

SALT AND CRYSTAL FORM OF CYCLOALKENE COMPOUND, AND PREPARATION METHOD THEREFOR AND USE THEREOF

FIELD OF THE INVENTION

[0001] The present disclosure belongs to the field of biomedicine, and specifically relates to a salt and crystal form of a cycloalkene compound, and a preparation method therefor and the use thereof.

BACKGROUND OF THE INVENTION

[0002] Diabetes mellitus is a common endocrine metabolic disease, which causes metabolic disorders due to various reasons and leads to multi-system and multi-organ damage. The incidence rate is high. There are about 425 million diabetic patients worldwide. The incidence rate of diabetes in China is about 10%, of which type II diabetes accounts for 90%, and the incidence rate is still increasing, and the age of onset is becoming increasingly younger.

[0003] Currently, there are many types of drugs on the market for the treatment of type 2 diabetes, including insulin, biguanides, glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase (DPP-IV) inhibitors, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, α -glucosidase inhibitors, etc., among which GLP-1 receptor agonists are the most concerned.

[0004] GLP-1 is a peptide-based hormone secreted by human intestinal L cells. Its receptors are distributed in pancreatic islet cells, various gastrointestinal cells, central nervous system and peripheral nervous system neurons. After activation, GLP-1 receptors have physiological effects such as promoting insulin secretion, inhibiting glucagon secretion, suppressing appetite and delaying gastric emptying. Clinical evidence shows that compared with other hypoglycemic drugs, GLP-1 receptor agonists have better hypoglycemic effects and are not prone to side effects such as hypoglycemia. In addition, it has additional cardiovascular benefits, and can reduce food intake and delay gastric emptying, which is conducive to weight control.

[0005] The GLP-1 receptor agonists currently on the market are all polypeptide-based drugs, most of which require subcutaneous administration, and patient compliance is poor, while the bioavailability of oral polypeptides is very low. Therefore, there is a great clinical demand for the development of oral small molecule GLP-1 receptor agonists.

[0006] At present, no small molecule GLP-1 receptor agonists have been approved. 3 small molecule GLP-1 receptor agonists have entered the clinical research stage, such as PF-06882961

and PF-07081532 developed by Pifzer, and TTP273 developed by vTv, which are currently in the clinical phase I/II research stage. Among them, PF-06882961 showed significant hypoglycemic and weight-reducing effects in early clinical trials, and its safety is similar to that of peptide-based GLP-1 receptor agonists. It is expected to provide more treatment options for patients with diabetes, obesity, and NASH in the future.

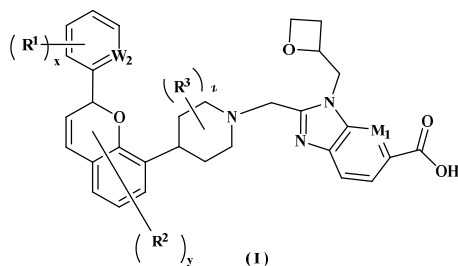
[0007] There is a huge clinical demand for GLP-1 receptor agonists. Oral small molecule GLP-1 receptor agonists with lower cost and better compliance have the potential to treat a variety of metabolic diseases and have broad market prospects.

[0008] PCT/CN2022/110017 discloses the structures of a series of polycyclic compounds of cycloalkene derivatives. In subsequent research and development, in order to make the product easy to handle, filter and dry, and to find a suitable crystal that is easy to store and has long-term stability, the present disclosure conducts a comprehensive study on the salt form of the above-mentioned compounds.

SUMMARY OF THE INVENTION

[0009] All contents involved in patent PCT/CN2022/110017 are added to the present disclosure by reference.

[0010] The purpose of the present disclosure is to provide an base salt of a compound as represented by general formula (I) or a stereoisomer thereof, wherein the structure of the compound is as represented by formula (I):



wherein:

each R^1 is independently selected from hydrogen, deuterium, fluorine, chlorine, cyano, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} deuterioalkoxy or C_{1-3} haloalkoxy; preferably, hydrogen, deuterium, fluorine, chlorine, methoxy or $-OCD_3$;

each R^2 is independently selected from hydrogen, deuterium, fluorine, chlorine, cyano, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} deuterioalkoxy or C_{1-3} haloalkoxy; preferably hydrogen, deuterium, fluorine, chlorine or methyl;

each R^3 is independently selected from hydrogen, deuterium or fluorine; preferably hydrogen;

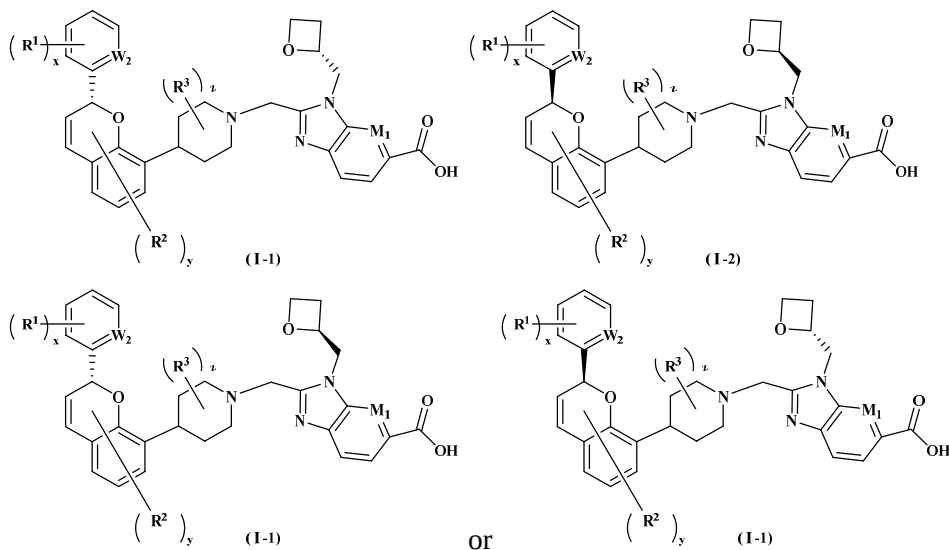
M_1 is N or CH; preferably CH;

W₂ is N or CH; preferably CH;

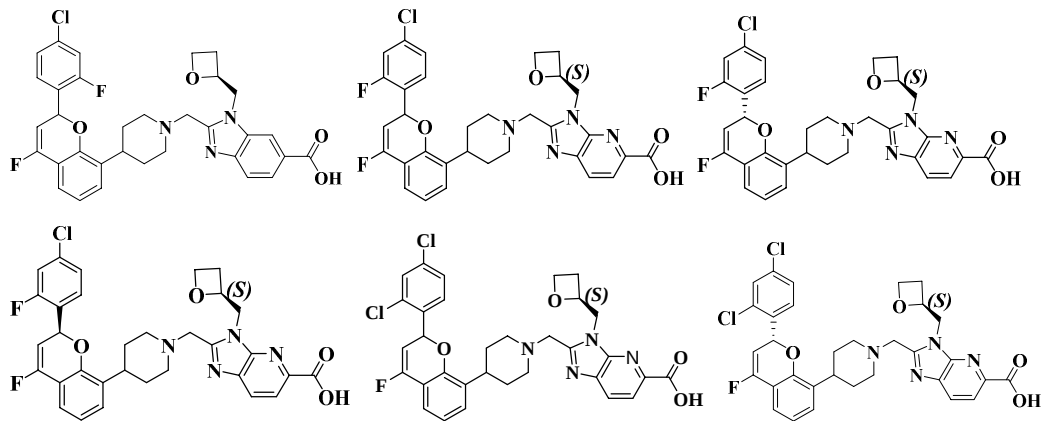
x, y and z are each independently 0, 1 or 2;

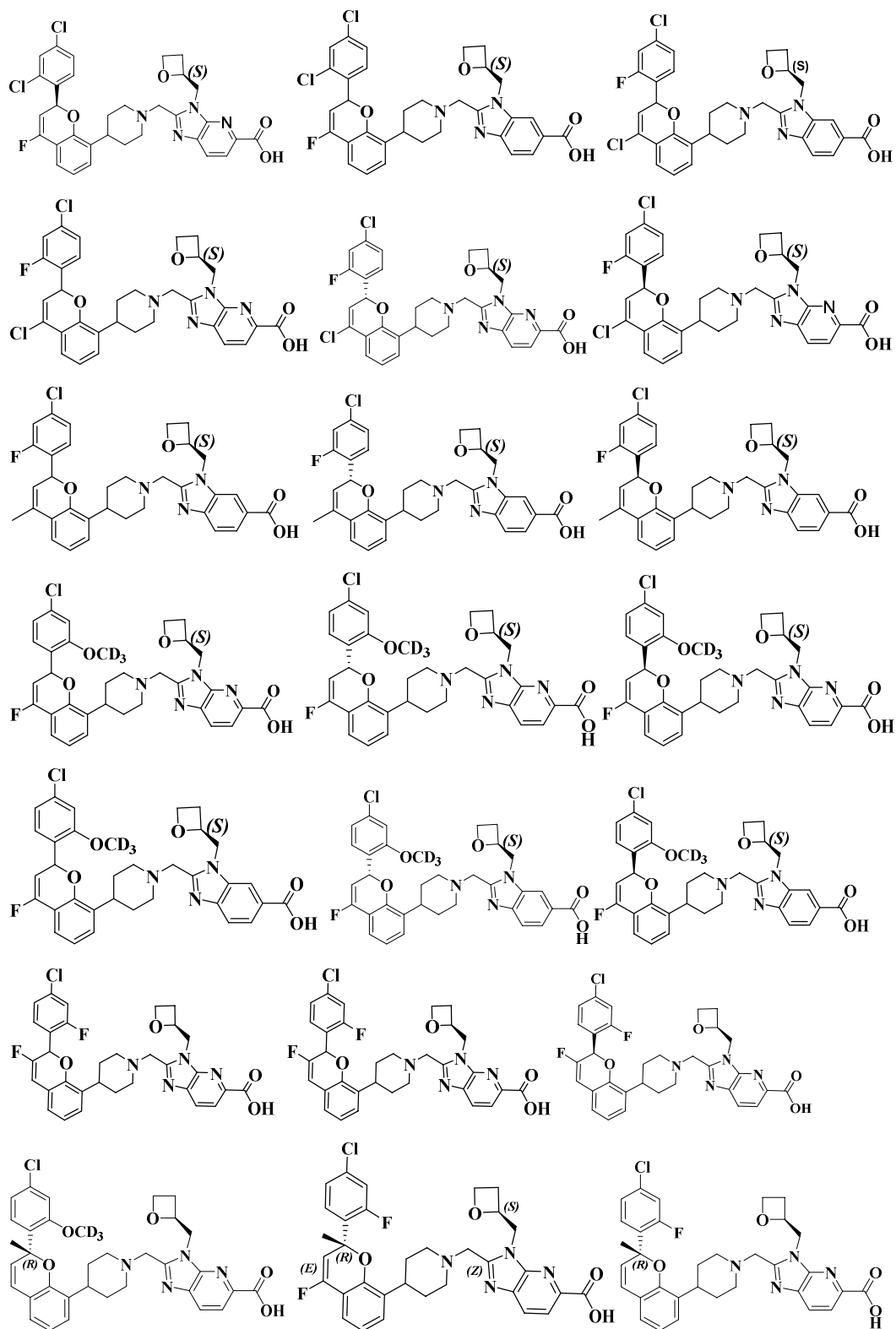
wherein the base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; and the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof.

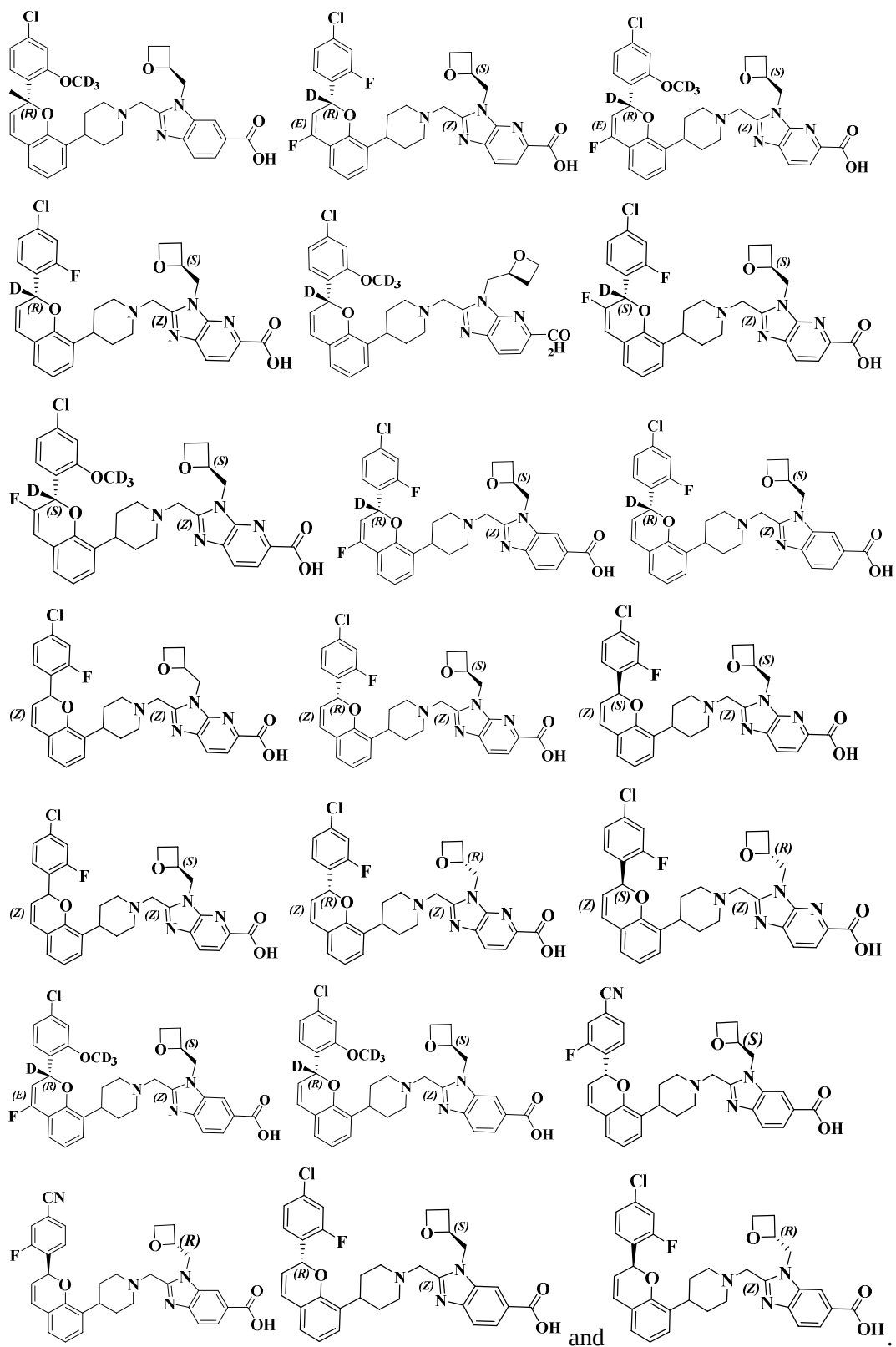
[0011] In further preferred certain embodiments of the present disclosure, the compound is further as represented by the following general formula (I-1) - (I-4):



[0012] In certain embodiments of the present disclosure, the general formula (I) is selected from the following compounds:







wherein the base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine,

or a mixture thereof; and the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, or a mixture thereof.

[0013] In a preferred embodiment of the present disclosure, a base salt of a compound of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid or a stereoisomer thereof is provided, wherein the compound or the stereoisomer thereof and base salt are tromethamine salt.

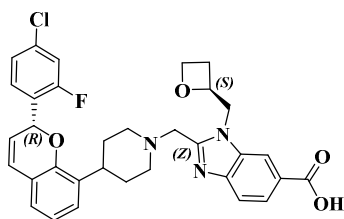
[0014] In a further preferred embodiment of the present disclosure, the number of the base is 0.5-3, preferably 0.5, 1, 1.5, 2, 2.5 or 3, further preferably 0.5, 1, 2 or 3, and even further preferably 1.

[0015] In certain embodiments of the present disclosure, the crystal form is a crystal form of the salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, wherein the crystal form is an anhydrous crystal form.

[0016] In certain embodiments of the present disclosure, the crystal form is a crystal form of the salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, wherein the crystal form is a hydrate containing 0.2 to 3 waters, preferably 0.5 water, 1 water, 2 waters or 3 waters.

[0017] In certain embodiments of the present disclosure, the water molecules of the hydrate are channel water or crystal water.

[0018] In a preferred embodiment of the present disclosure, a base salt of a compound of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid or a stereoisomer thereof is provided, wherein the compound has a structure as follows:



[0019] In certain embodiments of the present disclosure, the crystal form is the crystal form A of the tromethamine salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid, where: the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has a characteristic peak at 2θ of $7.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $9.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $11.6\pm 0.2^\circ$, or has a

characteristic peak at 2θ of $14.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $19.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $22.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $23.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $25.1\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ .

[0020] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has a characteristic peak at one or more of 2θ of $7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$ or $15.1\pm0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, $20.0\pm0.2^\circ$, $20.5\pm0.2^\circ$ or $21.1\pm0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ; for example:

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $15.1\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $18.7\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $19.3\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $20.5\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $20.0\pm0.2^\circ$;

$9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$, $15.1\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $18.7\pm0.2^\circ$, $20.0\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $19.3\pm0.2^\circ$, $20.5\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$, $20.5\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $19.3\pm0.2^\circ$, $20.5\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $20.0\pm0.2^\circ$, $21.1\pm0.2^\circ$;

$9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.1\pm0.2^\circ$;

$7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$, $14.5\pm0.2^\circ$, $15.1\pm0.2^\circ$, $18.7\pm0.2^\circ$;

7.7±0.2°, 9.8±0.2°, 14.0±0.2°, 14.5±0.2°, 18.7±0.2°, 19.3±0.2°;
 7.7±0.2°, 9.8±0.2°, 14.0±0.2°, 18.7±0.2°, 19.3±0.2°, 20.0±0.2°;
 7.7±0.2°, 9.8±0.2°, 14.0±0.2°, 19.3±0.2°, 20.5±0.2°, 21.1±0.2°;
 7.7±0.2°, 9.8±0.2°, 14.5±0.2°, 18.7±0.2°, 20.5±0.2°, 21.1±0.2°;
 7.7±0.2°, 9.8±0.2°, 14.0±0.2°, 19.3±0.2°, 20.5±0.2°, 21.1±0.2°;
 7.7±0.2°, 14.0±0.2°, 14.5±0.2°, 19.3±0.2°, 20.0±0.2°, 21.1±0.2°;
 9.8±0.2°, 14.0±0.2°, 14.5±0.2°, 18.7±0.2°, 19.3±0.2°, 21.1±0.2°;

more preferably, the X-ray powder diffraction pattern thereof optionally also has a diffraction peak at one or more of 2θ of 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 18.0±0.2°, 20.5±0.2° or 22.6±0.2°; preferably at any 2 to 4, or any 5 or 6 of the above-mentioned 2θ, and further preferably at any 4 or 6 of the above-mentioned 2θ; for example:

10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 18.0±0.2°;
 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 20.5±0.2°;
 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 22.6±0.2°;
 10.8±0.2°, 11.6±0.2°, 18.0±0.2°, 20.5±0.2°;
 11.6±0.2°, 14.5±0.2°, 18.0±0.2°, 20.5±0.2°;
 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 18.0±0.2°, 20.5±0.2°;
 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 20.5±0.2°, 22.6±0.2°;
 10.8±0.2°, 11.6±0.2°, 14.5±0.2°, 18.0±0.2°, 20.5±0.2°, 22.6±0.2°;

[0021] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has characteristic peaks at 2θ of 9.8±0.2° and 14.0±0.2°; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 7.7±0.2° and 15.1±0.2°; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 18.7±0.2°, 19.3±0.2°, 20.0±0.2° and 21.1±0.2°; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 14.5±0.2° and 20.5±0.2°; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of 10.8±0.2°, 11.6±0.2°, 18.0±0.2° and 22.6±0.2°.

[0022] In certain embodiments of the present disclosure, by using Cu-Kα radiation, the X-ray characteristic diffraction peaks represented by 2θ angles and interplanar spacing d values are shown in Table 1.

Table 1

Serial No.	XRPD ray diffraction data of the crystal form A of tromethamine salt			
	2θ (±0.2 °)	d value	Peak height	Proportion (I%)

1	7.73	11.4281	580	76.5
2	9.819	9.0002	736	97.1
3	10.771	8.2072	202	26.6
4	11.584	7.6329	226	29.8
5	12.883	6.866	49	6.5
6	13.993	6.3237	758	100
7	14.527	6.0926	335	44.2
8	14.824	5.9708	138	18.2
9	15.065	5.8759	577	76.1
10	15.877	5.5773	101	13.3
11	16.467	5.3789	60	7.9
12	17.928	4.9436	190	25.1
13	18.74	4.7312	369	48.7
14	19.344	4.5848	562	74.1
15	19.952	4.4464	518	68.3
16	20.542	4.32	340	44.9
17	20.81	4.265	101	13.3
18	21.132	4.2006	409	54
19	21.698	4.0924	80	10.6
20	22.633	3.9254	228	30.1
21	23.258	3.8213	53	7
22	23.661	3.7572	192	25.3
23	24.821	3.5841	144	19
24	25.102	3.5446	238	31.4
25	25.674	3.4669	180	23.7
26	26.036	3.4195	78	10.3
27	26.852	3.3175	78	10.3
28	27.395	3.253	115	15.2
29	27.715	3.2161	92	12.1
30	28.548	3.1241	47	6.2
31	28.716	3.1063	67	8.8
32	31.449	2.8422	45	5.9
33	32.729	2.734	72	9.5

34	35.727	2.5111	46	6.1
35	39.274	2.2921	46	6.1

[0023] The crystal form A of tromethamine salt of the compound of the present disclosure has an X-ray powder diffraction pattern substantially as shown in FIG. 1, a DSC pattern substantially as shown in FIG. 2, and a TGA pattern substantially as shown in FIG. 3.

[0024] In certain embodiments of the present disclosure, the crystal form is the crystal form B of tromethamine salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid. The X-ray powder diffraction pattern of the crystal form B of tromethamine salt has a characteristic peak at 2θ of $8.2\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $12.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $16.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $16.2\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $19.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.9\pm 0.2^\circ$, or has a characteristic peak at 2θ of $21.9\pm 0.2^\circ$, or has a characteristic peak at 2θ of $22.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $22.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $24.7\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ .

[0025] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form B of tromethamine salt has a characteristic peak at one or more of 2θ of $10.1\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$ or $21.9\pm 0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $8.2\pm 0.2^\circ$, $12.3\pm 0.2^\circ$, $14.8\pm 0.2^\circ$, $19.7\pm 0.2^\circ$, $20.5\pm 0.2^\circ$ or $22.1\pm 0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ; for example:

$10.1\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$;

$10.1\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$, $21.9\pm 0.2^\circ$;

$8.2\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$, $21.9\pm 0.2^\circ$;

$10.1\pm 0.2^\circ$, $12.3\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$;

$10.1\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $14.8\pm 0.2^\circ$, $18.7\pm 0.2^\circ$;

$10.1\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $18.7\pm 0.2^\circ$, $19.7\pm 0.2^\circ$;

$10.1\pm 0.2^\circ$, $12.3\pm 0.2^\circ$, $14.4\pm 0.2^\circ$, $21.9\pm 0.2^\circ$;

$10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $18.7\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$, $22.1\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$, $22.1\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $19.7\pm0.2^\circ$, $22.1\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $10.1\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $21.9\pm0.2^\circ$;
 $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $21.9\pm0.2^\circ$, $22.1\pm0.2^\circ$;
 $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.4\pm0.2^\circ$, $14.8\pm0.2^\circ$, $18.7\pm0.2^\circ$, $22.1\pm0.2^\circ$;

more preferably, the X-ray powder diffraction pattern thereof optionally also has a diffraction peak at one or more of 2θ of $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $19.7\pm0.2^\circ$ or $20.9\pm0.2^\circ$; preferably at any 2 to 4, or any 5 or 6 of the above-mentioned 2θ , and further preferably at any 4 or 6 of the above-mentioned 2θ ; for example:

$12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $20.9\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $20.9\pm0.2^\circ$;
 $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, , $19.7\pm0.2^\circ$, $20.9\pm0.2^\circ$;
 $12.3\pm0.2^\circ$, $16.0\pm0.2^\circ$, $16.2\pm0.2^\circ$, $18.3\pm0.2^\circ$, $19.7\pm0.2^\circ$, $20.9\pm0.2^\circ$;

[0026] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form B of tromethamine salt has characteristic peaks at 2θ of $10.1\pm0.2^\circ$ and $14.4\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $18.7\pm0.2^\circ$ and $21.9\pm0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has

characteristic peaks at 2θ of $8.2\pm 0.2^\circ$, $14.8\pm 0.2^\circ$, $20.5\pm 0.2^\circ$ and $22.1\pm 0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $12.3\pm 0.2^\circ$ and $19.7\pm 0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $16.0\pm 0.2^\circ$, $16.2\pm 0.2^\circ$, $18.3\pm 0.2^\circ$ and $20.9\pm 0.2^\circ$.

[0027] In certain embodiments of the present disclosure, by using Cu-K α radiation, the X-ray characteristic diffraction peaks represented by 2θ angles and interplanar spacing d values are shown in Table 2.

Table 2

Serial No.	XRPD ray diffraction data of the crystal form B of tromethamine salt			
	2θ ($\pm 0.2^\circ$)	d value	Peak height	Proportion (I%)
1	8.198	10.7767	551	50
2	10.059	8.7865	770	69.8
3	12.307	7.1859	305	27.7
4	14.397	6.1471	1103	100
5	14.847	5.9618	570	51.7
6	15.964	5.5472	172	15.6
7	16.163	5.4792	154	14
8	16.405	5.3991	79	7.2
9	17.198	5.1517	90	8.2
10	17.536	5.0531	111	10.1
11	17.721	5.0008	106	9.6
12	18.267	4.8525	150	13.6
13	18.679	4.7464	639	57.9
14	19.731	4.4958	274	24.8
15	20.542	4.3201	551	50
16	20.869	4.2532	249	22.6
17	21.881	4.0586	752	68.2
18	22.085	4.0216	556	50.4
19	22.362	3.9724	124	11.2
20	23.134	3.8415	92	8.3
21	23.51	3.7809	79	7.2
22	24.7	3.6014	149	13.5
23	26.219	3.3962	60	5.4

24	27.053	3.2933	71	6.4
25	29.789	2.9967	90	8.2
26	32.987	2.7132	50	4.5
27	33.377	2.6823	63	5.7
28	34.286	2.6132	44	4

[0028] The crystal form B of tromethamine salt of the compound of the present disclosure has an X-ray powder diffraction pattern substantially as shown in FIG. 4, and a DSC pattern substantially as shown in FIG. 5.

[0029] In certain embodiments of the present disclosure, the crystal form is the crystal form C of tromethamine salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid. The X-ray powder diffraction pattern of the crystal form C of tromethamine salt has a characteristic peak at 2θ of $3.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $7.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $9.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $13.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $16.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $16.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $19.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $19.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $21.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $22.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $23.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $26.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $28.3\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ .

the X-ray powder diffraction pattern of the crystal form C of tromethamine salt has a characteristic peak at one or more of 2θ of $3.6\pm 0.2^\circ$, $7.1\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $14.1\pm 0.2^\circ$ or $16.0\pm 0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $15.0\pm 0.2^\circ$, $16.5\pm 0.2^\circ$, $17.1\pm 0.2^\circ$, $17.6\pm 0.2^\circ$, $19.7\pm 0.2^\circ$ or $20.8\pm 0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ;

$3.6\pm 0.2^\circ$, $7.1\pm 0.2^\circ$, $9.7\pm 0.2^\circ$;

$3.6\pm 0.2^\circ$, $7.1\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $14.1\pm 0.2^\circ$;

$3.6\pm 0.2^\circ$, $7.1\pm 0.2^\circ$, $9.7\pm 0.2^\circ$, $14.1\pm 0.2^\circ$;

$3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $15.0\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $16.5\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.0\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.0\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.5\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.0\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.5\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $16.0\pm0.2^\circ$, $17.1\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$;
 $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $16.0\pm0.2^\circ$, $17.1\pm0.2^\circ$, $20.8\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.0\pm0.2^\circ$, $17.1\pm0.2^\circ$, $20.8\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.1\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $16.5\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$, $20.8\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$, $20.8\pm0.2^\circ$;
 $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $14.1\pm0.2^\circ$, $15.0\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $20.8\pm0.2^\circ$;
more preferably, the X-ray powder diffraction pattern thereof optionally also has a diffraction peak at one or more of 2θ of $13.5\pm0.2^\circ$, $17.1\pm0.2^\circ$, $19.0\pm0.2^\circ$, $19.7\pm0.2^\circ$, $21.8\pm0.2^\circ$ or $26.4\pm0.2^\circ$; preferably at any 2 to 4, or any 5 or 6 of the above-mentioned 2θ , and further preferably at any 4 or 6 of the above-mentioned 2θ ; for example:
 $13.5\pm0.2^\circ$, $17.1\pm0.2^\circ$, $19.0\pm0.2^\circ$, $19.7\pm0.2^\circ$;

13.5±0.2°, 17.1±0.2°, 19.0±0.2°, 21.8±0.2°;
 13.5±0.2°, 17.1±0.2°, 19.0±0.2°, 26.4±0.2°;
 17.1±0.2°, 19.0±0.2°, 21.8±0.2°, 26.4±0.2°;
 13.5±0.2°, 17.1±0.2°, 19.0±0.2°, 21.8±0.2°, 26.4±0.2°;
 13.5±0.2°, 17.1±0.2°, 19.0±0.2°, 19.7±0.2°, 21.8±0.2°;
 17.1±0.2°, 19.0±0.2°, 19.7±0.2°, 21.8±0.2°, 26.4±0.2°;
 13.5±0.2°, 17.1±0.2°, 19.0±0.2°, 19.7±0.2°, 21.8±0.2°, 26.4±0.2°;

[0030] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form C of tromethamine salt has characteristic peaks at 2θ of 3.6±0.2° and 7.1±0.2°; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 9.7±0.2° and 14.1±0.2°; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 15.0±0.2°, 16.0±0.2°, 16.5±0.2°, 17.6±0.2° and 20.8±0.2°; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 17.1±0.2° and 19.7±0.2°; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of 13.5±0.2°, 19.0±0.2°, 21.8±0.2° and 26.4±0.2°;

[0031] In certain embodiments of the present disclosure, by using Cu-Kα radiation, the X-ray characteristic diffraction peaks represented by 2θ angles and interplanar spacing d values are shown in Table 3.

Table 3

XRPD ray diffraction data of the crystal form C of tromethamine salt	
Serial No.	2θ (±0.2 °)
1	3.638
2	7.059
3	9.72
4	10.57
5	13.506
6	14.077
7	14.951
8	15.964
9	16.512
10	17.138
11	17.605
12	18.942

13	19.672
14	20.846
15	21.781
16	22.327
17	23.121
18	23.603
19	26.361
20	28.328
21	29.445
22	29.746
23	31.937
24	32.498
25	35.67

[0032] The crystal form C of tromethamine salt of the compound of the present disclosure has an X-ray powder diffraction pattern substantially as shown in FIG. 6, a DSC pattern substantially as shown in FIG. 7, and a TGA pattern substantially as shown in FIG. 8.

[0033] In certain embodiments of the present disclosure, the crystal form C of tromethamine salt is an anhydrate crystal form.

[0034] In certain embodiments of the present disclosure, the crystal form is the crystal form D of tromethamine salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid. The X-ray powder diffraction pattern of the crystal form D of tromethamine salt has a characteristic peak at 2θ of $7.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $7.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $9.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $11.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $13.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.9\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $19.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $21.2\pm 0.2^\circ$, or has a characteristic peak at 2θ of $21.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $23.3\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ .

[0035] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form D of tromethamine salt has a characteristic peak at one or more of 2θ of $7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$ or $14.0\pm 0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $7.7\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$, $19.3\pm 0.2^\circ$ or $20.0\pm 0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ; for example:

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $17.9\pm 0.2^\circ$;

$9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$;

$7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $19.3\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $17.9\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $18.8\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$;

$9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$;

$7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $19.3\pm 0.2^\circ$, $20.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $18.8\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $18.8\pm 0.2^\circ$, $20.0\pm 0.2^\circ$;

$7.4\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$, $20.0\pm 0.2^\circ$;

$9.8\pm 0.2^\circ$, $13.1\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$;

$7.7\pm 0.2^\circ$, $9.8\pm 0.2^\circ$, $14.0\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $20.0\pm 0.2^\circ$;

more preferably, the X-ray powder diffraction pattern thereof optionally also has a diffraction peak at one or more of 2θ of $14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $19.3\pm 0.2^\circ$ or $21.2\pm 0.2^\circ$;

preferably at any 2 to 4, or any 5 or 6 of the above-mentioned 2θ , and further preferably at any 4 or 6 of the above-mentioned 2θ ; for example:

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $19.3\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $21.2\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $21.2\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $19.3\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $19.3\pm 0.2^\circ$, $21.2\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $21.2\pm 0.2^\circ$;

$14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $19.3\pm 0.2^\circ$, $21.2\pm 0.2^\circ$;

[0036] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form D of tromethamine salt has characteristic peaks at 2θ of $9.8\pm 0.2^\circ$ and $14.0\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $7.4\pm 0.2^\circ$ and $13.1\pm 0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $7.7\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $18.8\pm 0.2^\circ$ and $20.0\pm 0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $17.9\pm 0.2^\circ$ and $19.3\pm 0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $14.5\pm 0.2^\circ$, $15.4\pm 0.2^\circ$, $15.8\pm 0.2^\circ$ and $21.2\pm 0.2^\circ$.

[0037] In certain embodiments of the present disclosure, by using Cu-K α radiation, the X-ray characteristic diffraction peaks represented by 2θ angles and interplanar spacing d values are shown in Table 4.

Table 4

Serial No.	XRPD ray diffraction data of the crystal form D of tromethamine salt			
	$2\theta (\pm 0.2^\circ)$	d value	Peak height	Proportion (I%)
1	7.351	12.0165	238	51.6
2	7.746	11.4043	214	46.4
3	9.835	8.9855	318	69
4	10.773	8.2057	128	27.8
5	11.582	7.6342	107	23.2
6	13.144	6.7301	280	60.7
7	13.978	6.3305	461	100
8	14.542	6.0863	199	43.2
9	14.809	5.9769	104	22.6

10	15.051	5.8816	225	48.8
11	15.437	5.7354	151	32.8
12	15.778	5.6121	216	46.9
13	16.406	5.3986	98	21.3
14	17.87	4.9594	229	49.7
15	18.758	4.7267	271	58.8
16	19.346	4.5844	220	47.7
17	19.971	4.4423	264	57.3
18	20.511	4.3265	201	43.6
19	21.235	4.1806	215	46.6
20	21.782	4.0769	166	36
21	22.653	3.922	125	27.1
22	23.323	3.8108	176	38.2
23	23.664	3.7567	111	24.1
24	24.587	3.6178	65	14.1
25	25.138	3.5396	116	25.2
26	25.675	3.4668	117	25.4
27	26.424	3.3702	76	16.5
28	27.418	3.2503	65	14.1
29	27.735	3.2138	55	11.9
30	28.78	3.0994	51	11.1

[0038] The crystal form D of tromethamine salt of the compound of the present disclosure has an X-ray powder diffraction pattern substantially as shown in FIG. 9, and a DSC pattern substantially as shown in FIG. 10.

[0039] In certain embodiments of the present disclosure, the crystal form is the crystal form E of tromethamine salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid. The X-ray powder diffraction pattern of the crystal form E of tromethamine salt has a characteristic peak at 2θ of $4.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $6.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $8.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $9.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $13.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $17.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of

18.9±0.2°, or has a characteristic peak at 2θ of 20.2±0.2°, or has a characteristic peak at 2θ of 20.5±0.2°, or has a characteristic peak at 2θ of 21.4±0.2°, or has a characteristic peak at 2θ of 21.9±0.2°, or has a characteristic peak at 2θ of 22.4±0.2°, or has a characteristic peak at 2θ of 23.4±0.2°, or has a characteristic peak at 2θ of 23.9±0.2°, or has a characteristic peak at 2θ of 25.2±0.2°; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ.

[0040] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form E of tromethamine salt has a characteristic peak at one or more of 2θ of 4.3±0.2°, 6.3±0.2°, 13.6±0.2° or 18.9±0.2°; preferably at 2 to 4 of the above-mentioned 2θ, more preferably at 3 or 4 of the above-mentioned 2θ, and most preferably at 4 of the above-mentioned 2θ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of 8.6±0.2°, 14.1±0.2°, 17.7±0.2°, 20.2±0.2°, 20.5±0.2° or 22.4±0.2°, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ; for example:

4.3±0.2°, 6.3±0.2°, 13.6±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°;

4.3±0.2°, 6.3±0.2°, 8.6±0.2°, 13.6±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 14.1±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 17.7±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°;

4.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°;

6.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°;

6.3±0.2°, 13.6±0.2°, 14.1±0.2°, 17.7±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°, 20.2±0.2°;

4.3±0.2°, 6.3±0.2°, 8.6±0.2°, 13.6±0.2°, 18.9±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 17.7±0.2°, 18.9±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°, 20.2±0.2°;

4.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°;

6.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°, 20.2±0.2°;

6.3±0.2°, 13.6±0.2°, 14.1±0.2°, 17.7±0.2°, 18.9±0.2°, 20.2±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°, 20.2±0.2°, 20.5±0.2°;

4.3±0.2°, 6.3±0.2°, 8.6±0.2°, 13.6±0.2°, 18.9±0.2°, 20.5±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°, 20.5±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 17.7±0.2°, 18.9±0.2°, 20.2±0.2°;

4.3±0.2°, 6.3±0.2°, 13.6±0.2°, 18.9±0.2°, 20.2±0.2°, 20.5±0.2°;
 4.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°, 20.2±0.2°;
 6.3±0.2°, 8.6±0.2°, 13.6±0.2°, 14.1±0.2°, 18.9±0.2°, 22.4±0.2°;
 6.3±0.2°, 13.6±0.2°, 14.1±0.2°, 17.7±0.2°, 18.9±0.2°, 22.4±0.2°;
 more preferably, the X-ray powder diffraction pattern thereof optionally also has a diffraction peak at one or more of 2θ of 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 20.5±0.2°, 21.4±0.2° or 21.9±0.2°; preferably at any 2 to 4, or any 5 or 6 of the above-mentioned 2θ, and further preferably at any 4 or 6 of the above-mentioned 2θ; for example:

9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 20.5±0.2°;
 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 21.4±0.2°;
 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 21.9±0.2°;
 9.3±0.2°, 18.5±0.2°, 20.5±0.2°, 21.4±0.2°;
 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 20.5±0.2°, 21.4±0.2°;
 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 21.4±0.2°, 21.9±0.2°;
 14.1±0.2°, 18.5±0.2°, 20.5±0.2°, 21.4±0.2°, 21.9±0.2°;
 9.3±0.2°, 14.1±0.2°, 18.5±0.2°, 20.5±0.2°, 21.4±0.2°, 21.9±0.2°;

[0041] In certain embodiments of the present disclosure, the X-ray powder diffraction pattern of the crystal form E of tromethamine salt has characteristic peaks at 2θ of 6.3±0.2° and 13.6±0.2°; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 4.3±0.2° and 18.9±0.2°; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 8.6±0.2°, 17.7±0.2°, 20.2±0.2° and 22.4±0.2°; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of 14.1±0.2° and 20.5±0.2°; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of 9.3±0.2°, 18.5±0.2°, 21.4±0.2° and 21.9±0.2°.

[0042] In certain embodiments of the present disclosure, by using Cu-Kα radiation, the X-ray characteristic diffraction peaks represented by 2θ angles and interplanar spacing d values are shown in Table 5.

Table 5

Serial No.	XRPD ray diffraction data of the crystal form E of tromethamine salt			
	2θ (±0.2 °)	d value	Peak height	Proportion (I%)
1	4.284	20.6084	249	90.2
2	6.315	13.9837	268	97.1
3	8.579	10.2983	110	39.9

4	9.267	9.5358	61	22.1
5	13.648	6.4829	276	100
6	14.094	6.2787	95	34.4
7	17.722	5.0006	131	47.5
8	18.515	4.7882	99	35.9
9	18.859	4.7016	192	69.6
10	20.177	4.3974	172	62.3
11	20.503	4.3281	109	39.5
12	21.41	4.1468	85	30.8
13	21.878	4.0591	81	29.3
14	22.448	3.9573	175	63.4
15	23.383	3.8012	88	31.9
16	23.872	3.7244	104	37.7
17	25.167	3.5357	57	20.7

[0043] The crystal form E of tromethamine salt of the compound of the present disclosure has an X-ray powder diffraction pattern substantially as shown in FIG. 11, and a DSC pattern substantially as shown in FIG. 12.

[0044] In a further preferred embodiment of the present disclosure, the above-mentioned crystal form is a solvent-containing crystal form, wherein the solvent is selected from water, methanol, acetone, ethyl acetate, acetonitrile, ethanol, 88% acetone, 2-methyl-tetrahydrofuran, dichloromethane, 1,4-dioxane, benzene, toluene, isopropanol, n-butanol, isobutanol, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, n-propanol, tert-butanol, 2-butanone, 3-pentanone, n-heptane, ethyl formate, isopropyl acetate, cyclohexane, methyl tert-butyl ether or isopropyl ether.

[0045] In a further preferred embodiment of the present disclosure, wherein the number of the solvents is 0.2-3, preferably 0.2, 0.5, 1, 1.5, 2, 2.5 or 3, more preferably 0.5, 1, 2 or 3.

[0046] The present disclosure further provides a method for preparing the compound as represented by general formula (I) or the stereoisomer and base salt thereof, which specifically comprises the following steps:

- 1) weighing an appropriate amount of a free acid and dissolving the free acid in a good solvent;
- 2) weighing an appropriate amount of a counter-ion base and dissolving the counter-ion base in an organic solvent; wherein the amount of the counter-ion base is preferably 1.0 to 1.5 equivalents;

3) combining the above two solutions, and stirring the combined solution to allow precipitation, or dropwise adding a poor solvent followed by the stirring to allow precipitation; and
4) subjecting the mixture to rapid centrifugation or standing to evaporate to dryness so as to obtain a target product;

wherein:

the good solvent is selected from acetone, tetrahydrofuran, ethyl formate, ethyl acetate, 2-methyl-tetrahydrofuran, 2-butanone, n-butanol, 1,4-dioxane, isobutanol, N,N-dimethylformamide, N,N-dimethylacetamide, n-propanol or tert-butanol; preferably 2-methyl-tetrahydrofuran, ethyl acetate, 2-butanone, acetone or ethyl formate;

the organic solvent is selected from methanol, ethanol, ethyl acetate, dichloromethane, acetone, n-hexane, petroleum ether, benzene, toluene, chloroform, acetonitrile, carbon tetrachloride, dichloroethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, 2-butanone, 3-pentanone, heptane, methyl tert-butyl ether, isopropyl ether, 1,4-dioxane, tert-butanol, or N,N-dimethylformamide; preferably methanol, ethanol, or acetonitrile; the above good solvent and organic solution must be miscible when used;

the poor solvent is selected from heptane, methyl tert-butyl ether, cyclohexane, toluene, isopropyl ether, and ethyl acetate; preferably methyl tert-butyl ether and isopropyl ether;

the counter-ion base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; preferably, diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, or a mixture thereof; further preferably, tromethamine; the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof, preferably sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or a mixture thereof.

[0047] The present disclosure further provides a method for preparing the compound as represented by general formula (I) or the stereoisomer and base salt thereof, which specifically comprises the following steps:

1) weighing an appropriate amount of a free acid, and suspending the free acid with a poor solvent;

2) weighing an appropriate amount of a counter-ion base and dissolving the counter-ion base in an organic solvent; wherein the amount of the counter-ion base is preferably 1.0 to 1.5 equivalents;

3) combining the above two solutions and stirring the combined solution to allow dissolution, followed by continue stirring;

4) subjecting the mixture to rapid centrifugation or standing to evaporate to dryness so as to obtain a target product;

wherein:

the poor solvent is selected from ethanol, ethyl acetate, ethyl formate, isopropanol, isopropyl acetate, methyl tert-butyl ether, dichloromethane, methanol, acetonitrile, chlorobenzene, benzene, toluene, n-butanol, isobutanol or 3-pentanone; preferably, ethanol, ethyl acetate, isopropanol and isopropyl acetate.

the organic solvent is selected from methanol, ethanol, ethyl acetate, dichloromethane, acetone, n-hexane, petroleum ether, benzene, toluene, chloroform, acetonitrile, carbon tetrachloride, dichloroethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, 2-butanone, 3-pentanone, heptane, methyl tert-butyl ether, isopropyl ether, 1,4-dioxane, tert-butanol, or N,N-dimethylformamide; preferably methanol, ethanol, or acetonitrile; the above good solvent and organic solution must be miscible when used;

the counter-ion base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; preferably, diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, or a mixture thereof; further preferably, tromethamine; the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof, preferably sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or a mixture thereof.

[0048] The present disclosure further provides a method for preparing the compound as represented by general formula (I) or the stereoisomer and base salt thereof, which specifically comprises the following steps:

1) weighing an appropriate amount of the base salt of the compound, and suspending the base salt with a poor solvent preferably at a suspension density of 50-200 mg/mL;

2) shaking the obtained suspension at a certain temperature for a certain time, preferably at a temperature of 25-50°C for preferably 1-15 days;

3) quickly centrifuging the suspension obtained above, removing a supernatant, placing a remaining solid in a vacuum drying oven and drying to a constant weight to afford a target product;

wherein:

the poor solvent is selected from dichloromethane, 1,4-dioxane, acetonitrile, chlorobenzene, benzene, toluene, acetone, ethyl acetate, water, 88% acetone, isopropyl acetate, 3-pentanone, ethyl formate, tetrahydrofuran, 2-methyl-tetrahydrofuran, isopropanol, n-butanol, isobutanol, n-propanol, methyl tert-butyl ether, n-heptane, tert-butanol or 2-butanone.

[0049] Another objective of the present disclosure is to provide a pharmaceutical composition comprising a therapeutically-effective amount of the above-mentioned compound or a stereoisomer and salt thereof, and one or more pharmaceutically acceptable carriers, diluents or excipients.

[0050] In the embodiments provided by the present disclosure, the pharmaceutical composition comprises a therapeutically effective amount of the base salt of the crystal form thereof, wherein the therapeutically effective amount is selected from 0.0001-99%, 0.0001-95%, 0.0001-90%, 0.0001-85%, 0.0001-80%, 0.0001-75%, 0.0001-70%, 0.001-60%, 0.001-55%, 0.01-50%, 0.01-40%, 0.01-30%, 0.01-20%, 0.01-10% or 0.01-5%.

[0051] The present disclosure further relates to any of the compound of general formula, the stereoisomer or pharmaceutically acceptable salt thereof, or the use of the pharmaceutical composition in the preparation of GLP-1 receptor agonist drugs.

[0052] The present disclosure further relates to the use of the compound as represented by the general formula, the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a drug for treating metabolism related diseases, wherein the metabolism related diseases are selected from diabetes, obesity or non-alcohol steatohepatitis related diseases or other related diseases caused by diabetes, obesity or non-alcoholic steatohepatitis.

[0053] The present disclosure further relates to the method of the compound as represented by general formula, or the stereoisomer or pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof in the preparation of a drug for treating metabolic diseases and related diseases.

[0054] The present disclosure further relates to a method for preventing and/or treating metabolism related diseases, which comprises administering to the patient a therapeutically

effective dose of the compound as represented by the general formula, the stereoisomers or pharmaceutically acceptable salts thereof, or the pharmaceutical composition thereof.

[0055] The present disclosure further provides a method for treating a disease condition with the compound or pharmaceutical composition of the present disclosure. The disease condition includes, but is not limited to, conditions related to GLP-1 receptor regulator.

[0056] The present disclosure further relates to a method for treating metabolism related diseases in mammals, comprising administering to the mammal a therapeutically effective amount of the compound of the present disclosure, or the pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof.

Brief Description of the Drawings

[0057] FIG. 1 is an XRPD diagram of crystal form A of tromethamine salt.

[0058] FIG. 2 is an DSC diagram of crystal form A of tromethamine salt.

[0059] FIG. 3 is an TGA diagram of crystal form A of tromethamine salt.

[0060] FIG. 4 is an XRPD diagram of crystal form B of tromethamine salt.

[0061] FIG. 5 is an DSC diagram of crystal form B of tromethamine salt.

[0062] FIG. 6 is an XRPD diagram of crystal form C of tromethamine salt.

[0063] FIG. 7 is an DSC diagram of crystal form C of tromethamine salt.

[0064] FIG. 8 is an TGA diagram of crystal form C of tromethamine salt.

[0065] FIG. 9 is an XRPD diagram of crystal form D of tromethamine salt.

[0066] FIG. 10 is an DSC diagram of crystal form D of tromethamine salt.

[0067] FIG. 11 is an XRPD diagram of crystal form E of tromethamine salt.

[0068] FIG. 12 is an DSC diagram of crystal form E of tromethamine salt.

DETAILED DESCRIPTION OF THE INVENTION

[0069] Unless stated to the contrary, the terms used in the description and claims have the following meanings.

[0070] In the present disclosure, alkyl refers to a saturated aliphatic hydrocarbon group, which is a straight or branched group containing 1 to 20 carbon atoms, preferably alkyl containing 1 to 8 carbon atoms, more preferably alkyl containing 1 to 6 carbon atoms, and most preferably alkyl containing 1 to 3 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2-ethylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl,

2,3-dimethylbutyl, n-heptyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 2-ethylpentyl, 3-ethylpentyl, n-octyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, n-nonyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2,2-diethylpentyl, n-decyl, 3,3-diethylhexyl, 2,2-diethylhexyl, and various branched isomers thereof, etc.

[0071] Alkyl can be substituted or unsubstituted. When the alkyl is substituted, the substituent can be substituted at any available connection point, and the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, oxo, carboxyl or a carboxylate group. In the present disclosure, alkyl is preferably methyl, ethyl, isopropyl, tert-butyl, haloalkyl, deuterioalkyl, alkoxy-substituted alkyl and hydroxyl-substituted alkyl; and the hydroxyl-substituted alkyl can be 2-hydroxyisopropyl or 1-hydroxyethyl.

[0072] In the present disclosure, alkoxy refers to -O-(alkyl) and -O-(unsubstituted cycloalkyl), wherein alkyl is as defined above, preferably alkyl containing 1 to 8 carbon atoms, more preferably alkyl containing 1 to 6 carbon atoms, and most preferably alkyl containing 1 to 3 carbon atoms. Non-limiting examples of alkoxy include: methoxy, ethoxy, propoxy, butoxy, cyclopropoxy, cyclobutoxy, cyclopentoxy, and cyclohexoxy. Alkoxy can be optionally substituted or unsubstituted. When the alkoxy is substituted, the substituent is preferably one or more of groups independently selected from alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylamino, halogen, mercapto, hydroxyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkoxy, heterocycloalkoxy, cycloalkylthio, heterocycloalkylthio, carboxyl or a carboxylate group.

[0073] Non-limiting examples of alkoxy also include: prop-2-oxy, etc.

[0074] In the present disclosure, "haloalkyl" refers to alkyl substituted with one or more halogen, wherein alkyl is defined as above. Non-limiting examples of haloalkyl include: trifluoromethyl and trifluoroethyl.

[0075] Non-limiting examples of haloalkyl also include: difluoromethyl, 1,1,2,2-tetrafluoroethyl, perfluoroethyl, etc.

[0076] In the present disclosure, haloalkoxy refers to alkoxy substituted with one or more halogen, wherein alkoxy is defined as above.

- [0077] The haloalkoxy can be fully halogenated or partially halogenated, and the number of halo can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc. Halogen is preferably F, Cl, Br, or I. For example, haloalkoxy can be trifluoromethoxy, difluoromethoxy, 1,1,2,2-tetrafluoroethoxy, perfluoroethoxy, etc.
- [0078] In the present disclosure, hydroxyalkyl refers to alkyl substituted with hydroxyl, wherein alkyl is defined as above.
- [0079] In the present disclosure, haloalkyl refers to alkyl substituted with one or more halogen, wherein alkyl is defined as above.
- [0080] In the present disclosure, haloalkoxy refers to alkoxy substituted with one or more halogen, wherein alkoxy is defined as above.
- [0081] "Hydroxyl" refers to an -OH group.
- [0082] "Halogen" refers to fluorine, chlorine, bromine, or iodine.
- [0083] "Amino" refers to -NH₂.
- [0084] "Cyano" refers to -CN.
- [0085] "Nitro" refers to -NO₂.
- [0086] "THF" refers to tetrahydrofuran.
- [0087] "EtOAc" refers to ethyl acetate.
- [0088] "DMSO" refers to dimethyl sulfoxide.
- [0089] "LDA" refers to lithium diisopropylamide.
- [0090] "DMAP" refers to 4-dimethylaminopyridine.
- [0091] "EtMgBr" refers to ethyl magnesium bromide.
- [0092] "HOSu" refers to N-hydroxysuccinimide.
- [0093] "EDCl" refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.
- [0094] "IPA" refers to isopropanol.
- [0095] "MeOH" refers to methanol.
- [0096] "EtOH" refers to ethanol.
- [0097] "Acetone" refers to acetone.
- [0098] "MEK" refers to butanone.
- [0099] "2-Me-THF" refers to 2-methyltetrahydrofuran.
- [0100] "BuOH" refers to butanol.
- [0101] "Dioxane" refers to dioxane.
- [0102] "DMF" refers to N, N-dimethylformamide.
- [0103] "DIPEA" refers to N,N-diisopropylethylamine.
- [0104] "HEPES" refers to 4-hydroxyethylpiperazine ethanesulfonic acid.

- [0105] "Tris" refers to tromethamine.
- [0106] Different terms such as "X is selected from A, B, or C", "X is selected from A, B and C", "X is A, B or C", and "X is A, B and C" all express the same meaning, that is, X can be any one or more of A, B, and C.
- [0107] "Optional" or "optionally" means that the event or circumstance subsequently described may but need not to occur, and the description includes the occasion where the event or circumstance occurs or does not occur.
- [0108] "Substituted" means that one or more hydrogen atoms, preferably at most 5, more preferably 1-3 hydrogen atoms in the group are each independently substituted with a corresponding number of substituents. It goes without saying, the substituents may be only in possible chemical positions thereof, and those skilled in the art can determine the possible or impossible substitutions (by experiment or theory) without paying too much effort. For example, the amino or a hydroxyl having free hydrogen may be unstable when combined the carbon atoms having an unsaturated (e.g., olefinic) bond.
- [0109] "Stereoisomerism" comprises three types, geometric isomerism (cis-trans isomerism), optical isomerism, and conformational isomerism.
- [0110] As used herein, the names of compounds are intended to encompass all possible isomeric forms, including stereoisomers of the compounds (e.g., enantiomers, diastereomers, racemates or racemic mixtures and any mixtures thereof).
- [0111] The hydrogen atoms of the present disclosure can be replaced with the isotope deuterium thereof, and any hydrogen atom in the example compounds involved in the present disclosure can also be replaced with a deuterium atom.
- [0112] "Pharmaceutical composition" denotes a mixture containing one or more compounds described herein or physiologically/pharmaceutically acceptable salts or prodrug thereof and other chemical components, as well as other components, such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of pharmaceutical compositions is to facilitate administration to living organisms and facilitate the absorption of active ingredients to exert biological activity.
- [0113] X-ray powder diffraction pattern (XRPD) refers to the experimentally observed diffraction pattern or the parameters derived therefrom. The X-ray powder diffraction pattern is characterized by the peak position (abscissa) and the peak intensity (ordinate). Those skilled in the art will appreciate that the experimental error depends on the conditions of the instrument, the preparation of the sample and the purity of the sample. In particular, it is well known to those skilled in the art that the X-ray diffraction pattern often changes with the conditions of the

instrument, and those skilled in the art should understand that the appropriate error tolerance of XRPD can be: $2\theta \pm 0.5^\circ$; $2\theta \pm 0.4^\circ$; $2\theta \pm 0.3^\circ$; or $2\theta \pm 0.2^\circ$. In particular, it should be noted that the relative intensity of the X-ray diffraction pattern may also change with experimental conditions, and thus the order of peak intensity cannot be used as the only or decisive factor. In addition, due to the influence of experimental factors such as sample height, peak angles may shift as a whole, and a certain shift is usually allowed. Therefore, those skilled in the art will appreciate that any crystal form having the characteristic peak identical or similar to those of the pattern of the present disclosure falls within the scope of the present disclosure.

[0114] "TGA" refers to thermogravimetric analysis (TGA) experiment.

[0115] "DSC" refers to differential scanning calorimetry (DSC) experiment.

[0116] "HPLC" refers to high performance liquid chromatography (HPLC) experiment.

[0117] "PK" refers to pharmacokinetic (PK) experiment.

[0118] "KF" refers to Karl Fischer moisture measurement (KF) experiment.

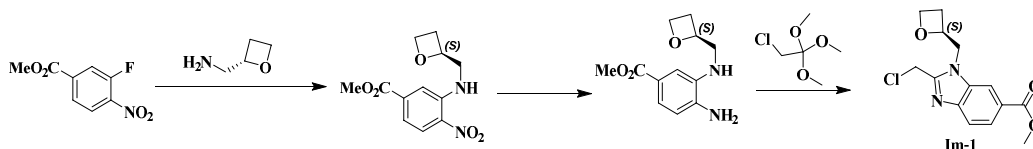
[0119] The present disclosure will be further described below in conjunction with examples, but these examples are not meant to limit the scope of the present disclosure.

Example

[0120] The following examples are used to explain the present disclosure, but these examples should not be considered to limit the scope of the present disclosure. If the specific conditions of the experimental method are not specifically illustrated in the examples of the present disclosure, the conventional conditions or recommended conditions of the raw material and product manufacturers are generally followed. Reagents without specific source designation are commercially available conventional reagents.

Intermediate Im-1

Synthesis of (methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate)



Step 1

Methyl (S)-4-nitro-3-((oxetan-2-ylmethyl)amino)benzoate

[0121] In a 50 mL reaction bottle, 3-fluoro-4-(1-((6-(piperidin-4-yl)pyridin-2-yl)oxo)cyclopropyl)benzonitrile (2 g, 10.04 mmol), K_2CO_3 (2.78 g, 20.08 mmol) were dissolved in tetrahydrofuran (30 mL), and then (S)-oxetan-2-ylmethylamine (874 mg, 10.04 mmol) was added, and the reaction liquid was stirred at room temperature for 12 h. After the reaction was

stopped, water (20 mL) was added to quench the reaction, and the obtained mixture was extracted with ethyl acetate (15 mL $\times$ 2). The combined organic phases were washed with saturated sodium chloride (10 mL), dried over anhydrous sodium sulfate, and filtered, and the resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product methyl (S)-4-nitro-3-((oxetan-2-ylmethyl)amino)benzoate (2.0 mg, yellow solid), yield: 74.8%.

[0122] MS m/z (ESI): 267.0 [M+1].

Step 2

Methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate

[0123] Methyl (S)-4-nitro-3-((oxetan-2-ylmethyl)amino)benzoate (3 g, 11.27 mmol) was dissolved in methanol (30 mL), and then 10% Pd/C (300 mg) was added. The obtained mixture was subjected to hydrogen replacement three times, and reacted under stirring for 3 h. The reaction liquid was filtered, and the organic phase was dried and then dried by rotary evaporation to obtain the title product methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (2.6 g, yellow solid), yield: 97.7%.

[0124] MS m/z (ESI): 237.1 [M+1].

Step 3

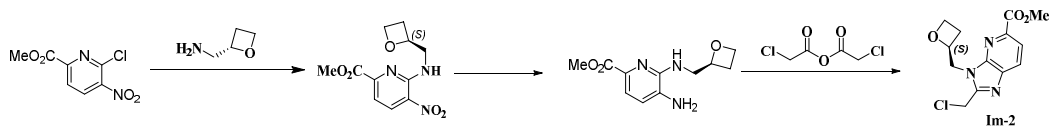
Methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate

[0125] In a 50 mL reaction bottle, methyl (S)-4-amino-3-((oxetan-2-ylmethyl)amino)benzoate (2 g, 8.46 mmol) and p-toluenesulfonic acid (86 mg, 499.41 μ mol) were dissolved in tetrahydrofuran (100 mL), and then 2-chloro-1,1,1-trimethoxyethane (1.3 g, 8.41 mmol) was added. The reaction liquid was stirred at 60°C for 1 h. After the reaction was stopped, the reaction liquid was cooled to room temperature and concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product methyl (S)-2-(chloromethyl)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylate (Im-1) (1.3 g, yellow solid), yield: 52.0%.

[0126] MS m/z (ESI): 295.0 [M+1].

Intermediate Im-2

Synthesis of (methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-d]pyridine-5-carboxylate)



Step 1

Methyl (S)-5-nitro-6-((oxetan-2-ylmethyl)amino)2-picolinate

[0127] Methyl 6-chloro-5-nitro-2-picolinate was used as the raw material and step 1 of intermediate Im-1 was referenced to obtain the title product methyl (S)-5-nitro-6-((oxetan-2-ylmethyl)amino)2-picolinate.

[0128] MS m/z (ESI): 268.1 [M+1].

Step 2

Methyl (S)-5-amino-6-((oxetan-2-ylmethyl)amino)2-picolinate.

[0129] Methyl (S)-5-nitro-6-((oxetan-2-ylmethyl)amino)2-picolinate was used as the raw material and step 2 of intermediate Im-1 was referenced to obtain the title product methyl (S)-5-amino-6-((oxetan-2-ylmethyl)amino)2-picolinate.

[0130] MS m/z (ESI): 238.1 [M+1].

Step 3

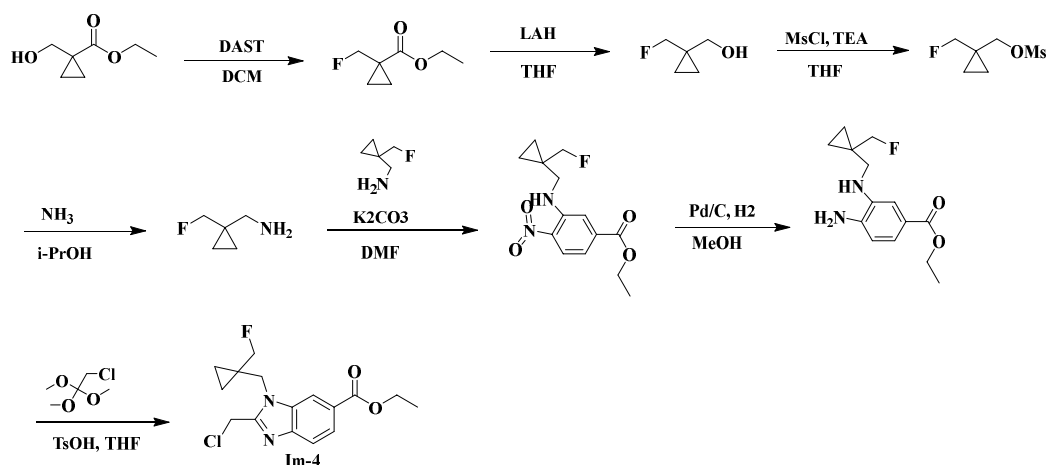
(methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-d]pyridine-5-carboxylate

[0131] At room temperature, methyl (S)-5-amino-6-((oxetan-2-ylmethyl)amino)2-picolinate (340 mg, 1.43 mmol) was dissolved in tetrahydrofuran (5 mL), and then a solution of chloroacetic anhydride (257.27 mg, 1.50 mmol) in tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred at room temperature for 30 minutes, then heated to 60°C, reacted for 2 h, cooled to room temperature, and LCMS indicated that the reaction was completed. The reaction liquid was diluted with ethyl acetate (30 mL), then washed with saturated sodium bicarbonate solution (15 mL × 3), washed with saturated sodium chloride solution (15 mL × 3), and the organic phase was dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to obtain the title product (methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-d]pyridine-5-carboxylate (Im-2) (yellow oil, 0.4 g), yield: 94.4%, the crude product was directly used for the next step.

[0132] MS m/z (ESI): 296.1 [M+1].

Intermediate Im-3

Synthesis of ethyl 2-(chloromethyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate



Step 1

Ethyl 1-(fluoromethyl)cyclopropane-1-carboxylate

[0133] Ethyl 1-(hydroxymethyl)cyclopropylcarboxylate (7 g, 48.55 mmol) was dissolved in DCM (100 mL), and DAST (8.61 g, 53.41 mmol) was added thereto at -78°C. The reaction system was naturally warmed to room temperature and stirred for 16 h. After the reaction was completed, 50 mL of water was added thereto, and the obtained mixture was extracted with dichloromethane (50 mL × 2), washed with saturated sodium chloride solution (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated to obtain the title product ethyl 1-(fluoromethyl)cyclopropane-1-carboxylate (6.5 g, yellow oil), yield: 91.6%.

[0134] ¹H NMR (400 MHz, CDCl₃): δ 4.52 (dd, 1.5 Hz, 2H), 4.17 (q, 2H), 1.41 – 1.33 (m, 2H), 1.26 (t, 3H), 1.05 – 0.95 (m, 2H).

Step 2

1-(fluoromethyl)cyclopropylmethanol

[0135] Ethyl 1-(fluoromethyl)cyclopropane-1-carboxylate (6.5 g, 44.47 mmol) was dissolved in THF (60 mL), and LiAlH₄ (2.53 g, 66.71 mmol) was added thereto in an ice-water bath. The reaction system was naturally warmed to room temperature and stirred for 16 h. After the reaction was completed, 15 g of sodium sulfate decahydrate was added thereto to quench the reaction, and the mixture was filtered and concentrated to obtain the title product 1-(fluoromethyl)cyclopropylmethanol (3.5 g, yellow oil), yield: 75.6%.

[0136] ¹H NMR (400 MHz, CDCl₃): δ 4.36 (d, 2H), 3.58 (s, 2H), 0.60 (m, 4H).

Step 3

(1-(fluoromethyl)cyclopropyl)methylmethanesulfonate

[0137] 1-(fluoromethyl)cyclopropylmethanol (1.3 g, 12.49 mmol) was dissolved in DCM (30 mL), and methanesulfonyl chloride (1.86 g, 16.23 mmol, 1.26 mL) and triethylamine (2.53 g, 24.97 mmol, 3.48 mL) were added dropwise thereto in an ice-water bath. The reaction system

was stirred at 20°C. After the reaction was completed, saturated NaHCO₃ (10 mL) was added dropwise to quench the reaction, and the obtained mixture was extracted with dichloromethane (20 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated to obtain the crude product (1-

(fluoromethyl)cyclopropyl)methylmethanesulfonate (2.0 g, light yellow oil), yield: 87.0% .

[0138] ¹H NMR (400 MHz, CDCl₃) δ 4.32 (d, 2H), 4.19 (s, 2H), 3.05 (s, 3H), 0.81 – 0.72 (m, 4H).

Step 4

(1-(fluoromethyl)cyclopropyl)methylamine

[0139] (1-(fluoromethyl)cyclopropyl)methylmethanesulfonate (1.0 g, 5.49 mmol) was dissolved in NH₃/i-PrOH (10 mL), and the reaction system was heated at 60°C under a microwave for 6 h. After the reaction was completed, the mixture was concentrated to obtain the title product (1-(fluoromethyl)cyclopropyl)methylamine (600 mg, yellow oil). The crude product was directly used for the next reaction.

Step 5

Ethyl 3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)-4-nitrobenzoate

[0140] Ethyl 3-fluoro-4-nitrobenzoate (1.24 g, 5.82 mmol) was dissolved in DMF (30 mL), and (1-(fluoromethyl)cyclopropyl)methylamine (600 mg, 5.82 mmol) and K₂CO₃ (1.61 g, 11.64 mmol) were added thereto. The reaction system was stirred at 20°C for four h. After the reaction was completed, water (10 mL) was added thereto for dilution, and the obtained mixture was extracted with ethyl acetate (20 mL × 2), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product ethyl 3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)-4-nitrobenzoate (1.2 g, light yellow solid), yield: 69.6%.

[0141] MS m/z (ESI): 297.1 [M+1].

[0142] ¹H NMR (400 MHz, CDCl₃): δ 8.22 (d, 1H), 7.56 (s, 1H), 7.25 (d, 1H), 4.41 (q, 2H), 4.30 (d, 2H), 3.42 (d, 2H), 1.41 (t, 3H), 0.76 (m, 4H).

Step 6

Ethyl 4-amino-3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)benzoate

[0143] Ethyl 3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)-4-nitrobenzoate (1.2 g, 4.05 mmol) was dissolved in MeOH (30 mL), and Pd/C (200 mg, 10% purity) was added thereto. After displacement three times with hydrogen, the reaction system was placed in an 20°C and

stirred for 2 h. After the reaction was completed, the mixture was filtered through diatomaceous earth and the filtrate was concentrated to obtain the title product ethyl 4-amino-3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)benzoate (1.0 g, yellow solid), yield: 92.7%.

[0144] MS m/z (ESI): 267.1 [M+1].

Step 7

Ethyl 2-(chloromethyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate

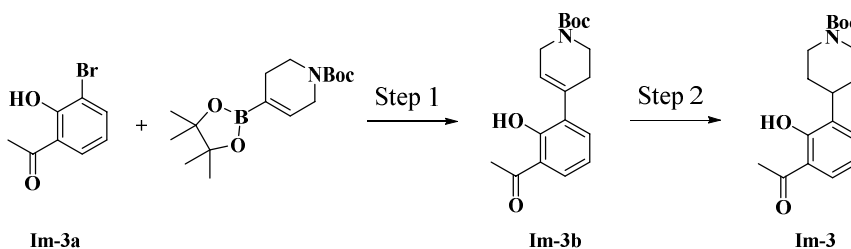
[0145] Ethyl 4-amino-3-(((1-(fluoromethyl)cyclopropyl)methyl)amino)benzoate (1.0 g, 3.76 mmol) was dissolved in MeCN (30 mL), and p-toluenesulfonic acid (193.99 mg, 1.13 mmol) and 2-chloro-1,1,1-trimethoxyethane (1.16 g, 7.51 mmol) were added thereto. The reaction system was stirred in an oil bath at 60°C for 4 h. After the reaction was completed, the mixture was concentrated to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain ethyl 2-(chloromethyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylate (700 mg, yellow solid), yield: 57.4%.

[0146] MS m/z (ESI): 325.1 [M+1].

[0147] ¹H NMR (400 MHz, CDCl₃): δ 8.21 (s, 1H), 8.04(d,1H), 7.81 (d, 1H), 4.97 (s, 2H), 4.47 (s, 2H), 4.44 (q, 2H), 4.03 (d, 2H), 1.43 (t, 3H), 0.92 – 0.82 (m, 4H).

Intermediate Im-4

Tert-butyl-4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate



by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl- 4-(3-acetyl-2-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate **Im-4b** (26 g, colorless oil), yield: 88.1%.

[0149] MS m/z (ESI): 318.1 [M+1].

Step 2

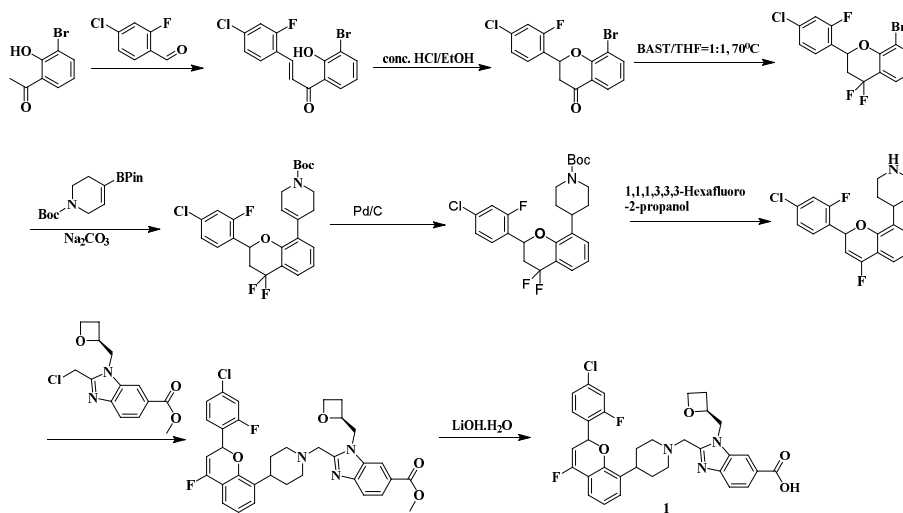
Tert-butyl-4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate

[0150] Tert-butyl-4-(3-acetyl-2-hydroxyphenyl)-3,6-dihydropyridine-1(2H)-carboxylate **Im-4b** (26 g, 0.08 mol) and Pd/C (2.6 g, 10% wt.) were dispersed in methanol (300 mL), hydrogen was introduced 3 times, and air was discharged. The reaction liquid was reacted under stirring for 12 h. After the reaction was stopped, the reaction liquid was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl-4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im-4** (25 g, white solid), yield: 95.6%.

[0151] MS m/z (ESI): 320.1 [M+1].

Example 1

2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



Step 1

(E)-1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one

[0152] Sodium tetraborate decahydrate (45.97 g, 66.50 mmol) was added to a solution of 1-(3-bromo-2-hydroxyphenyl)ethyl ketone (13 g, 60.45 mmol) and 4-chloro-2-fluorobenzaldehyde (10.06 g, 63.48 mmol) in ethanol (125 mL) and water (200 mL), then the mixture was stirred at 90°C for 12 h, cooled, and filtered, and the filter cake was washed with water, and dried to obtain

the title product (*E*)-1-(3-bromo-2-hydroxy-phenyl)-3-(4-chloro-2-fluoro-phenyl)prop-2-en-1-one (20 g, yellow solid), yield: 93.0%.

[0153] MS m/z (ESI): 354.9 [M+1]

Step 2

8-bromo-2-(4-chloro-2-fluoro-phenyl)chroman-4-one

[0154] A solution of (*E*)-1-(3-bromo-2-hydroxy-phenyl)-3-(4-chloro-2-fluoro-phenyl)prop-2-en-1-one (2 g, 5.62 mmol) and concentrated hydrochloric acid (4 mL) in ethanol (10 mL) was stirred at 110°C under microwave conditions for 20 h, and the mixture was cooled, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 8-bromo-2-(4-chloro-2-fluoro-phenyl)chroman-4-one (1.8 g, yellow solid), yield: 90.0%.

[0155] MS m/z (ESI): 355.0 [M+1]

Step 3

8-bromo-2-(4-chloro-2-fluoro-phenyl)-4,4-fifluoro-chromane

[0156] 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-sulfanyl)ethylamine (10 mL) was dropwise added to a solution of 8-bromo-2-(4-chloro-2-fluoro-phenyl)chroman-4-one (1.8 g, 5.06 mmol) in tetrahydrofuran (10 mL), and then the mixture was stirred at 70°C for 12 h and cooled. Water was added to quench the reaction, and the obtained mixture was extracted with dichloromethane (50 mL × 3). The organic phase was washed with saturated sodium bicarbonate solution (50 mL × 2) and saturated sodium chloride solution (50 mL × 2), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 8-bromo-2-(4-chloro-2-fluoro-phenyl)-4,4-fifluoro-chromane (400 mg, yellow solid), yield: 20.9% .

[0157] MS m/z (ESI): 377.0 [M+1]

Step 4

Tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-fifluoro-chroman-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylate

[0158] A mixture of 8-bromo-2-(4-chloro-2-fluoro-phenyl)-4,4-fifluoro-chromane (400 mg, 1.06 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (360.32 mg, 1.17 mmol), sodium carbonate (280.71 mg, 2.65 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium chloride (77.44 mg, 105.94 μmol), 1,4-dioxane (10 mL) and water (2 mL) was stirred at 100°C for 2 h under nitrogen protection, and cooled, and water was added. The obtained mixture was extracted with dichloromethane (10 mL × 2), and the

organic phase was washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-difluoro-chroman-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (450 mg, yellow oil), yield 88.5%.

[0159] MS m/z (ESI): 480.1 [M+1]

Step 5

Tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-difluoro-chroman-8-yl]piperidine-1-carboxylate
[0160] A mixture of tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-difluoro-chroman-8-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (450 mg, 937.66 μmol), palladium on carbon (80 mg, 10%), and ethyl acetate (30 mL) was subjected to hydrogen replacement three times and reacted under stirring for 5 h. The mixture was filtered and dried by rotary evaporation to obtain the title product tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-difluoro-chroman-8-yl]piperidine-1-carboxylate (380 mg, light yellow oil), yield: 84.1%

[0161] MS m/z (ESI): 482.2 [M+1]

Step 6

4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]piperidine

[0162] A mixture of tert-butyl 4-[2-(4-chloro-2-fluoro-phenyl)-4,4-difluoro-chroman-8-yl]piperidine-1-carboxylate (340 mg, 705.49 μmol) and hexafluoroisopropanol (10 mL) was stirred at 80°C under microwave conditions for 4 h and cooled, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]piperidine (40 mg, colorless oil), yield: 15.7%.

[0163] MS m/z (ESI): 362.1 [M+1]

Step 7

Methyl 2-[[4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]-1-piperidinyl]methyl]-3-[[1-(fluoromethyl)cyclopropyl]methyl]benzimidazole-5-carboxylate

[0164] A mixture of 4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]piperidine (40 mg, 110.55 μmol), Im-1 (46.68 mg, 143.72 μmol), potassium carbonate (61.03 mg, 442.22 μmol) and acetonitrile (5 mL) was stirred at 50°C for 3 h, and cooled, and 5 mL of water was added. The obtained mixture was extracted with dichloromethane (20 mL × 3), and the organic phase was washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting

residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product ethyl 2-[[4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]-1-piperidinyl]methyl]-3-[[1-(fluoromethyl)cyclopropyl]methyl]benzimidazole-5-carboxylate (30 mg, colorless oil), yield: 43.7%.

[0165] MS m/z (ESI): 620.2 [M+1]

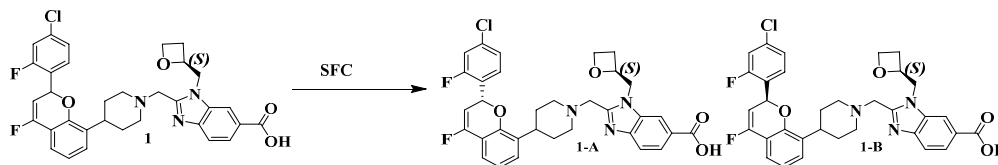
Step 8

2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0166] A mixture of methyl 2-[[4-[2-(4-chloro-2-fluoro-phenyl)-4-fluoro-2H-chromen-8-yl]-1-piperidinyl]methyl]-3-[[1-(fluoromethyl)cyclopropyl]methyl] benzimidazole-5-carboxylate (30 mg, 48.38 μ mol), lithium hydroxide monohydrate (20 mg, 476.62 μ mol), methanol (2 mL), water (2 mL), and tetrahydrofuran (3 mL) was stirred at room temperature for 12 h, formic acid was added to adjust the pH = 6, and the obtained mixture was dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (20 mg, white solid), yield: 68.2%.

[0167] MS m/z (ESI): 606.2 [M+1].

[0168] 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid was subjected to chiral separation to obtain



[0169] 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (1-A)

[0170] MS m/z (ESI): 606.2 [M+1].

[0171] 2-((4-((S)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (1-B)

[0172] MS m/z (ESI): 606.2 [M+1].

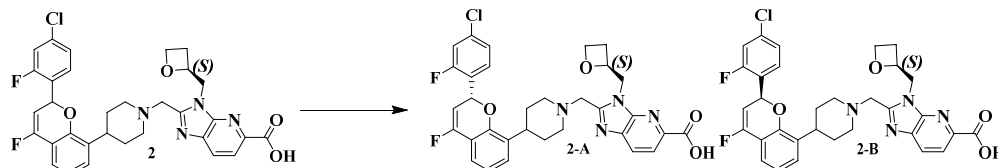
Example 2

2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0173] Im-1 was replaced with Im-2 and example 1 was referenced to obtain 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0174] MS m/z (ESI): 607.2 [M+1].

[0175] 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid was subjected to chiral resolution to obtain



[0176] 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 2-A)

[0177] MS m/z (ESI): 607.2 [M+1].

[0178] 2-((4-((S)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 2-B)

[0179] MS m/z (ESI): 607.2 [M+1].

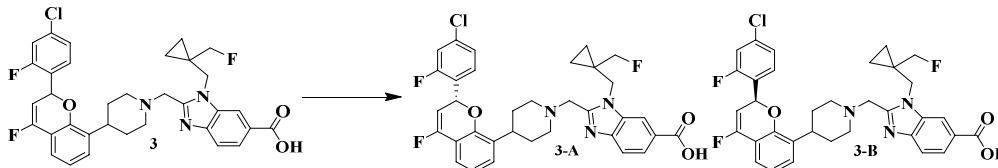
Example 3

2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0180] Im-1 was replaced with Im-3 and example 1 was referenced to obtain 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0181] MS m/z (ESI): 622.2 [M+1].

[0182] 2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid was subjected to chiral separation to obtain



[0183] (R)-2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 3-A)

[0184] MS m/z (ESI): 622.2 [M+1].

[0185] (S)-2-((4-(2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-((1-(fluoromethyl)cyclopropyl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 3-B)

[0186] MS m/z (ESI): 622.2 [M+1].

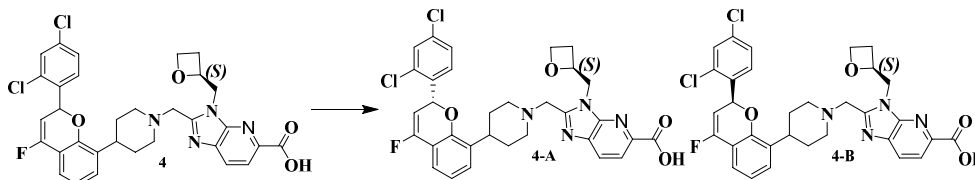
Example 4

2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0187] 4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidine and Im-2 were used as the raw materials, and example 1 was referenced to obtain 2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0188] MS m/z (ESI): 623.2 [M+1].

[0189] 2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid was subjected to chiral separation to obtain



[0190] 2-((4-((R)-2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 4-A)

[0191] MS m/z (ESI): 623.2 [M+1].

[0192] 2-((4-((S)-2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 4-B)

[0193] MS m/z (ESI): 623.2 [M+1].

Example 5

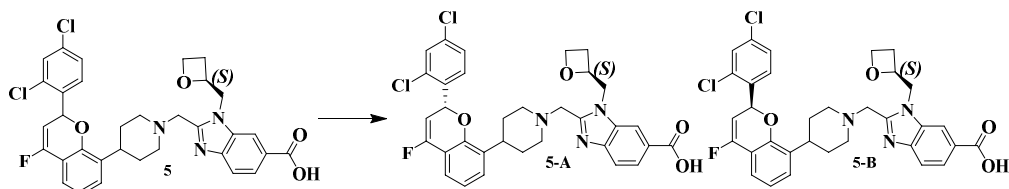
2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0194] 4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidine and Im-1 were used as the raw materials, and example 1 was referenced to obtain 2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-

2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0195] MS m/z (ESI):622.2 [M+1].

[0196] 2-((4-(2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid was subjected to chiral separation to obtain



[0197] 2-((4-((R)-2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 5-A)

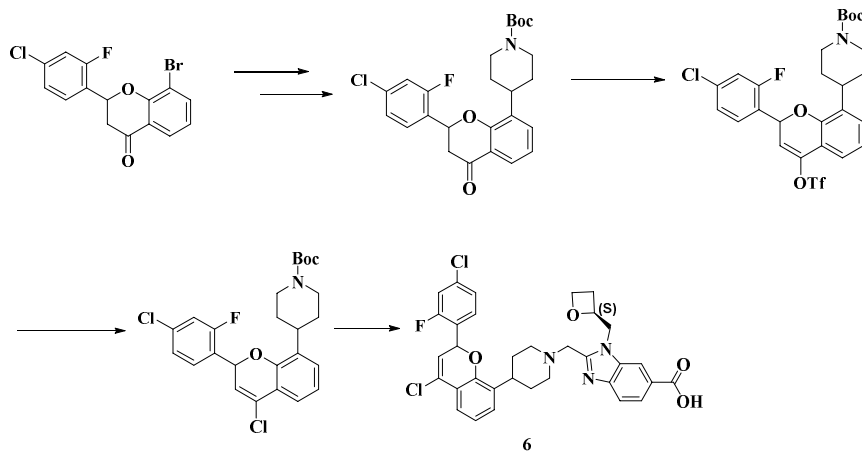
[0198] MS m/z (ESI):622.2 [M+1].

[0199] 2-((4-((S)-2-(2,4-dichlorophenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 5-B)

[0200] MS m/z (ESI):622.2 [M+1].

Example 6

2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



Step 1

Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-carboxychroman-8-yl)piperidine-1-carboxylate

[0201] 8-bromo-2-(4-chloro-2-fluorophenyl)chroman-4-one was used as the raw material, and the step 4 and step 5 of example 1 were referenced to obtain the product tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-carboxychroman-8-yl)piperidine-1-carboxylate.

[0202] MS m/z (ESI): 460.1[M+1].

Step 2

Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-(((trifluoromethyl)sulfonyl)oxo)-2H-chromen-8-yl)piperidine-1-carboxylate

[0203] Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-carboxychroman-8-yl)piperidine-1-carboxylate (1 g, 2.17 mmol) was dissolved in 20 mL of THF, and lithium bistrimethylsilylamide (2.4 mL, 2.40 mmol) was added at -78°C and reacted for 1 h. A solution of 2-[N,Nbis(trifluoromethanesulfonyl)amino]-5-chloropyridine (0.94 g, 2.4 mmol) in THF (20 mL) was added at -78°C, and the mixture was slowly warmed to room temperature and stirred for 5 h. Sodium bicarbonate (10 mL) was added to quench the reaction, and the obtained mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, and then washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-(((trifluoromethyl)sulfonyl)oxo)-2H-chromen-8-yl)piperidine-1-carboxylate (456 mg, yield: 35.5%).

[0204] MS m/z (ESI): 592.1[M+1].

Step 3

Tert-butyl 4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate

[0205] Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-4-(((trifluoromethyl)sulfonyl)oxo)-2H-chromen-8-yl)piperidine-1-carboxylate (0.5 g, 0.84 mmol) was dissolved in 10 mL of DMA/THF (v : v = 1 : 3), and nickel acetate tetrahydrate (24.8 mg, 0.1 mmol), Zn powder (10 mg, 0.16 mmol), 1,5-cyclooctadiene (11 mg, 0.1 mmol) and lithium chloride (53 mg, 1.3 mmol) were added, and the mixture was reacted at room temperature for 16 h under nitrogen protection. Water (10 mL) was added to quench the reaction, and the obtained mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, and then washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain tert-butyl 4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate (241 mg, yield: 60.0%).

[0206] MS m/z (ESI): 478.1[M+1].

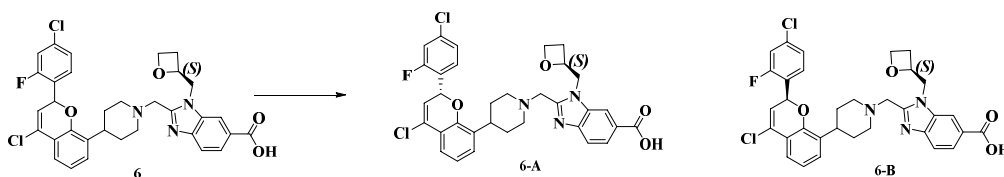
Step 4

2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0207] Tert-butyl 4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate and **Im-1** were used as the raw materials, and the step 6 to step 8 of example 1 were referenced to obtain the product 2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0208] MS m/z (ESI): 622.1[M+1].

[0209] 2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid was subjected to resolution to obtain the product



[0210] 2-((4-((R)-4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 6-A)

[0211] MS m/z (ESI): 622.1[M+1].

[0212] 2-((4-((S)-4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 6-B).

[0213] MS m/z (ESI): 622.1[M+1].

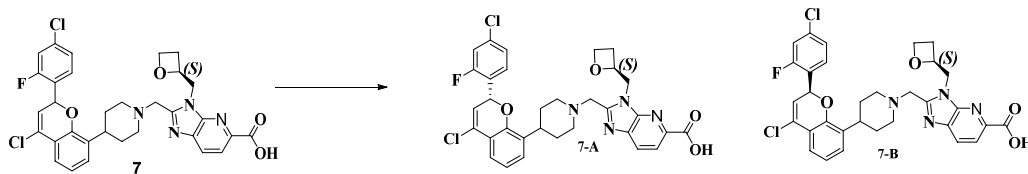
Example 7

2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

[0214] Tert-butyl 4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate and Im-2 were used as the raw materials, and the step 6 to step 8 of example 1 were referenced to obtain the product 2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid.

[0215] MS m/z (ESI): 623.1[M+1].

[0216] 2-((4-(4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid was subjected to resolution to obtain the product



[0217] 2-((4-((*R*)-4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((*S*)-oxetan-2-yl)methyl)-3H-imidazo[4,5-*b*]pyridine-5-carboxylic acid (example 7-A)

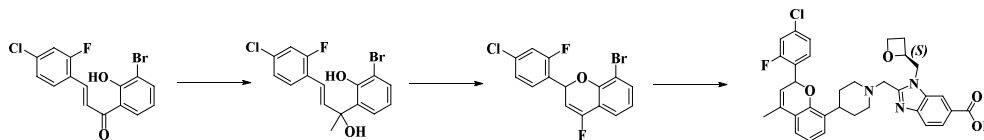
[0218] MS *m/z* (ESI): 623.1[M+1].

[0219] 2-((4-((*S*)-4-chloro-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((*S*)-oxetan-2-yl)methyl)-3H-imidazo[4,5-*b*]pyridine-5-carboxylic acid (example 7-B).

[0220] MS *m/z* (ESI): 623.1[M+1].

Example 8

2-((4-(2-(4-chloro-2-fluorophenyl)-4-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[*d*]imidazole-6-carboxylic acid



Step 1

(*E*)-2-bromo-6-(4-(4-chloro-2-fluorophenyl)-2-hydroxybut-3-ene-2-yl)phenol

[0221] (*E*)-1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one (1 g, 2.81 mmol) was dissolved in 30 mL of THF, methylmagnesium bromide (7 mL, 7 mmol) was added at 0°C, and the mixture was slowly warmed to room temperature and stirred for 3 h. Ammonium chloride (10 mL) was added to quench the reaction, and the obtained mixture was extracted with ethyl acetate (20 mL × 3). The organic phases were combined, and then washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain (*E*)-2-bromo-6-(4-(4-chloro-2-fluorophenyl)-2-hydroxybut-3-ene-2-yl)phenol (831 mg, yield: 79.6%).

[0222] MS *m/z* (ESI): 370.9 [M+1].

Step 2

8-bromo-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromene

[0223] (*E*)-2-bromo-6-(4-(4-chloro-2-fluorophenyl)-2-hydroxybut-3-ene-2-yl)phenol (0.5 g, 1.34 mmol) was dissolved in 15 mL of nitromethane, (2,3,4,5-tetrafluorophenyl)boric acid (52 mg, 0.26 mmol) was added, and the mixture was stirred at 60°C for 16 h. Water (10 mL) was added to quench the reaction, and the obtained mixture was extracted with ethyl acetate (20 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium

sulfate, and concentrated under reduced pressure to obtain a crude product. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain 8-bromo-2-(4-chloro-2-fluorophenyl)-4-fluoro-2*H*-chromene (326 mg, yield: 68.0%).

[0224] MS *m/z* (ESI): 356.9 [M+1].

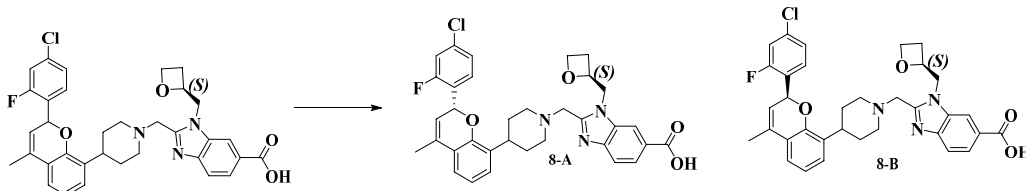
Step 3

2-((4-(2-(4-chloro-2-fluorophenyl)-4-methyl-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[d]imidazole-6-carboxylic acid

[0225] 8-bromo-2-(4-chloro-2-fluorophenyl)-4-fluoro-2*H*-chromene was used as the raw material, and the step 4, step 5, step 7 and step 8 of example 1 were referenced to obtain the product 2-((4-(2-(4-chloro-2-fluorophenyl)-4-methyl-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[d]imidazole-6-carboxylic acid.

[0226] MS *m/z* (ESI): 602.2 [M+1].

[0227] 2-((4-(2-(4-chloro-2-fluorophenyl)-4-methyl-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[d]imidazole-6-carboxylic acid was subjected to resolution to obtain the product



[0228] 2-((4-((*R*)-2-(4-chloro-2-fluorophenyl)-4-methyl-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[d]imidazole-6-carboxylic acid (example 8-A)

[0229] MS *m/z* (ESI): 602.2 [M+1].

[0230] 2-((4-((*S*)-2-(4-chloro-2-fluorophenyl)-4-methyl-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1*H*-benzo[d]imidazole-6-carboxylic acid (example 8-B).

[0231] MS *m/z* (ESI): 602.2 [M+1].

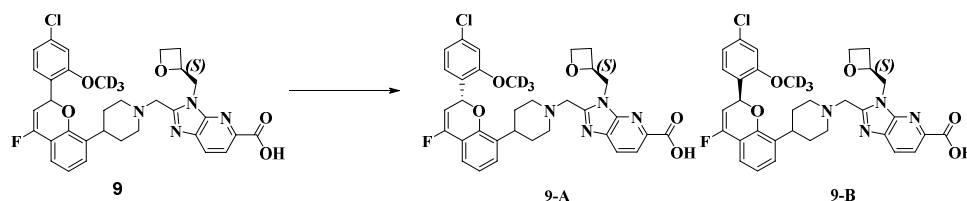
Example 9

2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-3-(((*S*)-oxetan-2-yl)methyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid

[0232] 4-chloro-2-(methoxy-d3)benzaldehyde was used as the raw material and example 2 was referenced to obtain the product 2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2*H*-chromen-8-yl)piperidin-1-yl)methyl)-3-(((*S*)-oxetan-2-yl)methyl)-3*H*-imidazo[4,5-*b*]pyridine-5-carboxylic acid.

[0233] MS *m/z* (ESI): 622.2 [M+1].

[0234] 2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid was subjected to chiral separation to obtain



[0235] 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid (example 9-A)

[0236] MS m/z (ESI): 622.2 [M+1].

[0237] 2-((4-((S)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid (example 9-B)

[0238] MS m/z (ESI): 622.2 [M+1].

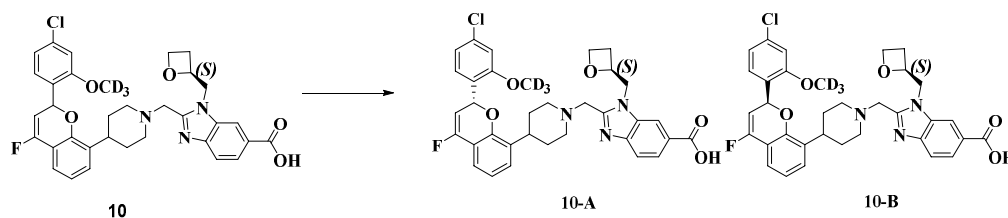
Example 10

2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

[0239] 4-chloro-2-(methoxy-d3)benzaldehyde was used as the raw material and example 1 was referenced to obtain the product 2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0240] MS m/z (ESI): 621.2[M+1].

[0241] 2-((4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid was subjected to chiral separation to obtain



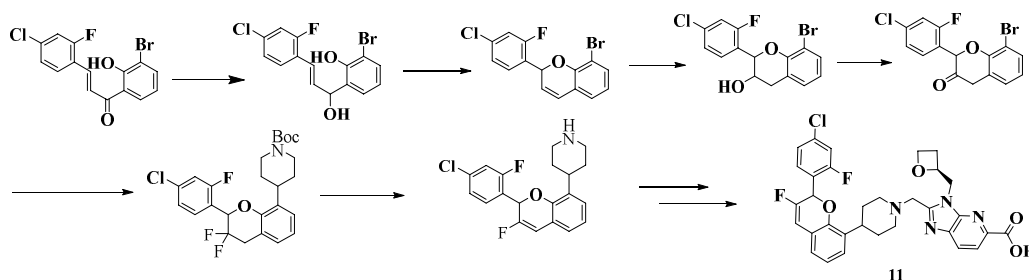
[0242] 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 10-A)

[0243] MS m/z (ESI): 621.2 [M+1].

- [0244] 2-((4-((*S*)-2-(4-chloro-2-(methoxy-d₃)phenyl)-4-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((*S*)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid (example 10-B)
- [0245] MS *m/z* (ESI): 621.2 [M+1].

Example 11

2-((4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((*S*)-oxetan-2-yl)methyl)-3H-imidazo[4,5-*b*]pyridine-5-carboxylic acid



Step 1

(*E*)-2-bromo-6-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)phenol

- [0246] (*E*)-1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one (500 mg, 1.41 mmol) was dissolved in methanol (15 mL), sodium borohydride (64 mg, 1.69 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water was added to quench the reaction, and the obtained mixture was extracted with dichloromethane (30 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain (*E*)-2-bromo-6-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)phenol (454 mg, yield: 90.0%)
- [0247] MS *m/z* (ESI): 356.9[M+1].

Step 2

8-bromo-2-(4-chloro-2-fluorophenyl)-2H-chromene

- [0248] (*E*)-2-bromo-6-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)phenol (300 mg, 0.84 mmol) was dissolved in dichloromethane (10 mL), *p*-toluenesulfonic acid (29 mg, 0.17 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water was added to quench the reaction, and the obtained mixture was extracted with dichloromethane (30 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain (8-bromo-2-(4-chloro-2-fluorophenyl)-2H-chromene (200 mg, yield: 70.1%).

[0249] MS m/z (ESI): 338.9[M+1].

Step 3

8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-ol

[0250] (8-bromo-2-(4-chloro-2-fluorophenyl)-2H-chromene (200 mg, 0.59 mmol) was dissolved in THF (10 mL), a solution of borane in THF (0.71 mL, 0.71 mmol) was added, and the mixture was stirred at 0°C for 1 h. 2 mL of water was added, then NaOH (71 mg, 1.77 mmol) and 0.1 mL of hydrogen peroxide solution were added, and the mixture was stirred at 40°C for 2 h. 10 mL of water was added to quench the reaction, and the obtained mixture was extracted with dichloromethane (30 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain 8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-ol (63 mg, yield: 29.8%)

[0251] MS m/z (ESI): 356.9[M+1].

Step 4

8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-one

[0252] 8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-ol (500 mg, 1.40 mmol) was dissolved in DCM (20 mL), Dess-Martin oxidant (0.71 mL, 1.67 mmol) was added, and the mixture was stirred at 0°C for 1 h. 10 mL of water was added to quench the reaction, and the obtained mixture was extracted with dichloromethane (30 mL × 3), washed with saturated sodium chloride solution (20 mL × 2), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain 8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-one (448 mg, yield: 89.9%)

[0253] MS m/z (ESI): 354.9[M+1].

Step 5

Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-3,3-difluorochroman-8-yl)piperidine-1-carboxylate

[0254] 8-bromo-2-(4-chloro-2-fluorophenyl)chroman-3-one was used as the raw material, and the step 3 to step 5 of example 1 were referenced to obtain the product tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-3,3-difluorochroman-8-yl)piperidine-1-carboxylate

[0255] MS m/z (ESI): 482.2[M+1].

Step 6

4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidine

[0256] Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-3,3-difluorochroman-8-yl)piperidine-1-carboxylate was used as the raw materials, and the step 6 of example 1 was referenced to obtain the product 4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidine

[0257] MS m/z (ESI): 362.1[M+1].

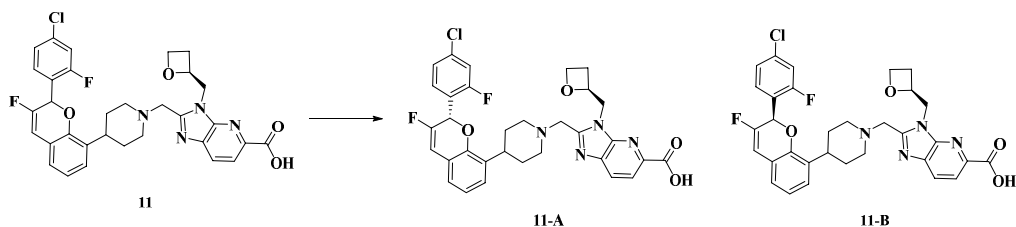
Step 7

2-((4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0258] 4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidine was used as the raw material, and the step 7 and step 8 of example 1 were referenced to obtain the product 2-((4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0259] MS m/z (ESI): 607.1[M+1].

[0260] 2-((4-(2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid was subjected to chiral resolution



[0261] 2-((4-((S)-2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 11-A)

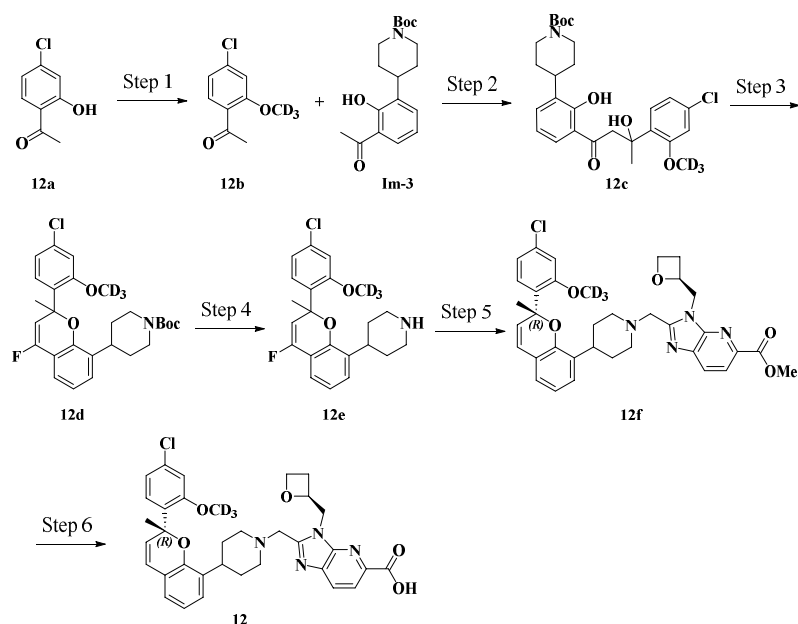
[0262] MS m/z (ESI): 607.1 [M+1].

[0263] 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid (example 11-B)

[0264] MS m/z (ESI): 607.1 [M+1].

Example 12

2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid



Step 1

1-(4-chloro-2-(methoxy-d3)phenyl)ethan-1-one

[0265] 1-(4-chloro-2-hydroxyphenyl)ethan-1-one **12a** (15 g, 87.93 mmol), deuterated iodomethane (16.57 g, 114.31 mmol), and anhydrous potassium carbonate (36.46 g, 0.26 mol) were dispersed in DMF (150 mL). The reaction liquid was heated to 50°C and reacted under vigorous stirring for 12 h. After the reaction was stopped, the reaction liquid was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 1-(4-chloro-2-(methoxy-d3)phenyl)ethan-1-one **12b** (15 g), yield: 90.9%.

[0266] MS m/z (ESI): 188.1 [M+1].

Step 2

Tert-butyl-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate

[0267] Tert-butyl-4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im-4** (25 g, 79.94 mmol) was dissolved in tetrahydrofuran (300 mL). The solution was cooled in a dry ice/ethanol bath, and LiHMDS (18.4 mL, 0.184 mol, 1 M solution in THF) was slowly added thereto. After the addition, the mixture was reacted under stirring for 30 minutes. 1-(4-chloro-2-(methoxy-d3)phenyl)ethan-1-one **12b** (15 g, 79.94 mmol) was dissolved in THF (30 mL), and the solution was slowly added dropwise to the aforementioned reaction liquid. The mixture was reacted under stirring for 40 minutes while maintaining the dry ice/ethanol bath temperature. After the reaction

was stopped, the dry ice/ethanol bath was removed, saturated ammonium chloride solution was added to the reaction liquid to quench the reaction, and the obtained mixture was extracted with ethyl acetate (300 mL × 2). The organic phases were combined, washed with saturated sodium chloride (500 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate **12c** (31 g), yield: 76.5%.

[0268] MS m/z (ESI): 507.2 [M+1].

Step 3

Tert-butyl-4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine-1-carboxylate

[0269] Tert-butyl-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate **12c** (2.00 g, 4.07 mmol) and BAST (10 mL) were dissolved in DMF (10 mL), then ethanol (20 µL) was added to the reaction liquid, and the mixture was reacted under stirring for 4 h. After the reaction was stopped, the reaction liquid was slowly added into ice water to quench the reaction, and the obtained mixture was extracted with ethyl acetate (50 mL × 2). The organic phases were combined, washed with water (100 mL), washed with saturated sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl-4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine-1-carboxylate **12d** (750 mg), yield: 38.7%.

[0270] MS m/z (ESI): 491.2 [M+1].

Step 4

4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine

[0271] Tert-butyl-4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine-1-carboxylate **12d** (750 mg, 1.53 mmol), boron trifluoride diethyl etherate (543 mg, 3.83 mmol), and powdered 4 Å molecular sieve (750 mg) were dispersed in dichloromethane (10 mL), and the mixture was reacted under stirring for 3 h while maintaining 0°C. After the reaction was stopped, saturated sodium bicarbonate solution was added to the reaction liquid to quench the reaction. The mixture was filtered through diatomaceous earth, and the filtrate was allowed to stand. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (20 mL × 2). The organic phases were combined, dried over anhydrous sodium

sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with dichloromethane and methanol as an eluent system to obtain the title product 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine **12e** (490 mg), yield: 82.1%.

[0272] MS m/z (ESI): 391.2 [M+1].

Step 5

Methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate

[0273] 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidine **12e** (490 mg, 1.25 mmol), methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate **Im-2** (371 mg, 1.25 mmol), and anhydrous potassium carbonate (518 mg, 3.75 mmol) were dispersed in acetonitrile (8 mL). The reaction liquid was heated to 50°C and reacted under vigorous stirring for 3 h. After the reaction was stopped, the reaction liquid was cooled to room temperature and filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with ethyl acetate as an eluent system, and then the purified resulting sample was sent to chiral preparative HPLC separation to obtain the title product methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate **12f** (210 mg), yield: 26.5%.

[0274] MS m/z (ESI): 632.2 [M+1].

Step 6

2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

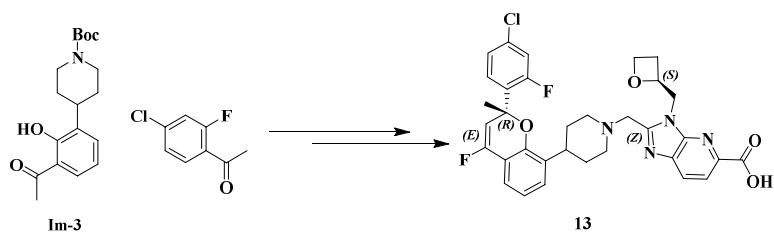
[0275] Methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate **12f** (210 mg, 332.19 µmol) and lithium hydroxide (133 mg, 3.32 mmol) were dissolved in 9 mL of a mixed solvent of THF, water and methanol (4 : 4 : 1), and the mixture was reacted under stirring for 3 h. After the reaction was stopped, formic acid was added to adjust the pH = 6, and the reaction liquid was concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to obtain the title product 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid **12** (170 mg), yield: 82.8%.

[0276] MS m/z (ESI): 618.2 [M+1].

[0277] ^1H NMR (400 MHz, MeOD) δ 8.16 – 7.97 (m, 2H), 7.29 (d, J = 8.2 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.94 – 6.85 (m, 2H), 6.81 (t, J = 7.5 Hz, 1H), 6.57 (d, J = 9.8 Hz, 1H), 5.78 (d, J = 9.8 Hz, 1H), 5.25 (dd, J = 7.5, 3.0 Hz, 1H), 4.96 (dd, J = 14.9, 6.7 Hz, 1H), 4.83 (dd, J = 14.9, 3.1 Hz, 1H), 4.66 – 4.53 (m, 1H), 4.48 – 4.35 (m, 1H), 4.25 (d, J = 14.2 Hz, 1H), 4.16 (d, J = 14.2 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 3.12 (d, J = 11.5 Hz, 1H), 2.91 (s, 1H), 2.83 – 2.70 (m, 1H), 2.61 – 2.41 (m, 3H), 1.85 (q, J = 3.9 Hz, 2H), 1.78 (s, 3H), 1.68 (d, J = 3.7 Hz, 1H), 1.59 (d, J = 14.9 Hz, 1H).

Example 13

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

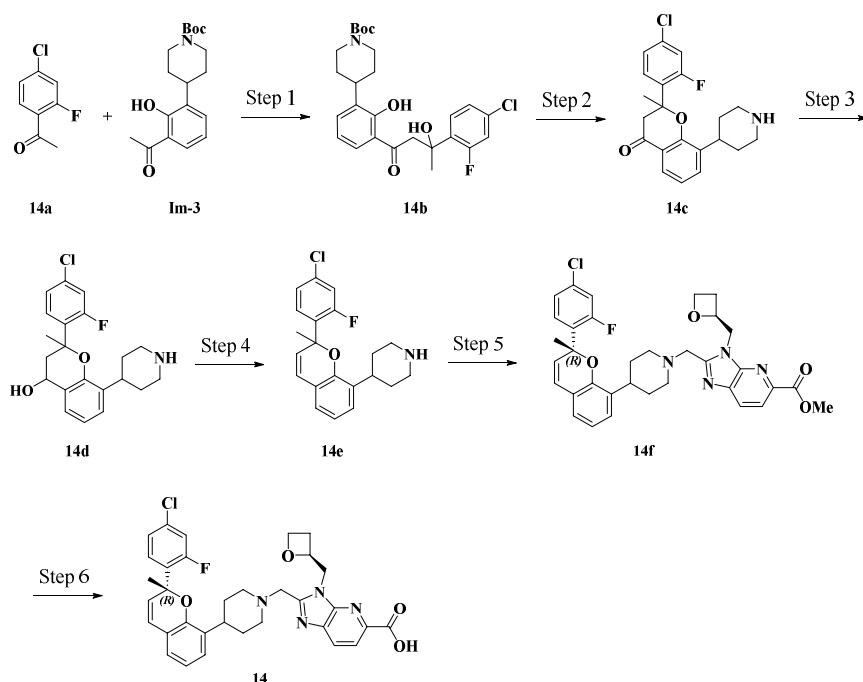


[0278] Tert-butyl 4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im-4** and 1-(4-chloro-2-fluorophenyl)ethan-1-one were used as the raw materials, and the step 2 to step 6 of example 12 were referenced to obtain 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid **13**.

[0279] MS m/z (ESI): 621.2 $[M+1]$.

Example 14

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid



Step 1

Tert-butyl-4-(3-(3-(4-chloro-2-fluorophenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate

[0280] Referring to the synthesis method of example 13, 1-(4-chloro-2-fluorophenyl)ethan-1-one **14a** (5 g, 28.97 mmol), Im-4 (9.25 g, 28.97 mmol), LiHMDS (66.6 mL, 66.63 mmol), and THF (100 mL) were dosed to obtain the title product tert-butyl-4-(3-(3-(4-chloro-2-fluorophenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate **17b** (7.60 g), yield: 53.3%.

[0281] MS m/z (ESI): 492.2 [M+1].

Step 2

2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-one

[0282] Tert-butyl-4-(3-(3-(4-chloro-2-fluorophenyl)-3-hydroxybutyryl)-2-hydroxyphenyl)piperidine-1-carboxylate **14b** (5 g, 10.16 mmol) and p-toluenesulfonic acid (5.25 g, 30.48 mmol) were dissolved in toluene (50 mL). The reaction liquid was heated to 100°C and reacted under stirring for 5 h. After the reaction was stopped, the reaction liquid was cooled to room temperature, and 2 M sodium hydroxide solution was added thereto to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with dichloromethane and methanol as an eluent system to

obtain the title product 2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-one **14c** (2.36 g), yield: 62.1%.

[0283] MS m/z (ESI): 374.1 [M+1].

Step 3

2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-ol

[0284] 2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-one **14c** (2 g, 5.35 mmol) was dissolved in methanol (30 mL). Sodium borohydride (396 mg, 10.70 mmol) was slowly added to the solution in portions under an ice bath. After the addition, the ice bath was removed and the reaction liquid was allowed to naturally warm to ambient temperature and reacted for 2 h. After the reaction was stopped, saturated ammonium chloride solution was added to the reaction liquid to quench the reaction, and the obtained mixture was adjusted to pH = 10 with 1 M sodium hydroxide solution. The obtained mixture was extracted with dichloromethane (50 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the title product 2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-ol **14d** (1.88 g), yield: 93.5%, the compound was directly used for the next reaction without purification.

[0285] MS m/z (ESI): 376.1 [M+1].

Step 4

4-(2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidine

[0286] 2-(4-chloro-2-fluorophenyl)-2-methyl-8-(piperidin-4-yl)chroman-4-ol **14d** (1.50 g, 3.99 mmol) and p-toluenesulfonic acid (2.06 g, 11.97 mmol) were dissolved in toluene (20 mL). The reaction liquid was heated to 100°C and reacted under stirring for 30 minutes. After the reaction was stopped, the reaction liquid was cooled to room temperature, and 2 M sodium hydroxide solution was added thereto to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (30 mL × 3). The organic phases were combined, dried over anhydrous sodium sulfate, and filtered, and the filtrate was concentrated under reduced pressure to obtain the title product 4-(2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidine **14e** (1.02 g), yield: 71.4%, the compound was directly used for the next reaction without purification.

[0287] MS m/z (ESI): 358.1 [M+1].

Step 5

Methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate

[0288] Referring to the synthesis method of the step 5 of example **13**, 4-(2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidine **14e** (500 mg, 1.40 mmol), methyl (S)-2-(chloromethyl)-3-(oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **Im-2** (413 mg, 1.40 mmol), anhydrous potassium carbonate (580 mg, 4.20 mmol), and acetonitrile (10 mL) were dosed to obtain the title product methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **17f** (263 mg), yield: 30.5%.

[0289] MS m/z (ESI): 617.2 [M+1].

Step 6

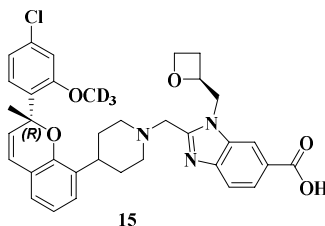
2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0290] Referring to the synthesis method of the step 6 of example **13**, methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **14f** (100 mg, 162 μ mol) and lithium hydroxide (39 mg, 1.62 mmol) were dosed to obtain the title product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid **14** (76 mg), yield: 77.8%.

[0291] MS m/z (ESI): 603.2 [M+1].

Example 15

2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

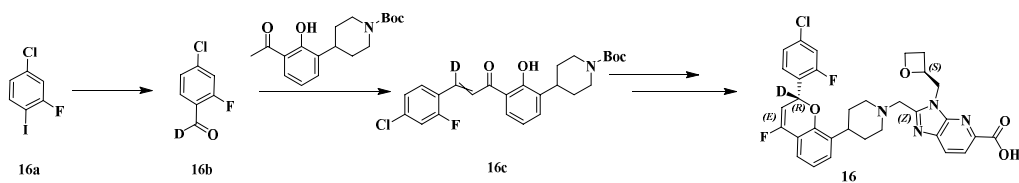


[0292] Reference to the synthesis method of example **12**, **Im-1** was used as the starting material to obtain the title product 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2-methyl-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0293] MS m/z (ESI): 617.3 [M+1].

Example 16

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid



Step 1

4-chloro-2-fluoro- α -2H-benzaldehyde

[0294] 4-chloro-2-fluoro-1-iodo-benzene (5 g, 19.50 mmol) and toluene (50 mL) were added to a 100 mL flask, and isopropanol magnesium chloride (12.9 mL, 3 M, 38.99 mmol) was added at -30°C, and the reaction liquid was reacted at -20°C for 2h. Then N,N-dimethylformamide-D7 (3.12 g, 38.99 mmol) was added to the reaction liquid, and the reaction was continued at 0°C for 1 h. After the reaction was stopped, the reaction liquid was quenched with a saturated ammonium chloride aqueous solution. Water (50 mL) was added, and the obtained mixture was extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 4-chloro-2-fluoro- α -2H-benzaldehyde **16b** (2.7 g), yield: 86.79%.

[0295] MS m/z (ESI): 160.0 [M+1].

Step 2

Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0296] 4-chloro-2-fluoro- α -2H-benzaldehyde **16b** (1.5 g, 9.40 mmol), tert-butyl 4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im-4** (3.00 g, 9.40 mmol) and tetrahydrofuran (40 mL) were added to a 100 mL flask, and sodium hydride (1.13 g, 28.20 mmol, 60% purity) was added at 0°C, then the reaction liquid was reacted at 25°C for 3h. After the reaction was stopped, the reaction liquid was quenched with a saturated ammonium chloride aqueous solution. Water (20 mL) was added, and the obtained mixture was extracted with ethyl acetate (20 mL $\times$ 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **16c** (3 g), yield: 69.23%.

[0297] MS m/z (ESI): 461.1 [M+1].

Step 3

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

[0298] Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-

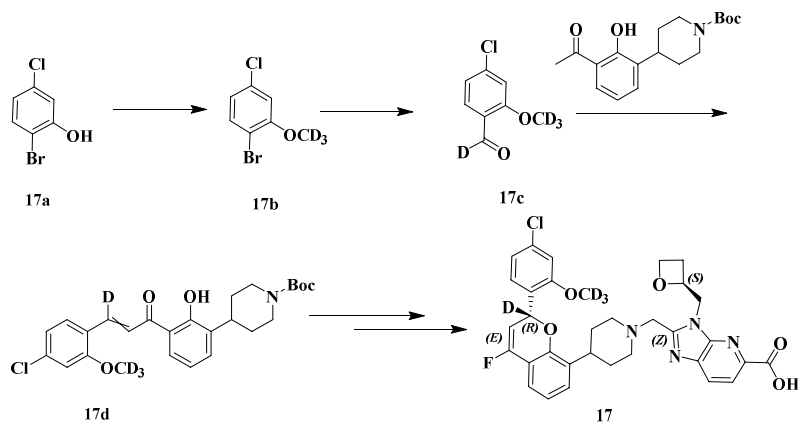
hydroxyphenyl)piperidine-1-carboxylate **16c** was used as the raw material, and the synthesis method of the step 3 to step 6 of example 36 was referenced to obtain 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid **16**.

[0299] MS m/z (ESI):608.1 [M+1].

[0300] ¹H NMR (400 MHz, DMSO-d₆) δ 8.10 (d, 1H), 7.97 (d, 1H), 7.54 (dd, 1H), 7.41 (t, 1H), 7.29 (dd, 1H), 7.24 – 7.15 (m, 2H), 6.96(t, 1H), 5.67 (d, 1H), 5.20 – 5.11 (m, 1H), 4.88 – 4.79 (m, 1H), 4.74 – 4.65 (m, 1H), 4.53 – 4.43 (m, 1H), 4.41 – 4.31 (m, 1H), 3.97 (d, 1H), 3.88 (d, 1H), 2.98 – 2.91 (m, 1H), 2.87 – 2.79 (m, 1H), 2.75 – 2.62 (m, 2H), 2.49 – 2.41 (m, 1H), 2.25 – 2.07 (m, 2H), 1.73 – 1.59 (m, 2H), 1.54 – 1.41 (m, 1H), 1.37 – 1.29 (m, 1H).

Example 17

2-((4-((R)-2-(4-chloro-2-(methoxy-d₃)phenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid



Step 1

1-bromo-4-chloro-2-(methoxy-d₃)benzene

[0301] 2-bromo-5-chlorophenol **17a** was used as the raw material, and the synthesis method of the step 1 of example 36 was referenced to obtain 1-bromo-4-chloro-2-(methoxy-d₃)benzene **17b**.

[0302] MS m/z (ESI):223.9 [M+1].

Step 2

4-chloro-2-(methoxy-d₃)α-2H>benzaldehyde

[0303] 1-bromo-4-chloro-2-(methoxy-d3)benzene **17b** was used as the raw material, and the synthesis method of the step 1 of example 16 was referenced to obtain 4-chloro-2-(methoxy-d3) < α -2H>benzaldehyde **17c**.

[0304] MS m/z (ESI):175.0 [M+1].

Step 3

Tert-butyl 4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0305] 4-chloro-2-(methoxy-d3) < α -2H>benzaldehyde **17c** was used as the raw material, and the synthesis method of the step 2 of example 16 was referenced to obtain tert-butyl 4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **17d**.

[0306] MS m/z (ESI):476.2 [M+1].

Step 4

2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

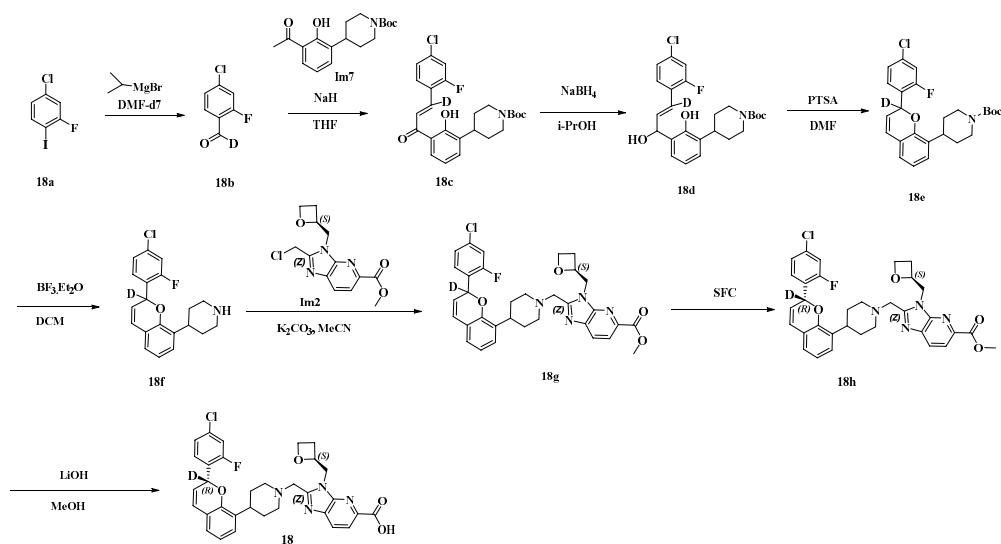
[0307] Tert-butyl 4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **17d** was used as the raw material, and the synthesis method of the step 3 to step 6 of example 12 was referenced to obtain 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid **17**.

[0308] MS m/z (ESI):623.2 [M+1].

[0309] ¹H NMR (400 MHz, Methanol-d4) δ 8.14 – 8.04 (m, 2H), 7.31 (d, 1H), 7.20 – 7.13 (m, 2H), 7.05 (d, 1H), 6.96 – 6.87 (m, 2H), 5.36 (d, 1H), 5.29 – 5.24 (m, 1H), 5.03 – 4.93 (m, 1H), 4.82 – 4.75 (m, 1H), 4.65 – 4.55 (m, 1H), 4.45 – 4.36 (m, 1H), 4.20 (d, 1H), 4.10 (d, 1H), 3.23 – 3.15 (m, 1H), 3.09 – 3.02 (m, 1H), 2.91 – 2.86 (m, 1H), 2.81 – 2.72 (m, 1H), 2.57 – 2.37 (m, 3H), 1.88 – 1.78 (m, 2H), 1.71 – 1.63 (m, 1H), 1.59 – 1.52 (m, 1H).

Example 18

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid



Step 1

4-chloro-2-fluoro- α -2H-benzaldehyde

[0310] 4-chloro-2-fluoro-1-iodo-benzene **18a** (5 g, 19.50 mmol) and toluene (50 mL) were added to a 100 mL flask, and isopropanol magnesium chloride (12.9 mL, 3 M, 38.99 mmol) was added at -30°C , and the reaction liquid was reacted at -20°C for 2 h. Then N,N-dimethylformamide-D7 (3.12 g, 38.99 mmol) was added to the reaction liquid, and the reaction was continued at 0°C for 1 h. After the reaction was stopped, the reaction liquid was quenched with a saturated ammonium chloride aqueous solution. Water (50 mL) was added, and the obtained mixture was extracted with ethyl acetate ($20\text{ mL} \times 3$). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 4-chloro-2-fluoro- α -2H-benzaldehyde **18b** (2.7 g), yield: 86.79%.

[0311] MS m/z (ESI): 160.0 $[\text{M}+1]$.

Step 2

Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0312] 4-chloro-2-fluoro- α -2H-benzaldehyde **18b** (1.5 g, 9.40 mmol), tert-butyl 4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im-4** (3.00 g, 9.40 mmol) and tetrahydrofuran (40 mL) were added to a 100 mL flask, and sodium hydride (1.13 g, 28.20 mmol, 60% purity) was added at 0°C , then the reaction liquid was reacted at 25°C for 3 h. After the reaction was stopped, the reaction liquid was quenched with a saturated ammonium chloride aqueous solution. Water (20 mL) was added, and the obtained mixture was extracted with ethyl acetate ($20\text{ mL} \times 3$). The

organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **18c** (3 g), yield: 69.23%.

[0313] MS m/z (ESI): 461.1 [M+1].

Step 3

Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0314] Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **18c** (3 g, 6.51 mmol) and isopropanol (50 mL) were added to a 250 mL flask, and sodium borohydride (369.33 mg, 9.76 mmol) was added at 0°C. The reaction liquid was then reacted at 20°C for 3 h. After the reaction was stopped, the reaction liquid was quenched with water (10 mL), and the obtained mixture was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to obtain the title product tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **18d** (3 g), yield: 99.56%.

[0315] MS m/z (ESI): 463.1 [M+1].

Step 4

Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate

[0316] Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **18d** (3 g, 6.48 mmol) and N,N-dimethylformamide (30 mL) were added to a 100 mL flask, and p-toluenesulfonic acid (1.67 g, 9.72 mmol) was added at 25°C. The reaction liquid was then reacted at 50°C for 4 h. After the reaction was stopped, the reaction liquid was quenched with water (20 mL), and the obtained mixture was extracted with ethyl acetate (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate **18e** (1.7 g), yield: 58.96%.

[0317] MS m/z (ESI): 445.1 [M+1].

Step 5

4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine

[0318] Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate **18e** (1.7 g, 3.82 mmol) and dichloromethane (25 mL) were added to a 100 mL flask, and 4A molecular sieve (1.7 g) and boron trifluoride diethyl etherate (1.36 g, 9.55 mmol) were added at 0°C. The reaction liquid was then reacted at 0°C for 2 h. After the reaction was stopped, the reaction liquid was quenched with saturated sodium bicarbonate aqueous solution (10 mL). Water (10 mL) was added, and the obtained mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to obtain the title product 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine **18f** (1.3 g), yield: 98.67%.

[0319] MS m/z (ESI): 345.1 [M+1]

Step 6

Methyl 2-((4-(-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate

[0320] 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidine **18f** (1.3 g, 3.77 mmol) and acetonitrile (15 mL) were added to a 100 mL flask, and potassium carbonate (1.04 g, 7.54 mmol) and methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **Im2** (1.11 g, 3.77 mmol) were added at 25°C. The reaction liquid was then reacted at 25°C for 10 h. After the reaction was stopped, the reaction liquid was quenched with aqueous solution (10 mL), and the obtained mixture was extracted with dichloromethane (10 mL × 3). The organic phase was washed with saturated sodium chloride solution (10 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product methyl 2-((4-(-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **18g** (1.7 g), yield: 74.65%.

[0321] MS m/z (ESI): 604.2 [M+1]

Step 7

Methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate

[0322] Methyl 2-((4-(-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **18g** was subjected to chiral resolution to obtain methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **18h**.

- [0323] **Resolution conditions:** D-H 4.6*250
 [0324] Hexane : EtOH : MeOH : DEA = 70 : 15 : 15 : 0.1%
 [0325] F=1mL T = 35°C

Step 8

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

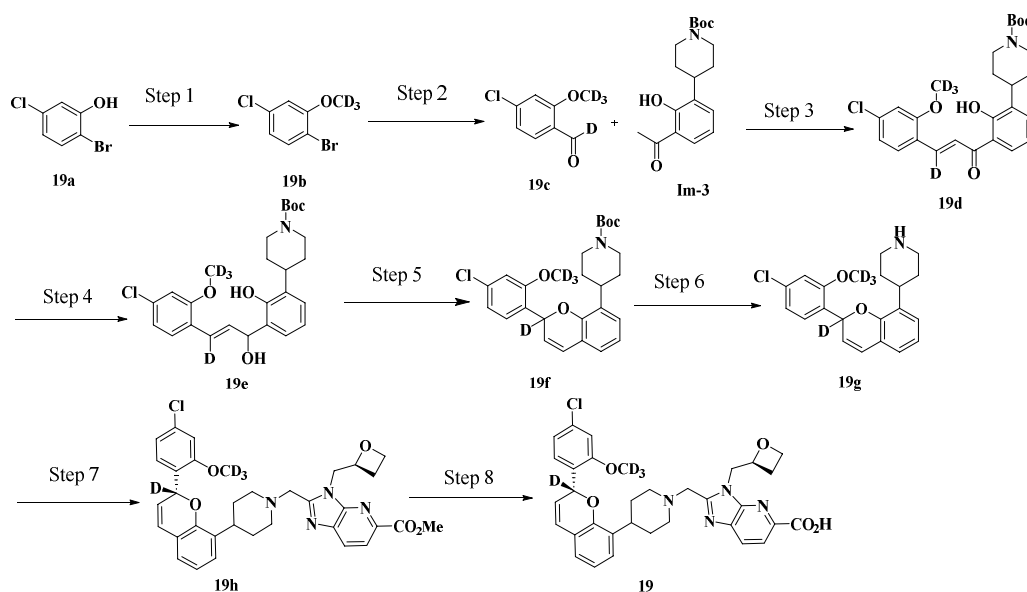
- [0326] Methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **18h** (100 mg, 165.54 μ mol) and methanol (2 mL) were added to a 25 mL flask, and lithium hydroxide (39.64 mg, 1.66 mmol) was dissolved in water (1 mL), and the mixture was added dropwise to the reaction liquid at 25°C. The reaction liquid was then reacted at 25°C for 1 h. After the reaction was stopped, the reaction liquid was quenched with formic acid (0.1 mL). Water (2 mL) was added, and the obtained mixture was extracted with dichloromethane (2 mL $\times$ 3). The organic phase was washed with saturated sodium chloride solution (2 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by prep-HPLC to obtain the title product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid **18** (70 mg), yield: 71.66%.

- [0327] MS m/z (ESI): 590.2 [M+1]

- [0328] ¹H NMR (400 MHz, DMSO) δ 8.08 (d, 1H), 7.96 (d, 1H), 7.52 (dd, 1H), 7.34 (t, 1H), 7.27 (dd, 1H), 7.05 (dd, 1H), 6.98 (dd, 1H), 6.85 (t, 1H), 6.75 (d, 1H), 5.91 (d, 1H), 5.18 – 5.11 (m, 1H), 4.87 – 4.80 (m, 1H), 4.72 – 4.65 (m, 1H), 4.53 – 4.43 (m, 1H), 4.39 – 4.31 (m, 1H), 3.96 (d, 1H), 3.87 (d, 1H), 3.01 – 2.90 (m, 1H), 2.89 – 2.79 (m, 1H), 2.77 – 2.61 (m, 2H), 2.48 – 2.45 (m, 1H), 2.27 – 2.08 (m, 2H), 1.73 – 1.61 (m, 2H), 1.54 – 1.42 (m, 1H), 1.42 – 1.34 (m, 1H).

Example 19

2-((4-((R)-2-(4-chloro-2-(methoxy-d₃)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid



Step 1

1-bromo-4-chloro-2-(methoxy-d3)benzene

[0329] 2-bromo-5-chlorophenol **19a** (10 g, 48.20 mmol), deuterated iodomethane (10.48 g, 72.30 mmol), anhydrous potassium carbonate (13.33 g, 96.41 mol) were dispersed in DMF (100 mL). The reaction liquid was heated to 50°C and reacted under vigorous stirring for 12 h. After the reaction was stopped, the reaction liquid was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product 1-bromo-4-chloro-2-(methoxy-d3)benzene **19b** (10 g), yield: 92.5%.

[0330] MS *m/z* (ESI): 223.9 [M+1].

Step 2

4-chloro-2-(methoxy-d3)benzaldehyde-d

[0331] 1-bromo-4-chloro-2-(methoxy-d3)benzene **19b** (1.6 g, 7.13 mmol) was dissolved in tetrahydrofuran (30 mL), and after nitrogen displacement, *n*-BuLi (2.5 M, 3.42 mL) was slowly added dropwise thereto at -78°C. After the dropwise addition was completed, stirring was maintained at -78°C for 1 h, and then *N,N*-dimethylformamide-D7 (856.71 mg, 10.69 mmol) was added dropwise thereto. The reaction system was further stirred for 3 h and naturally warmed to room temperature. Saturated ammonium chloride solution (20 mL) was slowly added dropwise thereto to quench the reaction, and then the obtained mixture was extracted with ethyl acetate (30 mL x 3), washed with saturated sodium chloride aqueous solution (30 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the 4-chloro-2-(methoxy-d3)-benzaldehyde-d **19c** (1.2 g, 6.87 mmol) as white solid, yield: 96.42%.

[0332] MS m/z (ESI): 175.0 [M+1].

Step 3

Tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0333] 4-chloro-2-(methoxy-d3)-benzaldehyde-d **19c** (700 mg, 4.01 mmol) and tert-butyl-4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **1m-4** (1.28 g, 4.01 mmol) were dissolved in tetrahydrofuran (40 mL), and sodium hydride (481.05 mg, 12.03 mmol, 60% purity) was added thereto in portions in an ice-water bath. The reaction system was stirred in an ice-water bath for 0.5 h, and then placed at room temperature 20°C and stirred for 2.5 h. After the reaction was completed, the reaction was quenched by dropwise adding water (20 mL), extracted with ethyl acetate (30 mL × 3), washed with a saturated sodium chloride aqueous solution (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **19d** (1.5 g). Yield: 78.6%

[0334] MS m/z (ESI): 476.2 [M+1].

Step 4

Tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate

[0335] Tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)acryloyl-3-d-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **19d** (1.4 g, 2.94 mmol) was dissolved in tetrahydrofuran (30 mL), and sodium borohydride (333.82 mg, 8.82 mmol) was added thereto in portions at room temperature. The reaction system was stirred for 2 h at room temperature. After the reaction was completed, water (20 mL) was added dropwise to quench the reaction, and the obtained mixture was extracted with ethyl acetate (30 mL × 3), washed with saturated sodium chloride aqueous solution (30 mL × 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the title product tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **19e** (1.4 g).

[0336] MS m/z (ESI): 478.2 [M+1].

Step 5

Tert-butyl 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate

[0337] Tert-butyl (E)-4-(3-(3-(4-chloro-2-(methoxy-d3)phenyl)-1-hydroxyallyl-3-d)-2-hydroxyphenyl)piperidine-1-carboxylate **19e** (1.40 g, 2.93 mmol) was dissolved in

dichloromethane (20 mL), and p-toluenesulfonic acid (151.62 mg, 880.49 μmol) was added thereto. The reaction system was stirred for 3 h at room temperature. After the reaction was completed, the solvent was directly concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate **19f** (600 mg, 1.30 mmol), yield 44.4%.

[0338] MS m/z (ESI): 460.2 [M+1].

Step 6

4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine

[0339] Tert-butyl 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine-1-carboxylate **19f** (260 mg, 565.22 μmol) was dissolved in dichloromethane (10 mL), and 4Å molecular sieve (260 mg) and boron trifluoride diethyl etherate (240.66 mg, 1.70 mmol) were added thereto in an ice-water bath. The reaction system was further stirred in the ice-water bath for 1 h. After the reaction was completed, saturated sodium bicarbonate solution (10 mL) was added dropwise to quench the reaction, and the obtained mixture was extracted with dichloromethane (20 mL x 3), washed with saturated sodium chloride aqueous solution (20 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the crude product 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine **19g** (200 mg).

[0340] MS m/z (ESI): 360.2 [M+1].

Step 7

Methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate

[0341] 4-(2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidine **19g** (200 mg, 555.74 μmol , crude), methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **Im-2** (180.17 mg, 611.31 μmol) and potassium carbonate (230.42 mg, 1.67 mmol) were dissolved in acetonitrile (10 mL). The reaction system was placed in an oil bath at 60°C and stirred for 4 h. After the reaction was completed, the reaction liquid was diluted by adding water (10 mL), extracted with ethyl acetate (20 mL x 3), washed with a saturated sodium chloride aqueous solution (20 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude product. The crude product was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system, and then the purified resulting sample was sent to chiral preparative HPLC separation to obtain the title product methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-

(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate **19h** (100 mg, 161.5 μ mol), yield: 29.1%.

[0342] MS m/z (ESI): 619.2 [M+1].

Step 8

2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

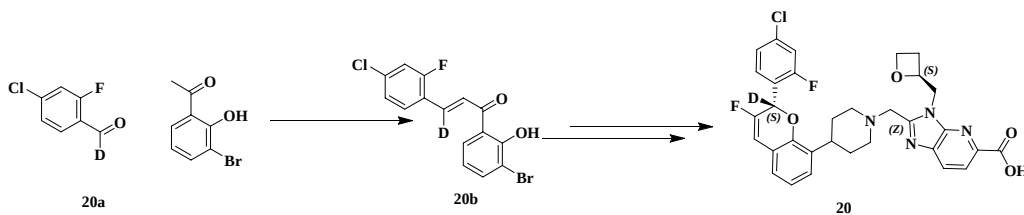
[0343] Methyl 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylate **19h** (100 mg, 161.5 μ mol) and lithium hydroxide (38.8 mg, 1.62 mmol) were dissolved in 9 mL of a mixed solvent of THF, water and methanol (4 : 4 : 1), and the mixture was reacted under stirring for 3 h. After the reaction was stopped, formic acid was added to adjust the pH = 6, and the reaction liquid was concentrated under reduced pressure. The resulting residue was purified by preparative HPLC to obtain the title product 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid **19** (60 mg), yield: 61.5%.

[0344] MS m/z (ESI): 605.2 [M+1].

[0345] ^1H NMR (400 MHz, DMSO) δ 8.08 (d, 1H), 7.96 (d, 1H), 7.22 (d, 1H), 7.14 (d, 1H), 7.02 (d, 1H), 6.99 – 6.91 (m, 2H), 6.82 (t, 1H), 6.66 (d, 1H), 5.86 (d, 1H), 5.17 – 5.11 (m, 1H), 4.86 – 4.77 (m, 1H), 4.73 – 4.65 (m, 1H), 4.51 – 4.45 (m, 1H), 4.38 – 4.30 (m, 1H), 3.97 – 3.84 (m, 2H), 2.98 – 2.91 (m, 1H), 2.87 – 2.81 (m, 1H), 2.76 – 2.64 (m, 2H), 2.47 – 2.45 (m, 1H), 2.24 – 2.09 (m, 2H), 1.70 – 1.64 (m, 2H), 1.50 – 1.38 (m, 2H).

Example 20

2-((4-((S)-2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid



Step 1

1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one-3-d

[0346] 4-chloro-2-fluoro- α -2H-benzaldehyde **20a** and 1-(3-bromo-2-hydroxyphenyl)ethan-1-one were used as the raw materials, and the synthesis method of the step 1 of example 1 was

referenced to obtain 1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one-3-d **20b**.

[0347] MS m/z (ESI):355.9 [M+1].

Step 2

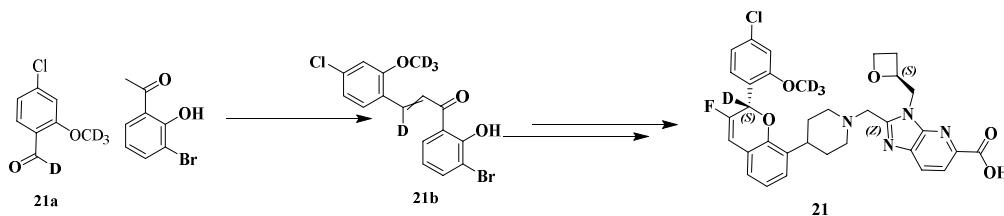
2-((4-((S)-2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0348] 1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-fluorophenyl)prop-2-en-1-one-3-d **20b** was used as the raw material, and the synthesis method of example 11 was referenced to obtain 2-((4-((S)-2-(4-chloro-2-fluorophenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid **20**.

[0349] MS m/z (ESI):608.1 [M+1].

Example 21

2-((4-((S)-2-(4-chloro-2-(methoxy-d3)phenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid



Step 1

1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-(methoxy-d3)phenyl)prop-2-en-1-one-3-d

[0350] 4-chloro-2-(methoxy-d3) α-2H>benzaldehyde **21a** and 1-(3-bromo-2-hydroxyphenyl)ethan-1-one were used as the raw materials, and the synthesis method of the step 1 of example 1 was referenced to obtain 1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-(methoxy-d3)phenyl)prop-2-en-1-one-3-d **21b**.

[0351] MS m/z (ESI):371.0 [M+1].

Step 2

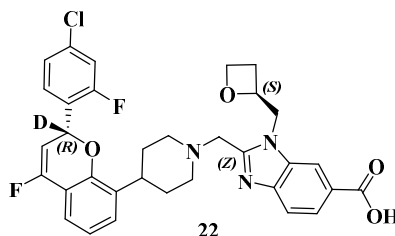
2-((4-((S)-2-(4-chloro-2-(methoxy-d3)phenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0352] 1-(3-bromo-2-hydroxyphenyl)-3-(4-chloro-2-(methoxy-d3)phenyl)prop-2-en-1-one-3-d **21b** was used as the raw material, and the synthesis method of example 11 was referenced to obtain 2-((4-((S)-2-(4-chloro-2-(methoxy-d3)phenyl)-3-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid **21**.

[0353] MS m/z (ESI):623.2 [M+1].

Example 22

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

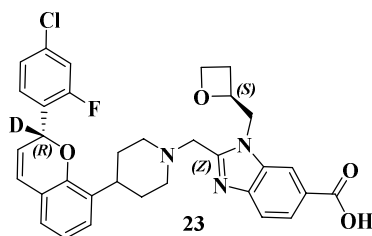


[0354] Intermediate Im1 was used as the raw material and example 16 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0355] MS m/z (ESI): 607.2 [M+1].

Example 23

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0356] Intermediate Im1 was used as the raw material and example 18 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0357] MS m/z (ESI): 589.2 [M+1].

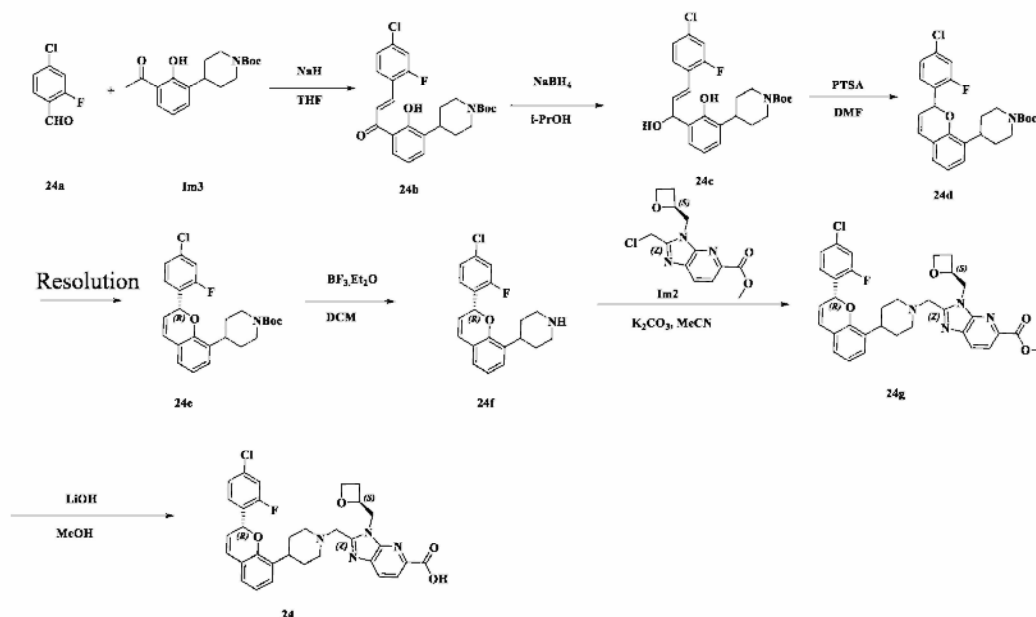
Example 24

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid

Method I

Example 18 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid.

Method II



Step 1

Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl)-2-hydroxyphenyl)piperidine-1-carboxylate [0358] Tert-butyl 4-(3-acetyl-2-hydroxyphenyl)piperidine-1-carboxylate **Im4** (20.3 g, 63.56 mmol) and tetrahydrofuran (300 mL) were added to a 1000 mL flask, the mixture was cooled at 0°C for 10 minutes, and sodium hydride (7.63 g, 190.67 mmol, 60% purity) was added. Then 4-chloro-2-fluorobenzaldehyde **24a** (10.08 g, 63.56 mmol) was dissolved in THF (100 mL), and the mixture was slowly added dropwise into the reaction liquid through a constant pressure dropping funnel over 20 minutes. After the addition, the mixture was warmed to 25°C and reacted for 2 h. After the reaction was stopped, the reaction liquid was quenched with saturated ammonium chloride aqueous solution (200 mL). Water (50 mL) was added, and the obtained mixture was extracted with ethyl acetate (200 mL × 3). The organic phase was washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. Ethyl acetate (60 mL) was added, and the mixture was slurried (stirred for 15 minutes) and filtered. The filter cake was washed with petroleum ether (30 mL) and dried to obtain the title product tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl)-2-hydroxyphenyl)piperidine-1-carboxylate **24b** (15.2 g), yield: 52.00%.

[0359] MS *m/z* (ESI): 460.1 [M+1].

Step 2

Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)-2-hydroxyphenyl)piperidine-1-carboxylate

[0360] Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)acryloyl)-2-hydroxyphenyl) piperidine-1-carboxylate **24b** (25 g, 54.36 mmol) and isopropanol (500 mL) were added to a 1000 mL flask, and sodium borohydride (3.08 g, 81.53 mmol) was added at 0°C. The reaction liquid was then reacted at 20°C for 3 h. After the reaction was stopped, the reaction liquid was quenched with water (100 mL), and the obtained mixture was extracted with ethyl acetate (200 mL × 3). The organic phase was washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to obtain the title product tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)-2-hydroxyphenyl) piperidine-1-carboxylate **24c** (25 g), yield: 99.56%.

[0361] MS m/z (ESI): 462.1 [M+1].

Step 3

Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate

[0362] Tert-butyl 4-(3-(3-(4-chloro-2-fluorophenyl)-1-hydroxyallyl)-2-hydroxyphenyl) piperidine-1-carboxylate **24c** (25 g, 54.12 mmol) and N,N-dimethylformamide (300 mL) were added to a 500 mL flask, and p-toluenesulfonic acid (13.98 g, 81.18 mmol) was added at 25°C. The reaction liquid was then reacted at 50°C for 4 h. After the reaction was stopped, the reaction liquid was quenched with water (200 mL), and the obtained mixture was extracted with ethyl acetate (200 mL × 3). The organic phase was washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate **24d** (13 g), yield: 54.11%.

[0363] MS m/z (ESI): 444.1 [M+1].

Step 4

Tert-butyl (R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate

[0364] Tert-butyl 4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate **24d** was subjected to chiral separation to obtain tert-butyl (R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate **24e**.

[0365] Resolution conditions

[0366] OD-H 4.6*150

[0367] Hexane: IPA : DEA =90 : 10 : 0.1%

[0368] F = 1mL T=35°C

[0369] MS m/z (ESI): 444.1 [M+1].

Step 5

(R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine

[0370] Tert-butyl (R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine-1-carboxylate **24e** (2.55 g, 5.74 mmol) and dichloromethane (50 mL) were added to a 100 mL flask, and 4A molecular sieve (2.55 g) and boron trifluoride diethyl etherate (2.04 g, 14.36 mmol) were added at 0°C. The reaction liquid was then reacted at 0°C for 2 h. After the reaction was stopped, the reaction liquid was quenched with saturated sodium bicarbonate aqueous solution (10 mL). Water (10 mL) was added, and the obtained mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation to obtain the title product (R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine **24f** (1.97 g, yield: 100%).

[0371] MS m/z (ESI): 344.1 [M+1]

Step 6

Methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate

[0372] (R)-4-(2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidine **24f** (1.97 g, 5.73 mmol) and acetonitrile (50 mL) were added to a 100 mL flask, and potassium carbonate (1.58 g, 11.46 mmol) and methyl (S)-2-(chloromethyl)-3-(oxetan-2-ylmethyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **Im2** (1.69 g, 5.73 mmol) were added at 25°C. The reaction liquid was then reacted at 25°C for 10 h. After the reaction was stopped, the reaction liquid was quenched with aqueous solution (20 mL), and the obtained mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by silica gel column chromatography with petroleum ether and ethyl acetate as an eluent system to obtain the title product methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **24g** (3.1 g), yield: 89.71%.

[0373] MS m/z (ESI): 603.2 [M+1]

Step 7

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylic acid

[0374] Methyl 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazolo[4,5-b]pyridine-5-carboxylate **24g** (3.1 g, 5.14 mmol) and methanol (25 mL) were added to a 100 mL flask, and lithium hydroxide (1.23 g, 51.40 mmol) was dissolved in water (10 mL), and the mixture was added dropwise to the reaction liquid at

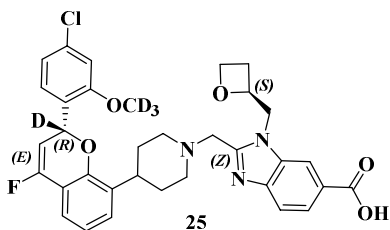
25°C. The reaction liquid was then reacted at 25°C for 1 h. After the reaction was stopped, the reaction liquid was quenched with formic acid (1 mL). Water (20 mL) was added, and the obtained mixture was extracted with dichloromethane (20 mL × 3). The organic phase was washed with saturated sodium chloride solution (20 mL), dried over anhydrous sodium sulfate, filtered, and dried by rotary evaporation. The resulting residue was purified by prep-HPLC to obtain the title product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-3H-imidazo[4,5-b]pyridine-5-carboxylic acid **24** (2.1 g), yield: 69.35%.

[0375] MS m/z (ESI): 589.1 [M+1]

[0376] ¹H NMR (400 MHz, MeOD) δ 8.14 – 8.03 (m, 2H), 7.40 (t, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.05 (dd, 1H), 6.92 (dd, 1H), 6.84 (t, 1H), 6.68 (dd, 1H), 6.21 (dd, 1H), 5.82 (dd, 1H), 5.30 – 5.24 (m, 1H), 5.03 – 4.93 (m, 1H), 4.85 – 4.81 (m, 1H), 4.64 – 4.54 (m, 1H), 4.45 – 4.35 (m, 1H), 4.23 (d, 1H), 4.13 (d, 1H), 3.25 – 3.18 (m, 1H), 3.12 – 3.05 (m, 1H), 2.95 – 2.85 (m, 1H), 2.83 – 2.70 (m, 1H), 2.57 – 2.38 (m, 3H), 1.88 – 1.78 (m, 2H), 1.78 – 1.63 (m, 1H), 1.59 – 1.51 (m, 1H).

Example 25

2-((4-((R)-2-(4-chloro-2-(methoxy-d₃)phenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

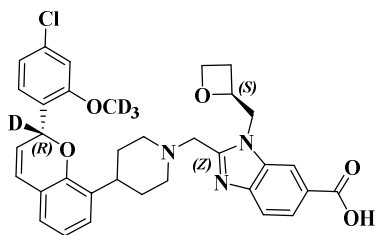


[0377] Example 17 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-(methoxy-d₃)phenyl)-4-fluoro-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0378] MS m/z (ESI): 622.2 [M+1].

Example 26

2-((4-((R)-2-(4-chloro-2-(methoxy-d₃)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid

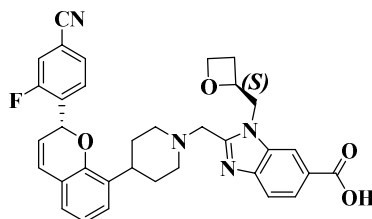


[0379] Example 19 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-(methoxy-d3)phenyl)-2H-chromen-8-yl-2-d)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0380] MS m/z (ESI): 604.2 [M+1].

Example 27

2-((4-((R)-2-(4-cyano-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



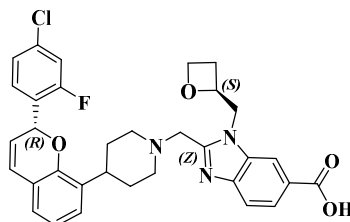
[0381] 4-cyano-2-fluorobenzaldehyde and intermediate Im-1 were used as the raw materials, and Example 18 was referenced to obtain the product 2-((4-((R)-2-(4-cyano-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-1-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0382] MS m/z (ESI): 579.2 [M+1].

[0383] ¹H NMR (400 MHz, DMSO) δ 8.25 (d, 1H), 7.95 (dd, 1H), 7.79 (dd, 1H), 7.70 (dd, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.07 (dd, 1H), 6.99 (dd, 1H), 6.87 (t, 1H), 6.75 (dd, 1H), 6.33 (dd, 1H), 5.93 (dd, 1H), 5.11 – 5.00 (m, 1H), 4.85 – 4.71 (m, 1H), 4.67 – 4.58 (m, 1H), 4.52 – 4.44 (m, 1H), 4.42 – 4.31 (m, 1H), 3.92 (d, 1H), 3.75 (d, 1H), 3.04 – 2.92 (m, 1H), 2.83 – 2.62 (m, 3H), 2.46 – 2.38 (m, 1H), 2.23 – 2.02 (m, 2H), 1.73 – 1.56 (m, 2H), 1.48 – 1.34 (m, 2H).

Example 28

2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid



[0384] Im-1 was used as the raw materials and example 24 was referenced to obtain the product 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid.

[0385] MS m/z (ESI): 588.2 [M+1].

[0386] ¹H NMR (400 MHz, MeOD) δ 8.30 (s, 1H), 7.96 (dd, 1H), 7.66 (d, 1H), 7.40 (t, 1H), 7.25 (s, 1H), 7.16 (d, 1H), 7.04 (dd, 1H), 6.92 (dd, 1H), 6.83 (d, 1H), 6.68 (dd, 1H), 6.23 – 6.19 (m, 1H), 5.83 (dd, 1H), 5.27 – 5.20 (m, 1H), 4.85 – 4.80 (m, 1H), 4.74 – 4.62 (m, 2H), 4.48 – 4.41 (m, 1H), 4.05 (d, 1H), 3.95 (d, 1H), 3.12 – 3.05 (m, 1H), 2.94 – 2.77 (m, 3H), 2.55 – 2.46 (m, 1H), 2.39 – 2.25 (m, 2H), 1.82 – 1.73 (m, 2H), 1.66 – 1.50 (m, 2H).

Biological assay and evaluation

[0387] The present disclosure will be further described and explained below in conjunction with test examples, and these examples are not meant to limit the scope of the present disclosure.

I. Determination of the ability of the compounds of the present disclosure to stimulate the production of cAMP in human GLP1 receptor stably transfected cell line

1. Experimental objective:

[0388] The objective of this test example is to test the ability of a compound to activate human GLP-1 receptors on the cell surface. EC₅₀ of the generation of AMP due to stimulation after agonism characterizes the ability of the compound to activate the human GLP-1 receptor.

2. Experimental reagents and instruments:

2.1 Experimental instruments:

[0389] Microplate reader (BioTek Synergy H1);

[0390] Pipette (Eppendorf & Rainin).

2.2 Experimental reagents:

[0391] DMEM/F12 medium was purchased from Gibco, with a catalog number of 11330032;

[0392] Casein was purchased from Sigma, with a catalog number of C3400;

[0393] 384-well plate was purchased from Sigma, with a catalog number of CLS4514;

[0394] IBMX was purchased from Sigma, with a catalog number of I7018;

[0395] Cisbio cAMP - Gs Dynamic kit was purchased from Cisbio, with a catalog number of 62AM4PEC.

3. Experimental method:

[0396] The frozen human GLP1 receptor stably transfected cell line CHO-K1/GLP-1R/CRE-luc was taken out from the liquid nitrogen tank, placed in a 37°C water bath kettle to thaw quickly, and resuspended with DMEM/F12 medium. The cells were washed once after centrifugation, resuspended with experimental buffer, that is, DMEM/F12 medium containing 0.1% casein, and the cell density was adjusted with experimental buffer, and the cells were plated onto a 384-well plate at a density of 2500 cells/5 µL/well, then 2.5 µL of IBMX working solution prepared with buffer was added to each well, the final concentration of IBMX was 0.5 mM, and 2.5 µL of serially diluted compound samples (starting from 1000 nM, 3-fold dilution, 11 concentrations)

were also added, centrifuged at 1000 rpm for 1min, shaken for 30 seconds to mix uniformly, and stood at room temperature and incubated for 30 minutes. Cisbio cAMP - Gs Dynamic kit was used for detection, and cAMP-d2 and Anti-cAMP-Eu³⁺-Cryptate were respectively diluted 20 folds with cAMP Lysis & Detection Buffer and mixed uniformly. 5 µL of diluted cAMP-d2 solution was added to each well, then 5 µL of diluted Anti-cAMP- Eu³⁺-Cryptate solution was added, shaken for 30 seconds to mix uniformly, and incubated at room temperature in the dark for 1 h. Biotek Synergy H1 microplate reader was used to read HTRF signals, with an excitation wavelength of 320 nm and emission wavelengths of 620 nm and 665 nm.

4. Experimental data processing method:

[0397] The signal ratio (665 nm/620 nm*10,000) was calculated, and the nonlinear fitting of the signal ratio and sample concentration was performed using a four-parameter equation in GraphPad Prism 6 to obtain the EC₅₀ value.

5. Experimental results:

Table 1

Example	EC50 (nM)
1	0.13
2-A	0.07
9-A	0.07
10-A	0.05
16	0.1
17	0.04
18	0.07
19	0.05
23	0.08
24	0.03
25	0.08
27	0.05
28	0.06

6. Experimental conclusion

[0398] According to the above scheme, the example compound of the present disclosure showed good biological activity in the experiment of stimulating the human GLP1 receptor stably transfected cell line to produce cAMP.

II. Effects of single administration of the compound of the present disclosure on intraperitoneal glucose tolerance of GLP-1R humanized mice

1. Experimental objective:

[0399] To evaluate the effects of a single administration of the compound of the present disclosure on blood glucose changes in the intraperitoneal glucose tolerance (*ipGTT*) experiment of GLP-1R humanized C57BL/6 mice.

2. Experiment materials:

[0400] C57BL/6_ *hGLP-1R*, male, 5-8 weeks; Ultra-clean bench; Electronic balance; Active blood glucose meter; Glucose.

3. Experimental operations and data processing:

[0401] 3.1 One day before the experiment, the animals were randomly divided into groups according to their body weights, with 5 animals in each group. All animals were deprived of food to fast overnight and fasted for more than 16 h before administration.

[0402] 3.2 A 0.2 g/mL glucose solution was prepared with pure water and filtered through a 0.22 μm filter membrane for later use.

[0403] 3.3 On the day of the test, the blood glucose level of each animal was measured in turn by tail-cutting method before administration, and recorded as the Baseline value;

[0404] Blood glucose test method: The mouse was placed in a restrainer, the tail tip was disinfected with alcohol cotton balls, then a little of the tail tip was cut with scissors. The first drop of blood was discarded, and the second drop of blood was dropped onto the prepared blood glucose test paper to test the blood glucose value.

[0405] 3.4 Administration was performed according to the body weights of the animals and the administration time of each animal was recorded. 1 h after administration, the blood glucose level of each animal was measured in turn and recorded as the blood glucose level at 0 min;

[0406] 3.5 Subsequently, according to the body weight of the day, pure water or glucose solution was intraperitoneally injected immediately, with a volume of 10 mL/kg and a glucose dose of 2 g/kg;

[0407] 3.6 The blood glucose level of each mouse was respectively measured at 15, 30, 60, 90 and 120 min after the injection of pure water or glucose solution, and the time and data was recorded;

[0408] 3.7 After the test was completed, all animals resumed feeding.

[0409] 3.8 Data processing:

[0410] The blood glucose (BG)-time curve was plotted, and the area under the blood glucose-time curve was calculated. The calculation formula was:

$$\text{AUC (mmol/L.hr)} = (\text{BG0} + \text{BG15}) \times 0.25/2 + (\text{BG15} + \text{BG30}) \times 0.25/2 + (\text{BG30} + \text{BG60}) \times 0.5/2 + (\text{BG60} + \text{BG90}) \times 0.5/2 + (\text{BG90} + \text{BG120}) \times 0.5/2.$$

[0411] Note: BG0, BG15, BG30, BG60, BG90 and BG120 represent the blood glucose values before sugar administration (0 min), 15, 30, 60, 90 and 120 min after sugar administration, respectively.

[0412] The blood glucose reduction rate at each time point and AUC was calculated according to the average blood glucose value and blood glucose AUC at each time point. The calculation formula was: blood glucose reduction rate = (blood glucose in the administration group/AUC - blood glucose in the model control group/AUC)/blood glucose in the model control group/AUC × 100%.

4 Experimental results:

Compound	Dose (mg/kg)	Number of animals	Blood glucose AUC reduction rate%
Vehicle	-	5	-
Example 17	0.3	5	53.09
Example 18	0.3	5	56.79
Example 19	0.3	5	46.57
Example 24	0.3	5	62.89

5. Experimental conclusion

[0413] According to the above experimental results, it can be seen that the example compounds of the present disclosure can effectively reduce blood glucose in mice.

III. Effects of long-term administration of the compound of the present disclosure on the body weight and food intake of GLP-1R humanized mice fed with a high-fat diet

1. Experimental objective:

[0414] The purpose of this test is to evaluate the effects of long-term administration of the compound on the body weight and food intake of GLP-1R humanized C57BL/6 mice fed with a high-fat diet.

2. Experimental reagents and instruments

[0415] C57BL/6_ *hGLP-1R*, male, 5-8 weeks; 60% high-fat diet (HFD); Ultra-clean bench; Electronic balance.

3. Experimental method

[0416] 3.1 On the day of starting high-fat diet feeding, C57BL/6 mice were randomly divided into two groups according to body weight. The first group of 7 mice was Blank, fed with normal control diet, and the remaining animals were modeling group, fed with high-fat diet until the end of the experiment.

[0417] 3.2 At the 8th week of HFD feeding, the animals of the modeling group were randomly divided into groups according to body weight, with 7 mice in each group. The first group was Vehicle group (Vehicle: 0.5% CMC-Na + 1% Tween 80), which was administered vehicle; The remaining group were administration group; Administration regimen: The corresponding compound was administered orally, with an administration cycle of 14 days, once a day, an administration dosage of 10 mg/kg, and an administration volume of 10 mL/kg. The Blank group continued to feed normal diet, and no administration operation was performed.

[0418] 3.3 The day of administration was defined as Day 0.

[0419] 3.4 At each administration, the animals were weighed and the data were recorded, and oral administration was performed according to body weight, with an administration volume of 10 mL/kg.

[0420] 3.5 Starting from the day 0 of the experiment, the food intake of each group of mice was measured every three days. Specifically, the feed was changed after each weighing and administration, and the added and remaining amounts were recorded.

[0421] 3.6 On Day 14, the end of the experiment, all mice were euthanized and dissected according to the grouping order, and the livers were removed and weighed.

4. Experimental data processing and statistical analysis

[0422] The body weight and body weight change rate of mice after administration were summarized and statistically analyzed. Calculation of body weight change rate: $(BW_t - BW_0) / BW_0 \times 100\%$. BW_t represents the body weight of mice on the day t of the experiment, and BW_0 represents the body weight of mice on the day 0 of the experiment.

[0423] Calculation of food intake: $(\text{Added amount (g)} - \text{Remaining amount (g)}) / \text{Number of animals per cage}$, the cumulative food intake was the sum of the daily food intake of each animal during the administration.

[0424] Experimental data were analyzed using GraphPad Prism software. The comparison between two groups was tested using t-test method. Comparisons among three or more groups were tested using one-way ANOVA method.

5. Experimental results

Compound	Dose (mg/kg)	Weight (g)-D0			Weight (g)-D10			Weight change (%)-D10
		Mean	±	SEM	Mean	±	SEM	Mean
Vehicle	-	28.52	±	0.54	28.28	±	0.58	-0.84%
Example 17	10	28.54	±	0.37	26.20	±	0.36	-8.19%
Example 16	10	28.40	±	0.67	26.01	±	0.85	-8.49%
Example 18	10	28.54	±	0.46	26.04	±	0.42	-8.75%

Compound	Dose (mg/kg)	Weight (g)-D0			Weight (g)-D10			Weight change (%)-D10
		Mean	±	SEM	Mean	±	SEM	Mean
Vehicle	-	28.09	±	0.81	28.23	±	0.75	0.55%
Example 19	10	28.37	±	1.06	26.57	±	1.14	-6.37%
Example 24	10	28.23	±	0.37	25.85	±	0.44	-8.44%
Example 28	10	28.34	±	0.46	25.65	±	0.77	-9.53%

6. Experimental conclusion

[0425] According to the above experimental results, it can be seen that long-term administration of the example compound of the present disclosure has a good weight-reducing effect on GLP-1R humanized C57BL/6 mice fed with a high-fat diet.

IV. Pharmacokinetic determination in SD rat

1. Study objective:

[0426] SD rats were used as test animals to study the pharmacokinetic behavior of the following compound examples in plasma of rat in vivo after oral administration at a dose of 50 mg/kg.

2. Experimental scheme

2.1 Experimental drugs:

[0427] Vehicle formula: 0.5% CMC-Na (1% Tween 80);

[0428] the examples of the present disclosure, made in house.

2.2 Experimental animals:

[0429] 3 SD rats per group, male.

2.3 Administration:

[0430] 3 SD rats per group, male, PO respectively at a dose of 50 mg/kg and an administration volume of 10 mL/kg after the rats were fasted overnight.

2.4 Sample collection:

[0431] Before and after administration, 0.2 mL of blood was collected from the jugular vein of rats at 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h and placed in EDTA-K₂ test tubes, which were centrifuged at 6000 rpm at 4°C for 6 min to separate plasma, and the plasma was stored at -80°C. The mice were fed at 4 h after administration.

2.5 Sample treatment:

[0432] 1) 160 uL of acetonitrile was added to 40 uL of plasma sample for precipitation, and same was mixed and centrifuged at 3500 × g for 5 to 20 min.

[0433] 2) 100 uL of the treated supernatant solution was taken and subjected to LC/MS/MS to analyze the concentrations of the test compound.

2.6 Liquid phase analysis

- Liquid phase conditions: Shimadzu LC-20AD pump
- Mass spectrometry conditions: AB Sciex API 4000 mass spectrometer
- Chromatographic column: Phenomenex Gemu 5 um C18 50 × 4.6 mm
- Mobile phase: liquid A was 0.1% aqueous formic acid solution, and liquid B was methanol
- Flow rate: 1.0 mL/min
- Elution time: 0-4.0 min, the eluent is as follows:

Time/min	Liquid A	Liquid B
0.01	90%	10%
0.5	90%	10%
0.8	5%	95%
2.4	5%	95%
2.5	90%	10%
4.0	Stop	

3. Experimental results and analysis

[0434] The main pharmacokinetic parameters were calculated using WinNonlin 8.2.

4. Experimental results

Compound	t _{max} (h)	C _{max} (ng/mL)	AUC _{0-t} (ng/mL*h)	AUC _{0-∞} (ng/mL*h)	t _{1/2} (h)
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Example 2-A	2.0	7157	35755	35838	3.1
Example 16	1.0	2303	10311	10831	2.0
Example 24	2.0	6403	19084	19114	3.8
Example 27	1.0	9397	12550	12555	1.6
Example 28	0.5	7980	21532	21556	2.0

5. Experimental conclusion:

[0435] As could be seen from the results of the pharmacokinetic experiment on rats in the table, the example compounds of the present disclosure, at a dose of 50 mg/kg, exhibited good metabolic properties and performed well on both exposure (AUC) and maximum blood drug concentration C_{max} .

Study on salt and crystal form

1.1 Experimental instruments

1.1.1 Some parameters of physical and chemical testing instruments

XRPD	Instrument model	BRUKER D8 ADVANCE
	Diffracted ray	CuK (40 kV, 25 mA)
	Scan rate	0.02°/S (2 θ value)
	Scan range	4° - 40°(2 θ value)
DSC	Instrument model	NETZSCH DSC 214 polyna
	Purge gas	Nitrogen
	Purge rate	40 mL/min
	Heating rate	10°C/min
	Temperature range	25°C-350°C
	Tray type	Aluminum tray
TGA	Instrument model	NETZSCH TG 209 Tarsus
	Purge gas	Nitrogen
	Purge rate	40 mL/min
	Heating rate	10°C/min
	Temperature range	Room temperature-400°C
	Tray type	Al ₂ O ₃

1.2 Instrument and liquid phase analysis conditions

1.2.1 Instruments and equipment

Name of instrument	Model
Analytical balance	METTLER TOLEDO XA105
Water purifier	Milli-Q Plus, Millipore
High performance liquid chromatograph	Agilent1260
Pump	Agilent G1311B
Sample injector	G1329B
Column oven	G1316A
Detector	G1315D

1.2.2 Chromatographic conditions

Instrument	Agilent 1260	
Mobile phase A	A: 0.05% TFA in H ₂ O	
Mobile phase B	B: 0.05%TFA in ACN	
Flow rate	1.0 mL/min	
Injection volume	3 μ L	
Chromatographic column	Waters X-bridge C18 (150*4.6mm,3.5 μ m)	
Column temperature	25°C	
Detection wavelength	225 nm	
Gradient (min)	A%	B%
0.00	60	40
8.00	20	80
12.00	20	80
12.01	60	40
15.00	60	40

Preparation of salt form of compound

2. Screening of salt form and crystal form of compound

2.1 Screening of salt form of compound

2.1.1 Experimental objective:

[0436] Different counter-ion bases were selected, and which counter-ion bases can form a salt of the compound were detected through appropriate crystallization methods.

2.1.2 Experimental steps:

1) Instruments and equipments

Name	Model	Source
Analytical balance	XA105	METTLER TOLEDO
Ultrasonic cleaner	SK5200LHC	Shanghai Kudos Ultrasonic Instrument
Pipette	Eppendorf (50 mL, 100 μ L)	Eppendorf

2) Operation procedure

3. Screening of salt form of free acid

3.1 Screening of salt form using solvent ACN system

[0437] A total of 181.82 mg of compound 28 was weighed, and 2.4 ml of ACN was added. A ball was formed, adhered to the wall, and not fully dissolved after ultrasonication and heating. 400 μ l of water was added, and the mixture was subjected to ultrasonication. The solid adhered to the wall was gradually dissolved, resulting in a stock solution that was slightly turbid with minor mechanical impurities. Each aliquot (245 μ l, equivalent to 15.91 mg of compound) was further treated by adding 1.1 equivalents of base solution (29.8 μ l), as detailed in the table below. After overnight at room temperature, a solid was precipitated. The detection XRD of the solid was obtained.

[0438] The obtained 2-3 had good crystallinity. DSC showed that 2-3 might be a solvate or a hydrate. TGA further illustrated that 2-3 was dehydrated or desolvated at low temperature.

Results of screening of salt form using ACN system

Serial No.	Counter-ion base	Stock/ μ l	Counter-ion acid/ μ l	Phenomenon after adding base	Room temperature overnight	ACN was added	Evaporated to dryness	EA was added and slurried	XRD
2-1	1 mol/L sodium hydroxide-aqueous solution	245	29.8	Turn red, dissolved clarification	Dissolved clarification	Oil formation	Oil formation	Solid	

2-2	1 mol/L potassium hydroxide-aqueous solution	245	29.8	Turn red, dissolved clarification	Dissolved clarification	Oil formation	Oil formation	Solid	
2-3	1 mol/L tromethamine-aqueous solution	245	29.8	Dissolved clarification	Solid	/	/	/	Form A

[0439] The experimental results showed that the results of screening of salt form using ACN system afforded crystal form A of tromethamine salt.

[0440] H-NMR analysis was performed on samples 2-3 to determine whether salt (Tris) was formed. The results showed that because the chemical shift of the methylene of Tris may overlap with the chemical shift of water, and the H of the hydroxyl did not produce a peak in H-NMR, it was impossible to determine whether Tris salt was formed by H-NMR.

[0441] The free form content was measured by HPLC-DAD to determine whether the salt was formed. As shown in the table below, the average free form content percentage of the two Tris salt samples was 80.58%, which was closest to the theoretical free form content percentage when binding 1 molecule of Tris and 1 molecule of water. Therefore, it was preliminarily determined that the Tris salt was a hydrate binding 1 molecule of water.

HPLC-DAD quantitative results of Tris salt of compound 28

Sample	sample 1	sample 2
Determination of free base content percentage in the compound	81.91	79.25
Theoretical free form content percentage when binding 1 molecule of Tris	82.93	
Theoretical free form content percentage when binding 1 molecule of Tris and 1 molecule of water	80.88	
Theoretical free form content percentage when binding 1 molecule of Tris and 1 molecule of acetonitrile	78.40	

Theoretical free form content percentage when binding 1 molecule of Tris, 1 molecule of acetonitrile and 1 molecule of water	76.56
Theoretical water content percentage when binding 1 molecule of Tris and 1 molecule of water	2.48

Remarks:

sample 1: ACN-H₂O-Tris (crystal form A)

sample 2: MeOH- Tris-Evap-EA Slurry (crystal form A)

[0442] The free form content was further measured using HPLC-ELSD to determine the salt formation ratio. The method was shown in the table below. The results showed that the average Tris content percentage of the two Tris salt samples was 16.13%, which was closest to the theoretical Tris content percentage when binding 1 molecule of Tris and 1 molecule of water.

Methods and conditions of HPLC-ELSD quantitative determination

Mobile phase	A: 75 mM ammonium acetate (pH 4.80); B: Acetonitrile
Chromatographic column	ZIC HILIC (150*4.6mm, 5um)
Column temperature	40°C
ELSD temperature	40°C
Pressure	3.5bar
Proportion	70%B (v/v)
Run time	10min

HPLC-ELSD quantitative results of Tris salt of compound 28

Sample	sample 1	sample 2
Determination of Tris amine content percentage in the compound	15.76	16.57
Theoretical Tris content percentage in a salt when binding 1 molecule of Tris	17.07	

Theoretical Tris content percentage in a salt when binding 1 molecule of Tris and 1 molecule of water	16.64
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Remarks:

sample 1: ACN-H₂O-Tris (crystal form A)

sample 2: MeOH- Tris-Evap-EA Slurry (crystal form A)

[0443] Combining the DSC pattern and TGA pattern, the weight loss (ACN-TRIS) before 80 degrees was about 2%, which was equivalent to the theoretical water content percentage in the Tris salt when binding 1 molecule of Tris and 1 molecule of water. It was further determined that the crystal form A of Tris salt was a monohydrate.

3.2 Screening of salt form using solvent DCM system

[0444] A total of 147.31 mg of compound 28 was weighed, and 2.2 ml of DCM was added to formulate a stock solution. After the dissolution was completed, each aliquot (200 ul, equivalent to 13.39 mg of compound) was evaporated to dryness at 40 degrees, then the following solvents (200 ul each) were respectively added for dissolution, then 1.1 equivalents of 1 mol/L tromethamine aqueous solution (25.1 uL) was respectively added, holes were pierced for evaporation to dryness. The phenomenon was shown in the following table.

Results of screening of salt form using DCM system

Serial No.	Solvent	Phenomenon after adding solvent	Phenomenon after adding Tris	Evaporation to dryness at room temperature	EA was added and slurried	XRD
3-4	Acetone	Dissolved clarification	Dissolved clarification	Oil formation	Solid	Crystal form C
3-5	MEK	Dissolved clarification	Dissolved clarification	Oil formation	Solid	Crystal form C
3-6	2-Me-THF	Dissolved clarification	Dissolved clarification	Oil formation	Solid	Crystal form C
3-8	1-BuOH	Dissolved clarification	Dissolved clarification	Oil formation	Solid	Crystal form C
3-9	2-BuOH	Dissolved clarification	Turbid, oil formation	Oil formation	Solid	Crystal form C

3-10	Dioxane	Dissolved clarification	Turbid, oil formation	Oil formation	Solid	Crystal form E
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[0445] The experimental results showed that the results of screening of salt form using DCM system afforded crystal forms C and E of tromethamine salt.

3.3 Screening of salt form using solvent ACN-H₂O system

[0446] 27.69 mg of compound 28 was weighed, and ACN : H₂O = 6 : 1 (v/v) (400 ul) was added, the oil was adhered to the wall and gradually dissolved at 40 degrees. 1.1 eq of 1 mol/L tromethamine aqueous solution (51.8 ul) was added. Dissolved clarification occurred, the solution was kept at 40 degrees for 3 h, with no solid precipitation observed. Stirring at room temperature also yielded no precipitation. After ultrasonication for 1 to 2 min, violent precipitation occurred followed by solidification. 200 ul of ACN : H₂O = 6 : 1 (v/v) was supplemented, and the mixture was stirred at room temperature for 3 h, filtered, oven-dried in vacuo at 40 degrees overnight, and then corresponding characterization was performed. The XRD pattern of the sample showed that the crystal form D of tromethamine salt was obtained, and was a monohydrate similar to the crystal form A of Tris salt as showed by the DSC pattern.

4. Preparation methods of different salt forms

(1) Preparation of crystal form A of tromethamine salt

[0447] 15.91 mg of free acid was weighed and 245 uL of acetonitrile : water = 6 : 1 (v/v) was added. The mixture was rendered slightly turbid with minor mechanical impurities after ultrasonication. 1.1 equivalents of 1 mol/L tromethamine aqueous solution (29.8 ul) was added. After overnight at room temperature, solid was precipitated, and centrifuged quickly. The supernatant was removed, and the solid was dried under vacuum at 40°C to constant weight to obtain the crystal form A of tromethamine salt. Upon detection and analysis, it had the XRPD graph as shown in FIG. 1, the DSC graph as shown in FIG. 2, and the TGA graph as shown in FIG. 3.

(2) Preparation of crystal form B of tromethamine salt

[0448] An appropriate amount of the crystal form A of tromethamine salt was taken, and the sample was heated to 88 degrees with TGA for 2 minutes. The obtained mixture was cooled to room temperature, and the crystal form B of tromethamine salt was obtained. Upon detection and analysis, it had the XRPD graph as shown in FIG. 4 and the DSC graph as shown in FIG. 5.

(3) Preparation of crystal form C of tromethamine salt

[0449] 229.54 mg of free form was weighed, and 0.4 ml of acetone was added. Dissolved clarification occurred after ultrasonication, and 1.6 ml of methanol was added. Dissolved

clarification occurred at room temperature, and 0.527 ml (1.1 eq) of 0.815 mol/L Tris ethanol-water (18.44% water by mass fraction) solution was added at 40 degrees. Dissolved clarification occurred. 5 ml of isopropyl ether was added, producing slight turbidity. After being maintained at 40 degrees for 30 min, substantial precipitation occurred. 3 ml of isopropyl ether was supplemented, and the mixture was held at 40°C overnight, yielding a well-defined solid. The mixture was cooled to room temperature, and centrifuged quickly. The supernatant was removed, and the solid was dried under vacuum at 40°C to constant weight to obtain the crystal form C of tromethamine salt. Upon detection and analysis, it had the XRPD graph as shown in FIG. 6, the DSC graph as shown in FIG. 7, and the TGA graph as shown in FIG. 8.

(4) Preparation of crystal form D of tromethamine salt

[0450] 27.69 mg of free form was weighed, and ACN : H₂O = 6 : 1 (v/v) (400 ul) was added, the oil was adhered to the wall and gradually dissolved at 40 degrees. 1.1 eq of 1 mol/L tromethamine aqueous solution (51.8 ul) was added. Dissolved clarification occurred, the solution was kept at 40 degrees for 3 h, with no solid precipitation observed. Stirring at room temperature also yielded no precipitation. After ultrasonication for 1 to 2 min, violent precipitation occurred followed by solidification. 200 ul of ACN : H₂O = 6 : 1 (v/v) was supplemented, and the mixture was stirred at room temperature for 3 h and centrifuged quickly. The supernatant was removed, and the solid was dried under vacuum at 40°C to constant weight to obtain the crystal form D of tromethamine salt. Upon detection and analysis, it had the XRPD graph as shown in FIG. 9, and the DSC graph as shown in FIG. 10.

(5) Preparation of crystal form E of tromethamine salt

[0451] 13.39 mg of free form was weighed, and 200 uL of dioxane was added. Dissolution was performed, and 1.1 equivalents of 1 mol/L tromethamine aqueous solution (25.1 uL) was added, resulting in turbidity and an oily appearance. Holes were pierced for evaporation to dryness, yielding an oil. 200 ul of ethyl acetate was added, and slurring was conducted at 40 degrees for 2 days, converting the material to a solid. After cooling to room temperature, rapid centrifugation was performed, and the supernatant was removed. The solid was dried under vacuum at 40°C to constant weight to obtain the crystal form E of tromethamine salt. After detection and analysis, the crystal form had an XRPD diagram as shown in FIG. 11 and a DSC diagram as shown in FIG. 12 as follows.

5. Thermodynamic stability experiment of crystal form

5.1 Experimental objective:

[0452] Through polycrystalline screening test, the relatively thermodynamically stable crystal form of salt was found.

5.2 Experimental scheme:

[0453] 5.2.1 The crystal form C of tromethamine salt was used as the starting raw material

[0454] 10 mg of the crystal form C of tromethamine salt was taken, and 200 ul of solvent was respectively added. The mixture was slurried at 40 degrees for 2 days, and centrifuged, and the solid was oven-dried in vacuo at 40 degrees overnight, and then XRD and other corresponding characterizations were performed. The results were shown in the table below. The XRD of the obtained solid showed that it was crystal form C, indicating that the crystal form C of tromethamine salt was very stable.

Serial No.	Solvent	Solvent volume ul	Phenomenon after slurrying for 2 days	XRD
13-1	EA	200	Solid	Crystal form C
13-2	IPAC	200	Solid	Crystal form C
13-3	MTBE	200	Solid	Crystal form C
13-4	IPE	200	Solid	Crystal form C
13-6	Heptane	200	Solid	Crystal form C
13-7	hexane	200	Solid	Crystal form C
13-8	EtOH	200	Solid	Crystal form C
13-9	IPA	200	Solid	Crystal form C
13-10	water	200	Dissolved clarification (Dissolved clarification after supplement of sample)	

6. Solubility determination of crystal form C of tromethamine salt

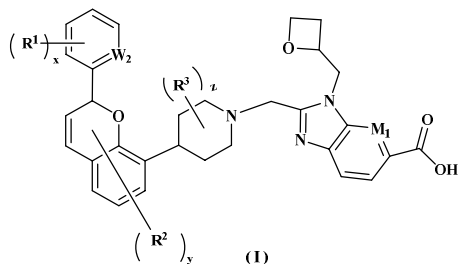
[0455] 1 to 2 mg of compound 28 was weighed into a 1.5 mL liquid phase vial, then 1 mL of pH buffer, artificial simulated gastric fluid (FaSSGF), artificial fasted-state simulated intestinal fluid (FaSSIF), artificial non-fasted-state simulated intestinal fluid (FeSSIF), and pure water were respectively added, and the mixture was placed on a constant temperature oscillator overnight at a temperature of 37 degrees. After 24 h, the sample solution was filtered with a 0.45 µm mixed water fiber filter membrane and then the filtrate was taken. The content was tested by HPLC. For the HPLC detection method, please refer to the solution stability analysis method in Section 1.2. The solubility of the compound in the buffer solution medium was shown in the following table.

Results of solubility of crystal form C of tromethamine salt in different pH buffers

Tromethamine salt	Medium	Solubility mg/ml
Crystal form C	USP Buffer pH 7.4	0.2539
	FaSSIF	0.4782
	FeSSIF	0.7560
	H ₂ O	0.0664

Claims

1. A base salt of a compound as represented by general formula (I) or a stereoisomer thereof, wherein the compound has a structure as follows:



wherein:

each R^1 is independently selected from hydrogen, deuterium, fluorine, chlorine, cyano, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} deuterioalkoxy or C_{1-3} haloalkoxy;

each R^2 is independently selected from hydrogen, deuterium, fluorine, chlorine, cyano, C_{1-3} alkyl, C_{1-3} deuterioalkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} deuterioalkoxy or C_{1-3} haloalkoxy;

each R^3 is independently selected from hydrogen, deuterium or halogen;

M_1 is N or CH;

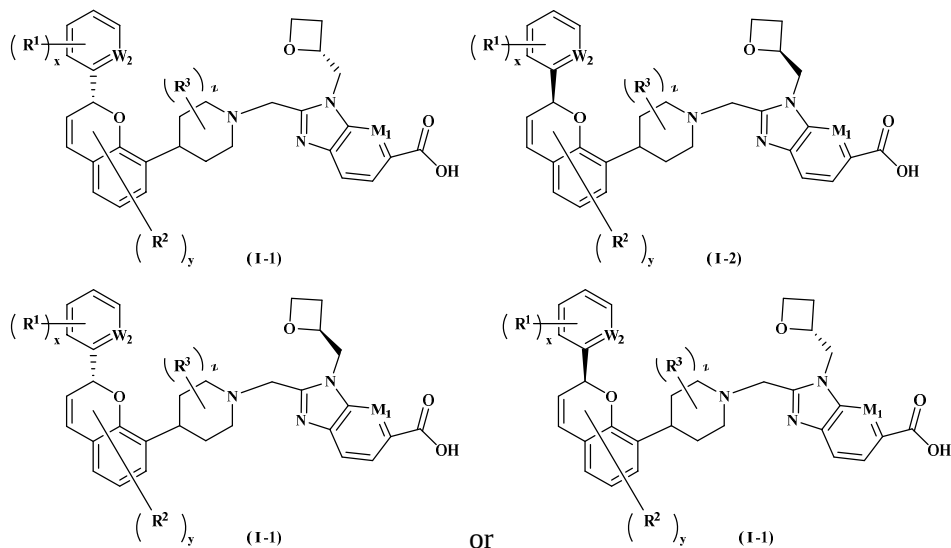
W_2 is N or CH;

x, y and z are each independently 0, 1 or 2;

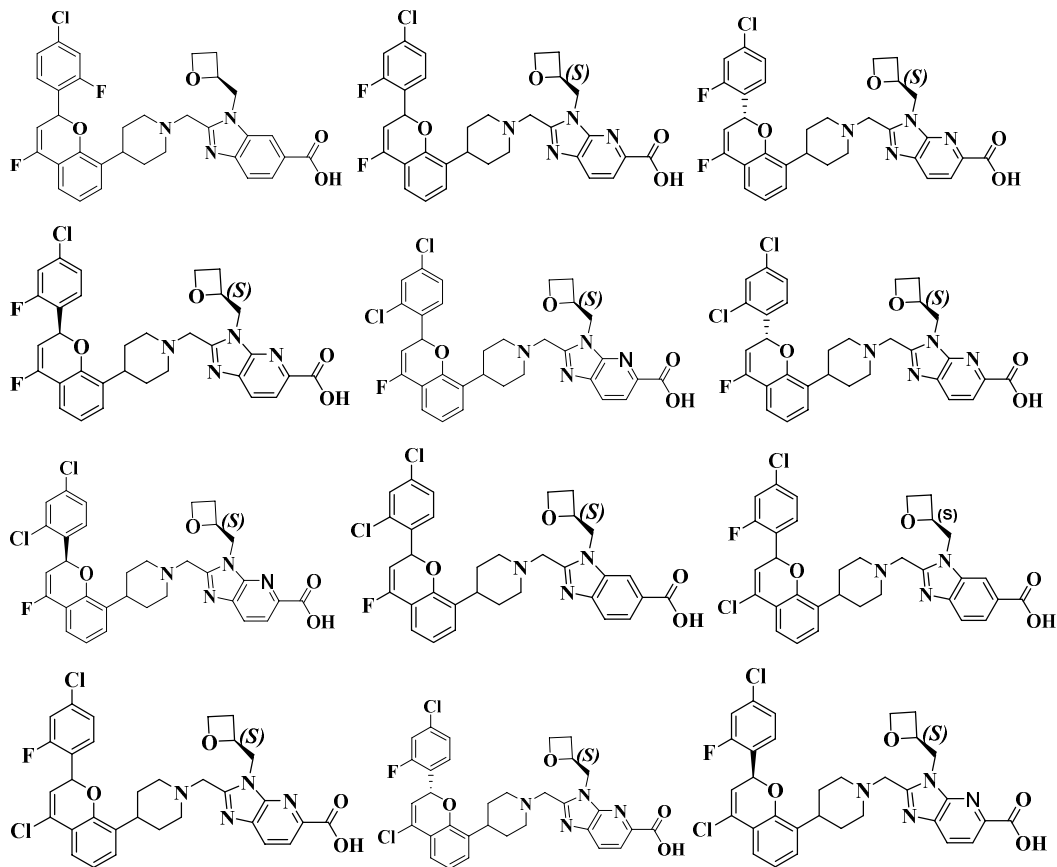
wherein the base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; and the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof.

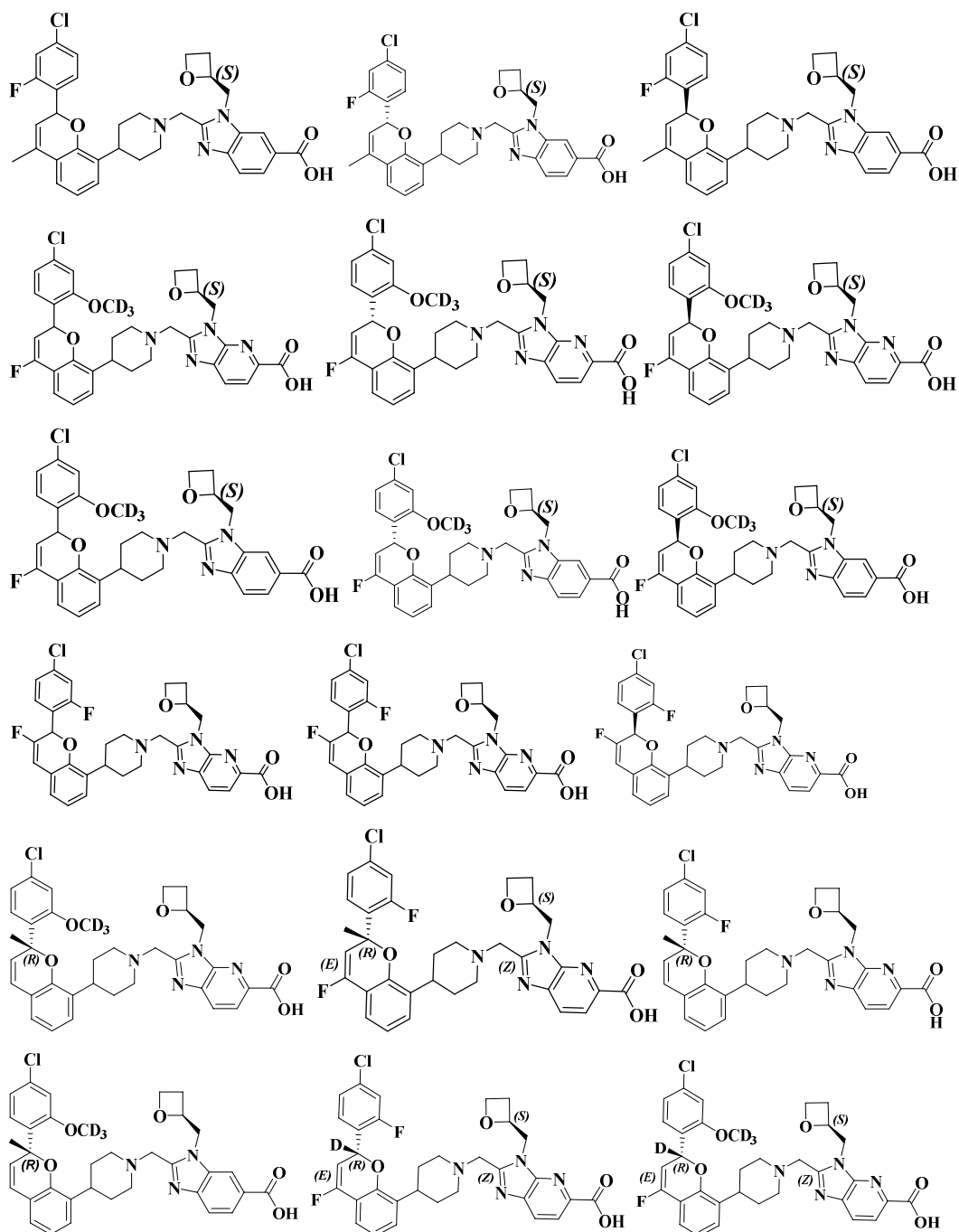
2. The base salt of the compound or the stereoisomer thereof according to claim 1, wherein each R_1 is independently selected from hydrogen, deuterium, fluorine, chlorine, methoxy or -OCD₃;
each R^2 is independently selected from hydrogen, deuterium, fluorine, chlorine or methyl;
each R^3 is independently hydrogen;
 M_1 is CH;
 W_2 is CH; and
x, y and z are each independently 0, 1 or 2.

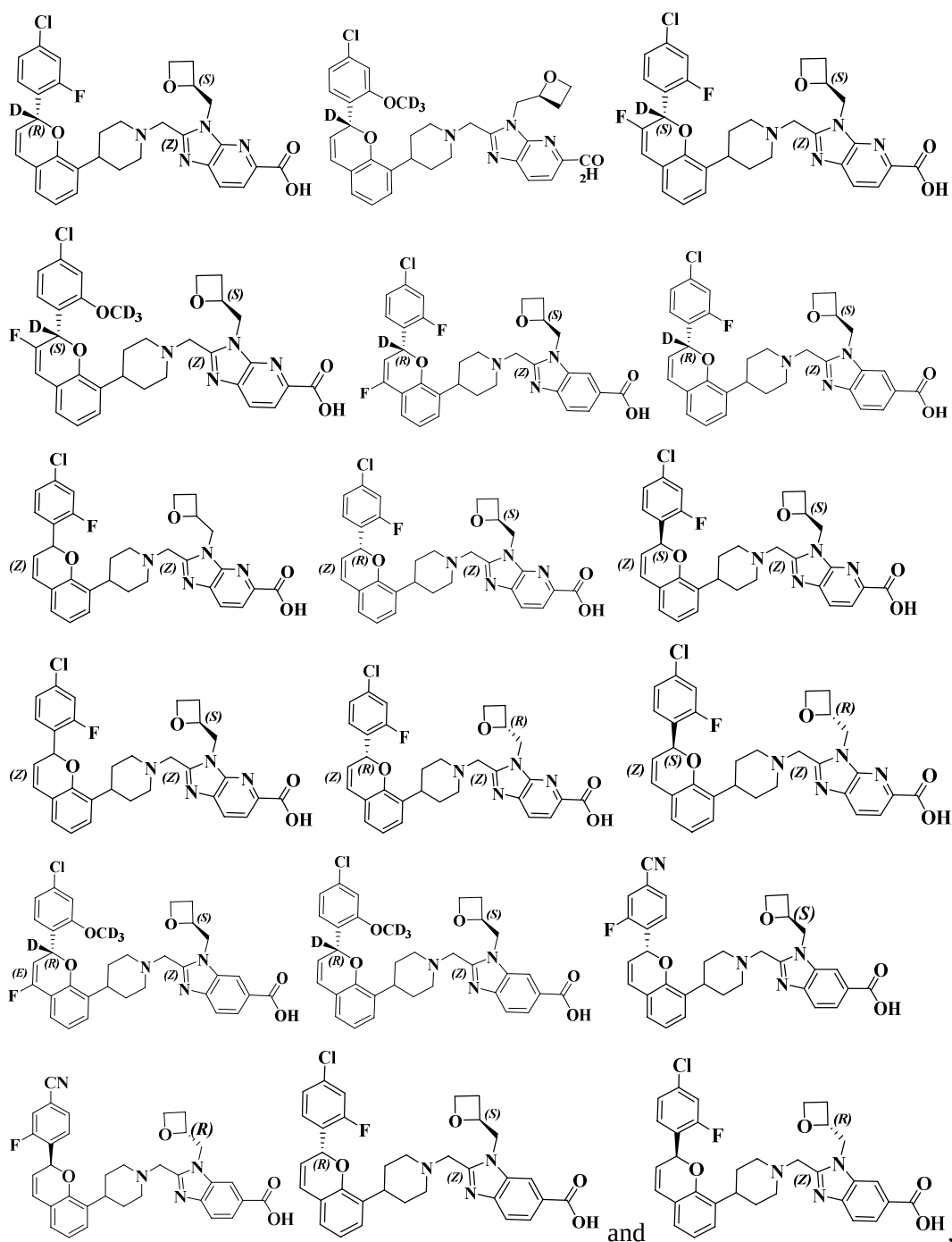
3. The base salt of the compound or the stereoisomer thereof according to claim 1, wherein the compound is further as represented by the following general formula (I-1) to (I-4):



4. The base salt of the compound or the stereoisomer thereof according to claims 1-3, wherein the general formula is selected from the following compounds:







wherein the base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, or a mixture thereof; and the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, or a mixture thereof.

5. The base salt of the compound according to claim 4, wherein the compound is 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-

benzo[d]imidazole-6-carboxylic acid, wherein the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine or a mixture thereof; and the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, or a mixture thereof.

6. The base salt of the compound according to any one of claims 1-5, wherein the number of the base is 0.5-3, preferably 0.5, 1, 1.5, 2, 2.5 or 3, further preferably 0.5, 1, 2 or 3, and even further preferably 1.
7. The base salt of the compound according to any one of claims 1-5, wherein the base salt is a hydrate or an anhydrate, preferably an anhydrate;
when the base salt is a hydrate, the number of water molecules is 0.2-3, preferably 0.2, 0.5, 1, 1.5, 2, 2.5 or 3, and more preferably 0.5, 1, 2 or 3.
8. The base salt of the compound according to claim 4, wherein the base salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid is in a crystal form.
9. The base salt of the compound according to claim 8, wherein the crystal form of the base salt of 2-((4-((R)-2-(4-chloro-2-fluorophenyl)-2H-chromen-8-yl)piperidin-1-yl)methyl)-3-(((S)-oxetan-2-yl)methyl)-1H-benzo[d]imidazole-6-carboxylic acid is selected from crystal forms A to E of tromethamine salt, wherein:
the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has a characteristic peak at 2θ of $7.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $9.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $11.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $15.9\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $18.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $19.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.0\pm 0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm 0.2^\circ$, or has a characteristic peak at 2θ of $21.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $22.6\pm 0.2^\circ$, or has a characteristic peak at 2θ of $23.7\pm 0.2^\circ$, or has a characteristic peak at 2θ of $25.1\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ ;
the X-ray powder diffraction pattern of the crystal form B of tromethamine salt has a characteristic peak at 2θ of $8.2\pm 0.2^\circ$, or has a characteristic peak at 2θ of $10.1\pm 0.2^\circ$, or has a characteristic peak at 2θ of $12.3\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.4\pm 0.2^\circ$, or has a characteristic peak at 2θ of $14.8\pm 0.2^\circ$, or has a characteristic peak at 2θ of $16.0\pm 0.2^\circ$, or has a

characteristic peak at 2θ of $16.2\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $19.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $22.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $22.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $24.7\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form C of tromethamine salt has a characteristic peak at 2θ of $3.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $7.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $9.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $10.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $13.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $16.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $16.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $19.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $19.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $22.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $23.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $26.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $28.3\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form D of tromethamine salt has a characteristic peak at 2θ of $7.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $7.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $9.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $10.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $11.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $13.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $15.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $19.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.0\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.2\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.8\pm0.2^\circ$, or has a characteristic peak at 2θ of $23.3\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form E of tromethamine salt has a characteristic peak at 2θ of $4.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $6.3\pm0.2^\circ$, or has a

characteristic peak at 2θ of $8.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $9.3\pm0.2^\circ$, or has a characteristic peak at 2θ of $13.6\pm0.2^\circ$, or has a characteristic peak at 2θ of $14.1\pm0.2^\circ$, or has a characteristic peak at 2θ of $17.7\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $18.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.2\pm0.2^\circ$, or has a characteristic peak at 2θ of $20.5\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $21.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $22.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $23.4\pm0.2^\circ$, or has a characteristic peak at 2θ of $23.9\pm0.2^\circ$, or has a characteristic peak at 2θ of $25.2\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern has characteristic peaks at any 2, 4, 6, 8, 10 or 12 of the above-mentioned 2θ .

10. The crystal form of tromethamine salt according to claim 8, wherein

the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has a characteristic peak at one or more of 2θ of $7.7\pm0.2^\circ$, $9.8\pm0.2^\circ$, $14.0\pm0.2^\circ$ or $15.1\pm0.2^\circ$, preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $14.5\pm0.2^\circ$, $18.7\pm0.2^\circ$, $19.3\pm0.2^\circ$, $20.0\pm0.2^\circ$, $20.5\pm0.2^\circ$ or $21.1\pm0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form B of tromethamine salt has a characteristic peak at one or more of 2θ of $10.1\pm0.2^\circ$, $14.4\pm0.2^\circ$, $18.7\pm0.2^\circ$ or $21.9\pm0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $8.2\pm0.2^\circ$, $12.3\pm0.2^\circ$, $14.8\pm0.2^\circ$, $19.7\pm0.2^\circ$, $20.5\pm0.2^\circ$ or $22.1\pm0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form C of tromethamine salt has a characteristic peak at one or more of 2θ of $3.6\pm0.2^\circ$, $7.1\pm0.2^\circ$, $9.7\pm0.2^\circ$, $14.1\pm0.2^\circ$ or $16.0\pm0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $15.0\pm0.2^\circ$, $16.5\pm0.2^\circ$, $17.1\pm0.2^\circ$, $17.6\pm0.2^\circ$, $19.7\pm0.2^\circ$ or $20.8\pm0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form D of tromethamine salt has a characteristic peak at one or more of 2θ of $7.4\pm0.2^\circ$, $9.8\pm0.2^\circ$, $13.1\pm0.2^\circ$ or $14.0\pm0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and

most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $7.7\pm 0.2^\circ$, $15.1\pm 0.2^\circ$, $17.9\pm 0.2^\circ$, $18.8\pm 0.2^\circ$, $19.3\pm 0.2^\circ$ or $20.0\pm 0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ ;

the X-ray powder diffraction pattern of the crystal form E of tromethamine salt has a characteristic peak at one or more of 2θ of $4.3\pm 0.2^\circ$, $6.3\pm 0.2^\circ$, $13.6\pm 0.2^\circ$ or $18.9\pm 0.2^\circ$; preferably at 2 to 4 of the above-mentioned 2θ , more preferably at 3 or 4 of the above-mentioned 2θ , and most preferably at 4 of the above-mentioned 2θ ; optionally, further, the X-ray powder diffraction pattern can further have a characteristic peak at one or more of 2θ of $8.6\pm 0.2^\circ$, $14.1\pm 0.2^\circ$, $17.7\pm 0.2^\circ$, $20.2\pm 0.2^\circ$, $20.5\pm 0.2^\circ$ or $22.4\pm 0.2^\circ$, preferably at 2, 3, 4 or 6 of the above-mentioned 2θ .

11. The crystal form of tromethamine salt according to claim 8, wherein

the X-ray powder diffraction pattern of the crystal form A of tromethamine salt has characteristic peaks at 2θ of $9.8\pm 0.2^\circ$ and $14.0\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $7.7\pm 0.2^\circ$ and $15.1\pm 0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $18.7\pm 0.2^\circ$, $19.3\pm 0.2^\circ$, $20.0\pm 0.2^\circ$ and $21.1\pm 0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $14.5\pm 0.2^\circ$ and $20.5\pm 0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $10.8\pm 0.2^\circ$, $11.6\pm 0.2^\circ$, $18.0\pm 0.2^\circ$ and $22.6\pm 0.2^\circ$; the X-ray powder diffraction pattern of the crystal form B of tromethamine salt has characteristic peaks at 2θ of $10.1\pm 0.2^\circ$ and $14.4\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $18.7\pm 0.2^\circ$ and $21.9\pm 0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $8.2\pm 0.2^\circ$, $14.8\pm 0.2^\circ$, $20.5\pm 0.2^\circ$ and $22.1\pm 0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $12.3\pm 0.2^\circ$ and $19.7\pm 0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $16.0\pm 0.2^\circ$, $16.2\pm 0.2^\circ$, $18.3\pm 0.2^\circ$ and $20.9\pm 0.2^\circ$; the X-ray powder diffraction pattern of the crystal form C of tromethamine salt has characteristic peaks at 2θ of $3.6\pm 0.2^\circ$ and $7.1\pm 0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $9.7\pm 0.2^\circ$ and $14.1\pm 0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $15.0\pm 0.2^\circ$, $16.0\pm 0.2^\circ$, $16.5\pm 0.2^\circ$, $17.6\pm 0.2^\circ$ and $20.8\pm 0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $17.1\pm 0.2^\circ$ and $19.7\pm 0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $13.5\pm 0.2^\circ$, $19.0\pm 0.2^\circ$, $21.8\pm 0.2^\circ$ and $26.4\pm 0.2^\circ$;

the X-ray powder diffraction pattern of the crystal form D of tromethamine salt has characteristic peaks at 2θ of $9.8\pm0.2^\circ$ and $14.0\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $7.4\pm0.2^\circ$ and $13.1\pm0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $7.7\pm0.2^\circ$, $15.1\pm0.2^\circ$, $18.8\pm0.2^\circ$ and $20.0\pm0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $17.9\pm0.2^\circ$ and $19.3\pm0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $14.5\pm0.2^\circ$, $15.4\pm0.2^\circ$, $15.8\pm0.2^\circ$ and $21.2\pm0.2^\circ$; the X-ray powder diffraction pattern of the crystal form E of tromethamine salt has characteristic peaks at 2θ of $6.3\pm0.2^\circ$ and $13.6\pm0.2^\circ$; preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $4.3\pm0.2^\circ$ and $18.9\pm0.2^\circ$; more preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $8.6\pm0.2^\circ$, $17.7\pm0.2^\circ$, $20.2\pm0.2^\circ$ and $22.4\pm0.2^\circ$; further preferably, the X-ray powder diffraction pattern further has characteristic peaks at 2θ of $14.1\pm0.2^\circ$ and $20.5\pm0.2^\circ$; more further preferably, the X-ray powder diffraction pattern further has a characteristic peak at one or more of $9.3\pm0.2^\circ$, $18.5\pm0.2^\circ$, $21.4\pm0.2^\circ$ and $21.9\pm0.2^\circ$.

12. The crystal form of tromethamine salt according to claim 8, wherein

the X-ray powder diffraction pattern of the form A is as shown in FIG. 1, and preferably, the form A has a DSC pattern as shown in FIG. 2, or has a TGA pattern as shown in FIG. 3;

the X-ray powder diffraction pattern of the form B at 2θ is as shown in FIG. 4, preferably, the form B has a DSC pattern as shown in FIG. 5;

the X-ray powder diffraction pattern of the form C at 2θ is as shown in FIG. 6, preferably, the form C has a DSC pattern as shown in FIG. 7, or has a TGA pattern as shown in FIG. 8;

the X-ray powder diffraction pattern of the form D at 2θ is as shown in FIG. 9, preferably, the form D has a DSC pattern as shown in FIG. 10;

and the X-ray powder diffraction pattern of the form E at 2θ is as shown in FIG. 11, preferably, the form E has a DSC pattern as shown in FIG. 12.

13. The crystal form of tromethamine salt according to claim 8, wherein the positions of diffraction peaks with the top ten relative peak intensities in the X-ray powder diffraction patterns of the crystal form A, the crystal form B, the crystal form C, the crystal form D and the crystal form E have a 2θ deviation of $\pm0.2^\circ$ to $\pm0.5^\circ$, preferably $\pm0.2^\circ$ to $\pm0.3^\circ$, and more preferably $\pm0.2^\circ$ from the corresponding positions of diffraction peaks in the FIG. 1, FIG. 4, FIG. 6, FIG. 9 and FIG. 11.

14. A method for preparing the base salt of the compound according to any one of claims 1-13, wherein the method specifically comprises the following steps:

1) weighing an appropriate amount of a free acid and dissolving the free acid in a good solvent;

2) weighing an appropriate amount of a counter-ion base and dissolving the counter-ion base in an organic solvent; wherein the amount of the counter-ion base is preferably 1.0 to 1.5 equivalents;

3) combining the above two solutions, and stirring the combined solution to allow precipitation, or dropwise adding a poor solvent followed by the stirring to allow precipitation; and

4) subjecting the mixture to rapid centrifugation or standing to evaporate to dryness so as to obtain a target product;

wherein:

the good solvent is selected from acetone, tetrahydrofuran, ethyl formate, ethyl acetate, 2-methyl-tetrahydrofuran, 2-butanone, n-butanol, 1,4-dioxane, isobutanol, N,N-dimethylformamide, N,N-dimethylacetamide, n-propanol or tert-butanol; preferably 2-methyl-tetrahydrofuran, ethyl acetate, 2-butanone, acetone or ethyl formate;

the organic solvent is selected from methanol, ethanol, ethyl acetate, dichloromethane, acetone, n-hexane, petroleum ether, benzene, toluene, chloroform, acetonitrile, carbon tetrachloride, dichloroethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, 2-butanone, 3-pentanone, heptane, methyl tert-butyl ether, isopropyl ether, 1,4-dioxane, tert-butanol, or N,N-dimethylformamide; preferably methanol, ethanol, or acetonitrile; the above good solvent and organic solution must be miscible when used;

the poor solvent is selected from heptane, methyl tert-butyl ether, cyclohexane, toluene, isopropyl ether, and ethyl acetate; preferably methyl tert-butyl ether and isopropyl ether;

the counter-ion base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; preferably, diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, or a mixture thereof; further preferably, tromethamine; the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof, preferably sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or a mixture thereof; alternatively,

1) weighing an appropriate amount of a free acid, and suspending the free acid with a poor solvent;

2) weighing an appropriate amount of a counter-ion base and dissolving the counter-ion base in an organic solvent; wherein the amount of the counter-ion base is preferably 1.0 to 1.5 equivalents;

3) combining the above two solutions and stirring the combined solution to allow dissolution, followed by continue stirring;

4) subjecting the mixture to rapid centrifugation or standing to evaporate to dryness so as to obtain a target product;

wherein:

the poor solvent is selected from ethanol, ethyl acetate, ethyl formate, isopropanol, isopropyl acetate, methyl tert-butyl ether, dichloromethane, methanol, acetonitrile, chlorobenzene, benzene, toluene, n-butanol, isobutanol or 3-pentanone; preferably, ethanol, ethyl acetate, isopropanol and isopropyl acetate;

the organic solvent is selected from methanol, ethanol, ethyl acetate, dichloromethane, acetone, n-hexane, petroleum ether, benzene, toluene, chloroform, acetonitrile, carbon tetrachloride, dichloroethane, tetrahydrofuran, 2-methyl-tetrahydrofuran, 2-butanone, 3-pentanone, heptane, methyl tert-butyl ether, isopropyl ether, 1,4-dioxane, tert-butanol, or N,N-dimethylformamide; preferably methanol, ethanol, or acetonitrile; the above good solvent and organic solution must be miscible when used;

the counter-ion base is an organic base or an inorganic base, and the organic base is selected from diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, meglumine, N-hydroxyethylmorpholine, piperazine, N-hydroxyethylpyrrolidine, N,N-dibenzylethylenediamine, 2-diethylaminoethanol, ethanolamine, betaine, L-arginine, lysine, phenethylbenzylamine, benzathine penicillin, dimethylaminoethanol, imidazole or a mixture thereof; preferably, diethylamine, diethanolamine, triethylamine, triethanolamine, choline hydroxide, tromethamine, or a mixture thereof; further preferably, tromethamine; the inorganic base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia water or a mixture thereof, preferably sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide or a mixture thereof; alternatively,

1) weighing an appropriate amount of the base salt of the compound, and suspending the base salt with a poor solvent preferably at a suspension density of 50-200 mg/mL;

2) shaking the obtained suspension at a certain temperature for a certain time, preferably at a temperature of 25-50°C for preferably 1-15 days;

3) quickly centrifuging the suspension obtained above, removing a supernatant, placing a remaining solid in a vacuum drying oven and drying to a constant weight to afford a target product;

wherein:

the poor solvent is selected from dichloromethane, 1,4-dioxane, acetonitrile, chlorobenzene, benzene, toluene, acetone, ethyl acetate, water, 88% acetone, isopropyl acetate, 3-pentanone, ethyl formate, tetrahydrofuran, 2-methyl-tetrahydrofuran, isopropanol, n-butanol, isobutanol, n-propanol, methyl tert-butyl ether, n-heptane, tert-butanol or 2-butanone.

15. A pharmaceutical composition comprising a therapeutically effective amount of the base salt or the crystal form thereof of the compound or the stereoisomer thereof according to any one of claims 1 to 14, and one or more pharmaceutically acceptable carriers, diluents or excipients.
16. The base salt or the crystal form thereof of the compound or the stereoisomer thereof according to any one of claims 1 to 14, and the pharmaceutical composition according to claim 15, comprising a therapeutically effective amount of the base salt or the crystal form thereof, and the therapeutically effective amount includes 0.0001-99%, 0.0001-95%, 0.0001-90%, 0.0001-85%, 0.0001-80%, 0.0001-75%, 0.0001-70%, 0.001-60%, 0.001-55%, 0.01-50%, 0.01-40%, 0.01-30%, 0.01-20%, 0.01-10% or 0.01-5%.
17. Use of the base salt or the crystal form thereof of the compound or the stereoisomer thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 15 in the preparation of a GLP-1 receptor agonist drug.
18. Use of the base salt or the crystal form thereof of the compound or the stereoisomer thereof according to any one of claims 1 to 14, or the pharmaceutical composition according to claim 15 in the preparation of a drug for treating metabolism related diseases, wherein preferably, the metabolism related diseases are selected from diabetes, obesity or non-alcohol steatohepatitis related diseases or other related diseases caused by diabetes, obesity or non-alcoholic steatohepatitis.