.400	5.40078	38.0
9	18.645	4.75531	69.7
10	20.849	4.25720	8.1
11	21.384	4.15185	7.6
12	21.731	4.08646	8.9
13	22.108	4.01748	8.0
14	23.021	3.86018	1.7
15	24.721	3.59845	7.3
16	26.169	3.40251	7.7
17	29.192	3.05676	7.9

[0252] Example 15: Preparation of amorphous form of amine salt of Compound A

[0253] 15 mg of Compound A was weighed, 0.3 mL of acetone was added, the mixture was stirred, 28 μL of 2 M ammonia aqueous solution was added, and 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the amine salt.

[0254] Example 16: Preparation of amorphous form of potassium salt of Compound A

[0255] 10 mg of Compound A was weighed, 200 μL of a mixed solution of tetrahydrofuran/tert-butyl dimethyl ether (THF : MTBE = 1 : 2) was added, followed by 9.3 μL of 2 M potassium hydroxide aqueous solution, and the mixture was pulped at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the potassium salt.

[0256] Example 17: Preparation of crystal form α of potassium salt of Compound A

[0257] 10 mg of Compound A was weighed, 200 μL of ethyl acetate was added, followed by 9.3 μL of 2 M potassium hydroxide aqueous solution, and the mixture was pulped at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form α of the potassium salt, the XRPD pattern was as shown in FIG. 8, and the positions of the characteristic peaks thereof were as shown in Table 8. The DSC pattern showed that the peak values of endothermic peaks were 87.46 °C, 159.28 °C, and 230.06 °C. The TGA pattern showed that the weight loss at 30-150 °C was 5.17%.

[0258] Table 8

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	9.564	9.23983	100.0
2	11.515	7.67827	65.3
3	14.683	6.02808	36.4
4	16.058	5.51498	26.4
5	17.033	5.20130	14.1

6	17.945	4.93920	4.7
7	18.859	4.70181	17.9
8	19.607	4.52406	59.2
9	20.391	4.35171	40.2
10	21.064	4.21428	11.3
11	22.592	3.93261	28.9
12	23.320	3.81134	16.1
13	24.449	3.63787	12.9
14	25.176	3.53444	19.8
15	25.933	3.43297	13.6
16	27.080	3.29008	12.7
17	27.708	3.21692	13.3

[0259] Example 18: Preparation of crystal form α of potassium salt of Compound A

[0260] 10 mg of Compound A was weighed, 200 μL of methyl tert-butyl ether was added, followed by 9.3 μL of 2 M potassium hydroxide aqueous solution, and the mixture was pulped at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form α of the potassium salt.

[0261] Example 19: Preparation of amorphous form of arginine salt of Compound A

[0262] 15 mg of Compound A was weighed, 0.3 mL of methanol was added, the mixture was stirred, 9.72 mg of arginine was added, 3 cycles of heating and cooling from 50 ^{o}C to 5 ^{o}C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the arginine salt.

[0263] Example 20: Preparation of amorphous form of sodium salt of Compound A

[0264] 10 mg of Compound A was weighed, 200 μL of methyl tert-butyl ether was added, followed by 9.3 μL of 2 M sodium hydroxide aqueous solution, and the mixture was pulped at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the

product was an amorphous form of the sodium salt.

[0265] Example 21: Preparation of crystal form I of sodium salt of Compound A

[0266] 15 mg of Compound A was weighed, 0.3 ml of methanol was added, 28 μL of 2 M sodium hydroxide aqueous solution was added, the mixture was stirred and dissolved, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after drying, a solid was obtained. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 9, and the positions of the characteristic peaks thereof were as shown in Table 9. The product was designated as crystal form I of the sodium salt. The DSC pattern showed that the peak values of endothermic peaks were 77.63 °C, 157.96 °C, 181.45 °C, and 232.77 °C. The TGA pattern showed that the weight loss at 30-150 °C was 3.05%.

[0267] Table 9

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	5.257	16.79552	100.0
2	5.806	15.20931	94.7
3	6.795	12.99734	57.6
4	10.106	8.74583	63.2
5	12.203	7.24689	54.3
6	20.693	4.28891	59.0

[0268] Example 22: Preparation of crystal form I of sodium salt of Compound A

[0269] 10 mg of Compound A was weighed, 200 μL of ethyl acetate was added, followed by 9.3 μL of 2M sodium hydroxide aqueous solution; and if it was not dissolved clear, the mixture was stirred overnight at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form I of the sodium salt.

[0270] Example 23: Preparation of crystal form II of sodium salt of Compound A

[0271] 15 mg of Compound A was weighed, 0.3 mL of acetone was added, 28 μL of 2 M sodium hydroxide aqueous solution was added, the mixture was stirred and dissolved, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation and drying, a solid was obtained. After detection by X-ray powder diffraction, the XRPD

pattern was as shown in FIG. 10, and the positions of the characteristic peaks thereof were as shown in Table 10. The product was designated as crystal form II of the sodium salt. The DSC pattern showed that the peak values of endothermic peaks were 118.67 °C and 235.34 °C. The TGA pattern showed that the weight loss at 30-150 °C was 2.85%.

[0272] Table 10

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	5.574	15.84162	65.2
2	9.754	9.06033	100.0
3	11.731	7.53794	85.6
4	14.856	5.95832	12.4
5	16.091	5.50357	12.0
6	19.730	4.49609	82.6
7	22.670	3.91923	5.7

[0273] Example 24: Preparation of crystal form II of sodium salt of Compound A

[0274] 15 mg of Compound A was weighed, and 0.3 mL of acetonitrile was added; and if it was not dissolved after stirring, 14 μL of 2 M sodium hydroxide aqueous solution was added for dissolution, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation and drying, a solid was obtained. After detection by X-ray powder diffraction, the product was crystal form II of the sodium salt.

[0275] Example 25: Preparation of amorphous form of meglumine salt of Compound A

[0276] 15 mg of Compound A was weighed, 0.3 mL of methanol was added, the mixture was stirred, 11.0 mg of meglumine was added, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the meglumine salt.

[0277] Example 26: Preparation of crystal form I of meglumine salt of Compound A

[0278] 15 mg of Compound A was weighed, 0.3 mL of acetonitrile was added, the mixture

was stirred, 5.5 mg of meglumine was added, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 11, and the positions of the characteristic peaks thereof were as shown in Table 11. The product was designated as crystal form I of the meglumine salt. The DSC pattern showed that the peak values of endothermic peaks were 60.00 °C and 104.48 °C. The TGA pattern showed that the weight loss at 30-110 °C was 0.18%.

[0279] Table 11

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	5.498	16.06202	100.0
2	8.314	10.62603	6.1
3	8.901	9.92698	11.4
4	11.013	8.02776	23.2
5	11.891	7.43643	6.3
6	12.810	6.90505	7.4
7	14.626	6.05172	22.3
8	15.683	5.64601	6.7
9	15.931	5.55878	9.0
10	17.942	4.93981	20.1
11	18.748	4.72941	4.5
12	19.454	4.55917	12.9
13	20.393	4.35126	9.6
14	21.419	4.14519	8.3
15	22.234	3.99506	7.5
16	22.668	3.91953	13.7
17	23.391	3.79994	8.0
18	23.936	3.71469	2.8
19	24.739	3.59590	7.5

20	25.696	3.46406	11.9
21	26.682	3.33824	4.7
22	33.209	2.69554	7.0

[0280] Example 27: Preparation of amorphous form of ethanolamine salt of Compound A

[0281] 15 mg of Compound A was weighed, 0.3 mL of methanol was added, the mixture was stirred, 28 μL of 2 M ethanolamine aqueous solution was added, and 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the ethanolamine salt.

[0282] Example 28: Preparation of crystal form I of p-toluenesulfonate salt of Compound A

[0283] 15 mg of Compound A was weighed, and 0.3 mL of acetonitrile was added; and if it was not dissolved after stirring, 9.61 mg of p-toluenesulfonic acid was added for dissolution, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation and drying, a solid was obtained. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 12, and the positions of the characteristic peaks thereof were as shown in Table 12. The product was designated as crystal form I of the p-toluenesulfonate salt. The DSC pattern showed that the peak value of an endothermic peak was 191.14 °C. The TGA pattern showed that the weight loss at 30-150 °C was 0.93%.

[0284] Table 12

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	5.453	16.19243	97.8
2	5.884	15.00779	66.0
3	8.063	10.95652	67.8
4	12.925	6.84366	61.8
5	13.825	6.40024	41.8

6	15.399	5.74960	45.5
7	16.071	5.51041	59.5
8	16.560	5.34900	39.4
9	17.066	5.19150	25.2
10	18.231	4.86231	47.5
11	19.778	4.48533	100.0
12	20.861	4.25472	33.0
13	21.917	4.05212	54.6
14	23.898	3.72055	31.2
15	24.467	3.63525	12.8
16	26.744	3.33064	36.5
17	28.136	3.16898	22.4

[0285] Example 29: Preparation of crystal form I of tartrate salt of Compound A

[0286] 10 mg of Compound A was weighed, and 200 μL of ethanol was added; and if it was not dissolved clear, 9.3 μL of 2 M L-tartaric acid aqueous solution was further added, and the mixture was stirred, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 13, and the positions of the characteristic peaks thereof were as shown in Table 13. The product was designated as crystal form I of the tartrate salt. The DSC pattern showed that the peak values of endothermic peaks were 115.94 °C and 138.28 °C. The TGA pattern showed that the weight loss at 30-110 °C was 2.60%.

[0287] Table 13

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	9.342	9.45908	12.3
2	10.132	8.72312	12.8
3	10.858	8.14155	13.7
4	11.272	7.84361	15.1
5	12.810	6.90483	44.8
6	14.448	6.12567	29.5

7	15.604	5.67430	28.0
8	18.824	4.71037	100.0
9	20.410	4.34785	29.1
10	21.890	4.05711	36.9
11	24.472	3.63456	39.4
12	27.880	3.19747	15.9

[0288] Example 30: Preparation of crystal form I of tartrate salt of Compound A

[0289] 10 mg of Compound A was weighed, 200 μL of ethyl acetate was added, followed by 9.3 μL of 2 M L-tartaric acid aqueous solution, and the mixture was stirred, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form I of the tartrate salt.

[0290] Example 31: Preparation of crystal form I of tartrate salt of Compound A

[0291] 10 mg of Compound A was weighed, 200 μL of methyl tert-butyl ether was added, followed by 9.3 μL of 2 M L-tartaric acid aqueous solution, and the mixture was stirred, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form I of the tartrate salt.

[0292] Example 32: Preparation of amorphous form of sulfate salt of Compound A

[0293] 15 mg of Compound A was weighed, 0.3 mL of acetonitrile was added, the mixture was stirred, 28 μL of 2 M sulfuric acid was added, 3 cycles of heating and cooling from 50 °C to 5 °C at 0.8 K/min were carried out, and after centrifugation, the supernatant was slowly volatilized to obtain a solid. After detection by X-ray powder diffraction, the X-ray powder diffraction pattern had no obvious characteristic peaks, and the product was an amorphous form of the sulfate salt.

[0294] Example 33: Preparation of crystal form α of malate salt of Compound A

[0295] 10 mg of Compound A was weighed, and 200 μL of ethyl acetate was added; and if it was not dissolved clear, 9.3 μL of 2 M L-malic acid aqueous solution was further added, and the mixture was stirred, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 14, and the positions of the characteristic peaks thereof were as shown in Table 15. The product was designated as crystal

form α of the malate salt. The DSC pattern showed that the peak values of endothermic peaks were 56.15 °C, 98.97 °C, and 126.79 °C. The TGA pattern showed that the weight loss at 30-130 °C was 1.75%.

[0296] Table 14

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	9.364	9.43652	10.9
2	10.050	8.79438	48.7
3	10.818	8.17138	36.2
4	11.213	7.88494	38.3
5	12.871	6.87232	27.2
6	13.774	6.42394	17.4
7	14.508	6.10037	46.1
8	15.693	5.64245	46.3
9	17.760	4.99004	11.9
10	18.924	4.68576	100.0
11	20.240	4.38383	53.9
12	21.829	4.06820	39.9
13	24.396	3.64574	18.5
14	25.100	3.54504	4.8
15	26.200	3.39860	12.3
16	27.936	3.19122	12.1
17	28.188	3.16326	10.4
18	30.508	2.92776	4.8
19	30.983	2.88400	5.6

[0297] Example 34: Preparation of crystal form α of malate salt of Compound A

[0298] 10 mg of Compound A was weighed, 200 μL of MTBE was added, followed by 9.3 μL of 2 M L-malic acid aqueous solution, and the mixture was stirred, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the product was crystal form α

of the malate salt.

[0299] Example 35: Preparation of crystal form I of hydrochloride salt of Compound A

[0300] 100 mg of Compound A was weighed, 1545 μl of 0.12 M hydrochloric acid aqueous solution was added, and the suspension was stirred overnight at room temperature, centrifuged and dried to obtain a solid. After detection by X-ray powder diffraction, the XRPD pattern was as shown in FIG. 15, and the positions of the characteristic peaks thereof were as shown in Table 15. The product was designated as crystal form I of the hydrochloride salt. The DSC pattern showed that the peak value of an endothermic peak was 163.16 °C. The TGA pattern showed that the weight loss at 30-170 °C was 2.50%.

[0301] Table 15

Peak number	**2θ value [° or degrees]**	**d[Å]**	**Relative intensity %**
1	9.939	8.89213	72.0
2	12.267	7.20959	16.9
3	13.123	6.74112	32.2
4	13.649	6.48262	33.9
5	14.333	6.17479	74.2
6	14.933	5.92798	93.6
7	16.616	5.33109	30.7
8	17.523	5.05706	90.9
9	18.480	4.79725	100.0
10	19.378	4.57689	39.7
11	20.134	4.40665	60.8
12	20.988	4.22925	34.1
13	22.377	3.96978	24.6
14	23.002	3.86339	30.5
15	24.477	3.63378	29.8
16	25.322	3.51441	30.5
17	26.399	3.37349	58.0
18	26.970	3.30335	47.7
19	27.609	3.22828	17.3
20	30.822	2.89865	23.3

21	32.119	2.78450	6.4
22	33.760	2.65286	17.7
23	25.541	2.52388	7.1

[0302] Test Example 2: Study on hygroscopicity of crystal forms of salts of Compound A

[0303] Surface Measurement Systems intrinsic DVS was used at 25 °C. The observed humidity ranged from 0% to 95%. The step was 10%. The criterion was that the mass change dM/dT for each step was less than 0.002%. TMAX was 360 min. Two cycles were carried out.

[0304] Table 16

Sample to be tested	0.0% RH to 80.0% RH	Crystal form
Crystal form A of tromethamine salt	5.02%	Unchanged
Crystal form D of tromethamine salt	2.45%	Unchanged
Crystal form E of tromethamine salt	7.27%	Unchanged
Crystal form I of tartrate salt	1.44%	Unchanged
Crystal form α of malate salt	2.45%	Unchanged

[0305] Test Example 3: Study on stability of crystal forms of salts of Compound A

[0306] A salt-type sample of Compound A was placed open and spread, and the stability of the sample was investigated under the conditions of illumination (4500 Lux), high temperature (40 °C and 60 °C) and high humidity (75% RH and 92.5% RH), respectively. The sampling and investigation period was 30 days.

[0307] Table 17. Stability data of crystal form A of tromethamine salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	99.5	Crystal form A of tromethamine salt

Illumination (4500 Lux)	7	98.9	Unchanged
	14	97.6	Unchanged
	30	90.8	Unchanged
40 °C	7	96.1	Unchanged
	14	91.7	Unchanged
	30	87.4	Unchanged
60 °C	7	93.5	Unchanged
	14	88.6	Unchanged
75% RH	7	99.4	Unchanged
	14	99.4	Unchanged
	30	99.3	Unchanged
92.5% RH	7	99.3	Unchanged
	14	99.0	Unchanged
	30	98.6	Unchanged

[0308] Table 18. Stability data of crystal form D of tromethamine salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	99.7	Crystal form D of tromethamine salt
Illumination (4500 Lux)	7	99.6	Unchanged
	14	99.6	Unchanged
	30	99.6	Unchanged
40 °C	7	99.5	Unchanged
	14	99.3	Unchanged
	30	99.3	Unchanged
60 °C	7	99.4	Unchanged
	14	99.1	Unchanged
	30	99.0	Unchanged
75% RH	7	99.7	Unchanged

	14	99.6	Unchanged
	30	99.6	Unchanged
92.5% RH	7	99.5	Unchanged
	14	99.4	Unchanged
	30	99.0	Unchanged

[0309] Table 19. Stability data of crystal form E of tromethamine salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	98.3	Crystal form E of tromethamine salt
Illumination (4500 Lux)	7	98.1	Unchanged
	14	97.9	Unchanged
	30	95.5	Unchanged
40 °C	7	96.0	Unchanged
	14	93.6	Unchanged
	30	85.0	Unchanged
60 °C	7	94.8	Unchanged
	30	81.8	Amorphous form
75% RH	7	98.3	Unchanged
	14	98.4	Unchanged
	30	98.3	Unchanged
92.5% RH	7	98.2	Unchanged
	14	98.2	Unchanged
	30	98.1	Amorphous form

[0310] Table 20. Stability data of crystal form I of hydrochloride salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	98.0	Crystal form I of hydrochloride salt

Illumination (4500 Lux)	5	97.9	Unchanged
	10	98.1	Unchanged
	30	98.0	Unchanged
40 °C	5	98.0	Unchanged
	10	98.1	Unchanged
	30	97.8	Unchanged
60 °C	5	97.6	Unchanged
	10	97.7	Unchanged
	30	97.7	Unchanged
75% RH	5	98.1	Unchanged
	10	98.0	Unchanged
	30	98.1	Unchanged
92.5% RH	5	98.1	Unchanged
	10	97.4	Unchanged
	30	96.9	Unchanged

[0311] Table 21. Stability data of crystal form α of malate salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	99.0	Crystal form α of malate salt
Illumination (4500 Lux)	5	98.9	Unchanged
	10	98.8	Unchanged
	30	98.7	Unchanged
40 °C	5	98.7	Unchanged
	10	98.6	Unchanged
	30	97.2	Unchanged
60 °C	5	97.9	Unchanged
	10	97.7	Unchanged
	30	97.2	Unchanged

75% RH	5	98.9	Unchanged
	10	98.9	Unchanged
	30	98.7	Unchanged
92.5% RH	5	99.0	Unchanged
	10	98.9	Unchanged
	30	98.8	Unchanged

[0312] Table 22. Stability data of crystal form I of tartrate salt

Condition	Time (days)	%Purity	Crystal form
Initial condition	0	98.8	Crystal form I of tartrate salt
Illumination (4500 Lux)	5	98.7	Unchanged
	10	98.6	Unchanged
	30	98.3	Unchanged
40 °C	5	98.4	Unchanged
	10	98.1	Unchanged
	30	97.6	Unchanged
60 °C	5	97.9	Unchanged
	10	97.2	Unchanged
	30	96.4	Unchanged
75% RH	5	98.6	Unchanged
	10	98.6	Unchanged
	30	98.4	Unchanged
92.5% RH	5	98.7	Unchanged
	10	98.6	Unchanged
	30	98.3	Unchanged

[0313] Conclusion: The crystal form D of the tromethamine salt, the crystal form I of the hydrochloride salt, the crystal form α of the malate salt, and the crystal form I of the tartrate salt had good physical and chemical stability after standing for 30 days under the conditions of

influencing factors; in addition, the crystal form A of the tromethamine salt had stable physical properties, the crystal form E of the tromethamine salt had slightly poor physical stability under high temperature and high humidity conditions, and the crystal forms A and E of the tromethamine salt had slightly poor chemical stability under high temperature conditions, but they could all meet the basic stability requirements of later formulation.

[0314] Test Example 4: Long-term/accelerated stability of crystal forms of salts of Compound A

[0315] A salt-type sample was sealed with an aluminum foil bag and placed under the conditions of 25 °C/60% RH and 40 °C/75% RH, respectively, to investigate the stability.

[0316] Table 23

	Placement condition	%Purity				Crystal form
Crystal form A of tromethamine salt		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	99.8	99.7	99.8	99.8	Unchanged
	40 °C/75% RH		99.6	99.6	99.6	Unchanged
Crystal form D of tromethamine salt	Placement condition	%Purity				Crystal form
		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	99.7	99.7	/	99.7	Unchanged
	40 °C/75% RH		99.5	/	99.1	Unchanged
Crystal form E of tromethamine salt	Placement condition	%Purity				Crystal form
		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	98.3	98.2	98.3	98.1	Unchanged
	40 °C/75% RH		97.7	97.7	97.2	Unchanged
Crystal form	Placement	%Purity				Crystal

I of hydrochloride salt	condition					form
		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	98.0	98.1	97.9	/	Unchanged
	40 °C/75% RH		97.8	97.8	/	Unchanged
Crystal form α of malate salt	Placement condition	%Purity				Crystal form
		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	99.0	98.8	/	98.7	Unchanged
	40 °C/75% RH		98.3	/	97.1	Unchanged
Crystal form I of tartrate salt	Placement condition	%Purity				Crystal form
		Initial condition	1 month	2 months	3 months	/
	25 °C/60% RH	98.8	98.4	/	98.2	Unchanged
	40 °C/75% RH		97.4	/	96.4	Unchanged

[0317] Conclusion: The long-term/accelerated stability experiment showed that the crystal forms A and D of the tromethamine salt and the crystal form I of the hydrochloride salt had good physical and chemical stability under long-term and accelerated conditions, and the crystal form E of the tromethamine salt and the crystal form I of the tartrate salt had good physical and chemical stability under long-term conditions.

What is claimed is:

1. A pharmaceutically acceptable salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein the pharmaceutically acceptable salt is selected from a tromethamine salt, an ammonium salt, a potassium salt, an arginine salt, a sodium salt, a meglumine salt, an ethanolamine salt, a p-toluenesulfonate salt, a tartrate salt, a sulfate salt, a malate salt, and a hydrochloride salt.

2. The pharmaceutically acceptable salt according to claim 1, wherein the chemical ratio of the compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid to an alkali molecule or an acid molecule is 1 : 0.5 to 1 : 3, preferably 1 : 0.5, 1 : 1, 1 : 2, or 1 : 3, most preferably 1 : 1 or 1 : 2.

3. A method for preparing the pharmaceutically acceptable salt according to claim 1 or 2, the method comprising a step of salt formation between compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid and an acid, or a step of salt formation between compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid and an alkali.

4. The method according to claim 3, wherein a solvent used in the salt formation reaction is selected from at least one of methanol, 2-butanone, ethyl acetate, 1,4-dioxane, methyl isobutyl ketone, methyl tert-butyl ether, dichloromethane, ethanol, isopropanol, tetrahydrofuran, dimethyl sulfoxide, acetone, acetonitrile, toluene, isopropyl acetate, and water.

5. Crystal form A of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction

pattern expressed with diffraction angle 2θ has characteristic peaks at 6.850, 9.982, 13.789, 16.148, and 22.138; preferably characteristic peaks at 6.850, 9.982, 12.697, 13.789, 15.763, 16.148, 18.016, 19.016, and 22.138; more preferably characteristic peaks at 6.850, 8.051, 9.982, 12.697, 13.789, 14.704, 14.990, 15.763, 16.148, 18.016, 19.016, 20.109, 22.138, 25.712, and 27.909; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 2.

6. Crystal form B of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 8.144, 10.511, 12.290, 20.632, and 21.699; preferably characteristic peaks at 8.144, 10.511, 12.290, 13.996, 14.665, 20.632, 21.699, and 24.743; more preferably characteristic peaks at 8.144, 10.511, 12.290, 13.996, 14.665, 15.607, 16.520, 18.883, 20.632, 21.699, 23.741, 24.743, 26.055, and 27.035; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 3.

7. Crystal form C of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 6.551, 9.269, 13.175, and 16.906; preferably characteristic peaks at 6.551, 9.269, 13.175, 14.802, 15.864, 16.906, 18.776, 20.430, and 25.496; more preferably characteristic peaks at 6.551, 8.392, 9.269, 13.175, 14.802, 15.864, 16.906, 18.776, 20.430, 22.211, 22.922, 23.574, 25.496, and 26.290; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 4.

8. Crystal form D of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction

pattern expressed with diffraction angle 2θ has characteristic peaks at 5.281, 10.292, 13.322, and 21.390; preferably characteristic peaks at 5.281, 9.912, 10.292, 10.961, 13.322, 21.390, 22.215, 23.979, 25.029, and 25.846; more preferably characteristic peaks at 5.281, 9.912, 10.292, 10.961, 11.613, 13.322, 15.351, 18.283, 19.214, 21.390, 22.215, 23.471, 23.979, 25.029, 25.846, 27.918, and 30.121; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 5.

9. Crystal form E of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 6.821, 10.035, 12.653, 13.727, and 14.787; preferably characteristic peaks at 6.821, 10.035, 12.653, 13.727, 14.787, 16.081, 16.648, 18.571, 20.151, and 22.204; more preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 6.

10. Crystal form F of a tromethamine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 7.674, 10.614, 16.400, and 18.645; preferably characteristic peaks at 6.777, 7.674, 10.614, 11.594, 14.408, 14.882, 16.400, and 18.645; more preferably characteristic peaks at 6.777, 7.674, 10.614, 11.594, 13.671, 14.408, 14.882, 16.400, 18.645, 20.849, 21.384, 21.731, 22.108, 24.721, 26.169, and 29.192; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 7.

11. A method for preparing the crystal form A, B, C, D, or E according to any one of claims 4 to 10, the method comprising (a) mixing compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, tromethamine and a solvent, and dissolving the mixture by means of stirring or heating, and (b) crystallization.

12. Crystal form α of a potassium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 9.564, 11.515, 14.683, 19.607, and 20.391; preferably characteristic peaks at 9.564, 11.515, 14.683, 16.058, 18.859, 19.607, 20.391, 22.592, 23.320, and 25.176; more preferably characteristic peaks at 9.564, 11.515, 14.683, 16.058, 17.033, 18.859, 19.607, 20.391, 21.064, 22.592, 23.320, 24.449, 25.176, 25.933, 27.080, and 27.708; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 8.

13. Crystal form I of a sodium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 5.257, 5.806, 6.795, 10.106, 12.203, and 20.693; preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 9.

14. Crystal form II of a sodium salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 9.754, 11.731, and 19.730; more preferably characteristic peaks at 5.574, 9.754, 11.731, 14.856, 16.091, 19.730, and 22.670; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 10.

15. Crystal form I of a meglumine salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 5.498, 11.013, 14.626,

and 17.942; preferably characteristic peaks at 5.498, 8.901, 11.013, 14.626, 17.942, 19.454, 22.668, and 25.696; more preferably characteristic peaks at 5.498, 8.314, 8.901, 11.013, 11.891, 12.810, 14.626, 15.683, 15.931, 17.942, 18.748, 19.454, 20.393, 21.419, 22.234, 22.668, 23.391, 24.739, and 25.696; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 11.

16. Crystal form I of a p-toluenesulfonate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 5.453, 5.884, 8.063, 12.925, 16.071, and 19.778; preferably characteristic peaks at 5.453, 5.884, 8.063, 12.925, 13.825, 15.399, 16.071, 18.231, 19.778, and 21.917; more preferably characteristic peaks at 5.453, 5.884, 8.063, 12.925, 13.825, 15.399, 16.071, 16.560, 17.066, 18.231, 19.778, 20.861, 21.917, 23.898, and 26.744; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 12.

17. Crystal form I of a tartrate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 12.810, 18.824, 21.890, and 24.472; preferably characteristic peaks at 12.810, 14.448, 15.604, 18.824, 20.410, 21.890, and 24.472; more preferably characteristic peaks at 9.342, 10.132, 10.858, 11.272, 12.810, 14.448, 15.604, 18.824, 20.410, 21.890, 24.472, and 27.880; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 13.

18. Crystal form α of a malate salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2θ has characteristic peaks at 10.050, 14.508, 15.693, 18.924, and 20.240; preferably characteristic peaks at 10.050, 10.818, 11.213, 12.871, 14.508, 15.693, 18.924,

20.240, 21.829, and 24.396; more preferably characteristic peaks at 9.364, 10.050, 10.818, 11.213, 12.871, 13.774, 14.508, 15.693, 17.760, 18.924, 20.240, 21.829, 24.396, 26.200, 27.936, and 28.188; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2θ is as shown in FIG. 14.

19. Crystal form I of a hydrochloride salt of compound 2-((4-((*S*)-3-(4-chloro-2-fluorophenyl)-2,3-dihydrobenzo[*b*][1,4]dioxan-5-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[*d*]imidazole-6-carboxylic acid, wherein an X-ray powder diffraction pattern expressed with diffraction angle 2*θ* has characteristic peaks at 9.939, 14.333, 14.933, 17.523, 18.480, and 20.134; preferably characteristic peaks at 9.939, 13.123, 13.649, 14.333, 14.933, 16.616, 17.523, 18.480, 19.378, 20.134, 20.988, 26.399, and 26.970; more preferably characteristic peaks at 9.939, 12.267, 13.123, 13.649, 14.333, 14.933, 16.616, 17.523, 18.480, 19.378, 20.134, 20.988, 22.377, 23.002, 24.477, 25.322, 26.399, 26.970, 27.609, 30.822, and 33.760; most preferably, the X-ray powder diffraction pattern expressed with diffraction angle 2*θ* is as shown in FIG. 15.

20. The crystal form according to any one of claims 5 to 19, wherein the error range of the 2*θ* value is ± 0.2.

21. A pharmaceutical composition comprising the pharmaceutically acceptable salt according to claim 1 or 2 or the crystal form according to any one of claims 5 to 20, and optionally a pharmaceutically acceptable excipient.

22. A method for preparing a pharmaceutical composition, the method comprising a step of mixing the crystal form according to any one of claims 5 to 20 with a pharmaceutically acceptable excipient.

23. Use of the crystal form according to any one of claims 5 to 20 or the composition according to claim 21 in the preparation of a medicament for treating or preventing a disease associated with GLP-1 receptor.

24. Use of the crystal form according to any one of claims 5 to 20 or the composition according to claim 21 in the preparation of a medicament for treating or preventing diabetes.