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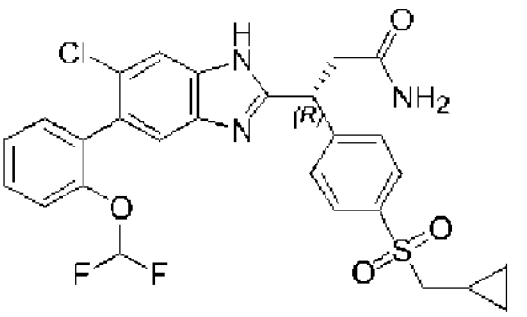
(54) Titre : SEL D'ADDITION ACIDE DU REGULATEUR DE RORγ
(54) Title: ACID ADDITION SALT OF RORγ REGULATOR

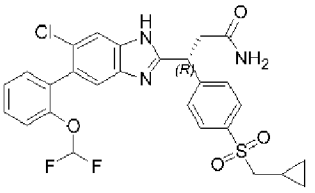


II

(57) Abrégé/Abstract:
An acid addition salt of a RORγ regulator. Specifically relating to the acid addition salt of the compound of formula II. More specifically relating to benzoate, oxalate, methanesulfonate, maleate, hydrobromate, hydrochloride salt, and acetate of the compound of formula II and the benzoate crystal form, benzoate amorphous form, oxalate crystal form, oxalate amorphous form, methanesulfonate amorphous form, maleate B crystal form, maleate C crystal form, maleate D crystal form, hydrobromate I crystal form, hydrochloride salt α crystal form, hydrochloride salt β crystal form, hydrochloride salt γ crystal form, and acetate crystal form of the compound of formula II.

ABSTRACT

An acid addition salt of a RORγ regulator. Specifically relating to the acid addition salt of the compound of formula II. More specifically relating to benzoate, oxalate, methanesulfonate, maleate, hydrobromate, hydrochloride salt, and acetate of the compound of formula II and the benzoate crystal form, benzoate amorphous form, oxalate crystal form, oxalate amorphous form, methanesulfonate amorphous form, maleate B crystal form, maleate C crystal form, maleate D crystal form, hydrobromate I crystal form, hydrochloride salt α crystal form, hydrochloride salt β crystal form, hydrochloride salt γ crystal form, and acetate crystal form of the compound of formula II.



formula II

CA 03156332 2022-4-27

ACID ADDITION SALT OF RORγ REGULATOR

The present application claims priority to Chinese Patent Application No. CN201911049930.5 filed on Oct. 31, 2019, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to the field of pharmaceutical chemistry, and in particular, to an acid addition salt of a compound of formula II as an RORγ regulator.

BACKGROUND

Nuclear receptors are ligand-regulated transcription factors that regulate development, immunity, and cellular metabolism, and are one of the major therapeutic target classes for human diseases. Retinoid-related orphan receptor gamma (RORγ) is a member of the nuclear receptor NR1 subfamily and has a typical nuclear receptor domain structure consisting of a DNA-binding domain, a ligand-binding domain, a hinge domain and an activation function 2 domain (Benoit G, et al., *Pharmacological Reviews*, 58(4):798–836, 2006; Zhang, Y., et al., *Acta Pharmacogica Sinica*, 36:71–87, 2015). In contrast to most other nuclear receptors that function as dimers, RORγ works as a monomer. It binds to specific DNA sequences usually consisting of TAAA/TNTAGGTCA, which are called ROR response elements (ROREs).

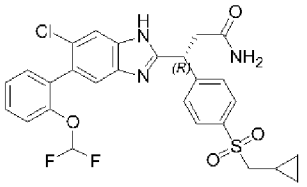
There are two RORγ subtypes, RORγ1 and RORγ2 (also known as RORγt) that arise from the same RORC gene, and possibly differ in selection of promoters (Villey I et al, *Eur. J. Immunol.*, 29(12):4072–80, 1999). Since the two RORγ subtypes (RORγ1 and RORγt) are derived from the same mRNA, they have identical ligand-binding domains, and are distinguished by N terminus only (Jetten, A. M., 2009; Ivanov, I. I. et al., 2006). Small molecule inhibitors generally bind to the ligand-binding domain to inhibit the function of the receptor. As such, they have no selectivity for the two RORγ subtypes, and are all referred to as RORγ small molecule inhibitors (or modulators) without subtyping.

The two RORγ subtypes have very different tissue distributions. RORγt is mainly expressed in thymus and several immune cells, while RORγ1 is expressed in many tissues, such as thymus, liver, muscle, testis, pancreas, prostate and heart. (Jetten, A. M., 2009; Zhang, Y. et al., 2015). It has been reported that one of the functions of RORγ1 is to regulate the human biochronometer,

and particularly, to regulate the circadian rhythm (Jetten, A. M., 2009). T helper 17 (Th17) cells are the major source of autoimmune disease (Ivanov, I. I. et al., 2006). Both RORγ subtypes are expressed in Th17 cells, regulating T cell differentiation and inducing gene transcription in Th17 cells (Ruan, Q., et al., 2011). Cytokines IL-6 and TGF-β induce differentiation of undifferentiated CD4 T helper cells into Th17 cells. RORγt highly expressed in Th17 cells induces transcription of IL-23 receptor gene in undifferentiated CD4 T helper cells, IL23 receptors in turn promote and stabilize production of Th17 cells, forming part of a positive feedback loop (Ivanov, I. I. et al., 2006; Jetten, A. M., 2009). Meanwhile, RORγt can induce the gene transcription of proinflammatory cytokines such as IL-17A, IL-17F, IL-21 and IL-22, and enhance the inflammation process. Like RORγt, RORγ1 is also expressed in Th17 cells, and can also regulate differentiation and induce gene transcription in Th17 cells (Ruan, Q., et al., 2011). Pharmacological antagonism against RORγ has therapeutic potential for autoimmune diseases, making it an attractive target for small molecule inhibitors.

RORγ has been identified as a key mediator in the pathogenesis of several diseases, such as rheumatoid arthritis, psoriasis vulgaris, multiple sclerosis, inflammatory bowel disease, Crohn's disease, sicca syndrome and asthma. (Louten et al., *J. Allergy Clin. Immunol.*, 123:1004–1011, 2009; Annuziato, F., et al., *Nat. Rev. Rheumatol.*, 5(6):325–331, 2009; Lizuka, M., et al., *J. Immunol.*, 194:56–67, 2014). Some other diseases, such as chronic xerophthalmia, Kawasaki's disease, mucosal leishmaniasis and Hashimoto's thyroiditis, are characterized by increased Th17 proportion and/or increased levels of Th17 marker cytokines, such as IL-17, IL-22 and IL-23. (Chen, Y. et al., *Mucosal. Immunol.*, 7(1):38–45, 2014; Jia, S., et al., *Clin. Exp. Immunol.*, 162:131–137, 2010; Boaventura, VS et al., *Eur. J. Immunol.*, 40:2830–2836, 2010; Figueroa-Vega, N. et al., *J. Clin. Endocrinol. Metab.*, 95:953–62, 2010). In each of the above examples, the inhibitory effect can be enhanced by inhibiting RORα. RORγt inhibitors are currently being developed for the treatment of autoimmune diseases such as psoriasis vulgaris and rheumatoid arthritis. See Jun R. Huh and Dan R. Littman, *Eur. J. Immunol.*, 42(9):2232–2237 (2012), WO2012/027965, WO2013/029338 and US2015/291607.

Patent Application No. PCT/US19/30526 provides an RORγ regulator having a structure of formula II:



formula II

which is incorporated herein in its entirety.

BRIEF SUMMARY

The present disclosure provides an acid addition salt of a compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, wherein the acid addition salt is an organic acid addition salt or an inorganic acid addition salt.

The present disclosure further relates to a method for preparing an acid addition salt of a compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, wherein the acid addition salt is an organic acid addition salt or an inorganic acid addition salt, and the method comprises mixing a certain amount of the compound of formula II with a proper amount of a solvent and the organic acid or the inorganic acid, and reacting for a period of time to obtain the salt of the compound of formula II with the corresponding acid, wherein the solvent is selected from the group consisting of one or more of a hydrocarbon solvent, an ether solvent, an alcohol solvent, an ester solvent, a ketone solvent, a nitrile solvent, a halogenated hydrocarbon solvent, a nitrogenous solvent, water and dimethyl sulfoxide.

In some embodiments, the organic acid addition salt is at least one selected from the group consisting of formate, acetate, propionate, butyrate, benzoate, malonate, succinate, pyruvate, methanesulfonate, ethanesulfonate, propanesulfonate, citrate, 4-nitrobenzoate, benzenesulfonate, *p*-toluenesulfonate, 1,2-ethanedisulfonate, β-naphthalenesulfonate, malate, propiolate, 2-butynoate, 2-hydroxy-ethanesulfonate, 3-butenoate, tartrate, fumarate, isethionate, maleate, lactate, lactobionate, pamoate, salicylate, galactarate, glucoheptonate, mandelate, 1,2-ethanedisulfonate, oxalate, trifluoroacetate, trifluoromethanesulfonate, adipate, suberate, sebacate, butyne-1,4-dioate, hexyne-1,6-dioate, glycolate, alginate, ascorbate, aspartate, glutamate, 2-phenoxybenzoate, 2-(4-hydroxybenzoyl)benzoate, acetoacetate, 2-hydroxyethanesulfonate, borate, chlorobenzoate, camphorate, itaconate, camphorsulfonate, methylbenzoate, dinitrobenzoate, sulfamate, galacturonate, cyclopentylpropionate, dodecylsulfate, acrylate, cyclopentanepropionate, glycerophosphate, methoxybenzoate,

digluconate, gluconate, heptanoate, hexanoate, pivalate, glucuronate, laurate, phthalate, phenylacetate, laurylsulfate, 2-acetoxybenzoate, nicotinate, cinnamate, oleate, palmitate, pectate, *p*-phthalate, glutarate, hydroxymaleate, hydroxybenzoate, phenylacetate, 3-hydroxy-2-naphthoate, 3-phenylpropionate, isobutyrate, neopentanoate, picrate, stearate, 2,2-dichloroacetate, acylated amino acid salt, alginate, 4-acetamidobenzenesulfonate, caprate, cholate, caprylate, nonanoate, cyclamate, phthalate, cysteine hydrochloride salt, sorbate, glycine hydrochloride salt, 1,5-naphthalenedisulfonate, xylenesulfonate, cystine dihydrochloride salt, undecanoate, polyvinyl sulfonate salt, sulfosalicylate, phenylbutyrate, 4-hydroxybutyrate, polyvinyl sulfate salt, naphthalene-1-sulphonate and valerate.

In some embodiments, the inorganic acid addition salt is at least one selected from the group consisting of hydrochloride, sulfate, bisulfate, nitrate, hydrobromide, hydroiodide, carbonate, bicarbonate, sulfite, bisulfite, pyrosulfate, monohydrogen phosphate, dihydrogen phosphate, perchlorate, persulfate, hemisulfate, disulfate, thiocyanate, phosphate, pyrophosphate and metaphosphate.

In some embodiments, the organic acid addition salt may be at least one selected from the group consisting of benzoate, oxalate, methanesulfonate, maleate and acetate, and the inorganic acid addition salt may be selected from the group consisting of hydrochloride and hydrobromide.

The present disclosure provides a crystalline form of benzoate, an amorphous form of benzoate, a crystalline form of oxalate, an amorphous form of oxalate, an amorphous form of methanesulfonate, a crystalline form B of maleate, a crystalline form C of maleate, a crystalline form D of maleate, a crystalline form I of hydrobromide, a crystalline form α of hydrochloride, a crystalline form β of hydrochloride, a crystalline form γ of hydrochloride and a crystalline form of acetate of a compound of formula II, and methods for preparing the same.

The present disclosure provides an amorphous form of a compound of formula II, having an XRPD pattern with no distinct sharp diffraction peaks; preferably, the amorphous form has an XRPD pattern as shown in FIG. 1.

The present disclosure provides a benzoate of a compound of formula II.

In some embodiments, the benzoate is an amorphous form having an XRPD pattern with no distinct sharp diffraction peaks; preferably, the amorphous form has an XRPD pattern as shown in FIG. 2.

In some embodiments, the benzoate is a crystalline form having an X-ray powder diffraction

pattern with characteristic peaks at diffraction angles 2θ of 5.305 and 7.411.

Furthermore, the crystalline form of the benzoate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.305, 7.411 and 22.031.

Furthermore, the crystalline form of the benzoate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.305, 7.411, 19.140 and 22.0314.

The present disclosure provides an oxalate of a compound of formula II.

In some embodiments, the oxalate is an amorphous form having an XRPD pattern with no distinct sharp diffraction peaks; preferably, the amorphous form has an XRPD pattern as shown in FIG. 5.

In some embodiments, the oxalate is a crystalline form having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 14.378, 18.463 and 21.670.

Furthermore, the crystalline form of the oxalate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 14.378, 18.463, 21.670 and 23.075.

Furthermore, the crystalline form of the oxalate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 14.378, 18.463, 21.670, 23.075 and 28.127.

The present disclosure provides a methanesulfonate of a compound of formula II.

In some embodiments, the methanesulfonate is an amorphous form having an XRPD pattern with no distinct sharp diffraction peaks; preferably, the amorphous form has an XRPD pattern as shown in FIG. 7.

The present disclosure provides a maleate of a compound of formula II.

In some embodiments, the maleate is a crystalline form B having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.624, 9.659, 13.815, 15.844 and 17.391.

Furthermore, the crystalline form B of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.624, 9.659, 13.815, 15.844, 17.391 and 21.802.

Furthermore, the crystalline form B of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.624, 9.659, 13.815, 15.844, 17.391, 18.619 and 21.802.

Furthermore, the crystalline form B of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.624, 9.659, 13.815, 15.844, 17.391, 18.619, 21.802, 23.667 and 26.441.

In some embodiments, the maleate is a crystalline form C having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.325, 8.635, 9.809, 13.649, 16.133, 16.765 and 18.346.

Furthermore, the crystalline form C of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.325, 8.635, 9.809, 13.649, 16.133, 16.765, 18.346, 21.689 and 23.586.

Furthermore, the crystalline form C of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.325, 8.635, 9.809, 11.661, 13.649, 16.133, 16.765, 18.346, 21.689, 23.586 and 25.303.

In some embodiments, the maleate is a crystalline form D having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 4.486, 7.288, 9.067, 10.001, 13.914, 18.229 and 18.940.

Furthermore, the crystalline form D of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 4.486, 5.998, 7.288, 9.067, 10.001, 13.914, 15.026, 16.227, 18.229 and 18.940.

Furthermore, the crystalline form D of the maleate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 4.486, 5.998, 7.288, 9.067, 10.001, 13.914, 15.026, 16.227, 18.229, 18.940, 23.076, 25.612 and 28.102.

The present disclosure provides a hydrobromide of a compound of formula II.

In some embodiments, the hydrobromide is a crystalline form I having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 12.579, 16.414, 17.075, 17.780 and 20.733.

Furthermore, the crystalline form I of the hydrobromide has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 12.579, 16.414, 17.075, 17.780, 19.675, 20.733, 21.262, 23.113, 23.906, 24.391, 26.550, 28.445, 28.930 and 29.547.

Furthermore, the crystalline form I of the hydrobromide has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 11.918, 12.579, 16.414, 17.075, 17.780, 18.750, 19.675, 20.733, 21.262, 23.113, 23.906, 24.391, 26.550, 28.445, 28.930, 29.547, 30.958, 32.236, 33.382, 38.670, 39.640, 40.830, 42.064, 43.342, 46.824, 48.190, 48.983 and 50.746.

The present disclosure provides a hydrochloride of a compound of formula II.

In some embodiments, the hydrochloride is a crystalline form α having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.931, 10.115, 13.920, 15.224, 17.425 and 18.309.

Furthermore, the crystalline form α of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.931, 10.115, 12.166, 13.920, 15.224, 16.041, 16.315, 16.748, 17.425, 18.309, 22.340, 23.359 and 24.570.

Furthermore, the crystalline form α of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.931, 10.115, 12.166, 13.920, 15.224, 16.041, 16.315, 16.748, 17.425, 18.309, 19.624, 20.235, 21.491, 22.340, 23.359, 23.905 and 24.570. Furthermore, the crystalline form α of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.931, 10.115, 12.166, 13.920, 15.224, 16.041, 16.315, 16.748, 17.425, 18.309, 19.624, 20.235, 21.491, 22.340, 23.359, 23.905, 24.570, 25.320, 25.811, 26.096, 27.624, 28.213, 29.190, 29.760, 31.266, 31.795, 32.324, 35.906 and 37.291.

In some embodiments, the hydrochloride is a crystalline form β having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.386, 8.191, 12.688, 16.607 and 20.036.

Furthermore, the crystalline form β of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.386, 8.191, 10.818, 12.688, 13.980, 14.915, 16.607, 20.036 and 21.372.

Furthermore, the crystalline form β of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.386, 8.191, 10.818, 12.688, 13.980, 14.915, 16.607, 18.076, 19.056, 20.036, 21.372, 22.040, 23.465, 24.355, 25.869, 26.582, 27.383, 29.253, 29.832, 30.946, 31.480, 32.504 and 33.439.

In some embodiments, the hydrochloride is a crystalline form γ having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.114, 11.997, 12.640, 13.772, 16.478, 17.897 and 20.337.

Furthermore, the crystalline form γ of the hydrochloride has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.114, 11.997, 12.640, 13.772, 16.478, 17.897, 20.337, 21.422, 23.228 and 24.472.

Furthermore, the crystalline form γ of the hydrochloride has an X-ray powder diffraction pattern

with characteristic peaks at diffraction angles 2θ of 8.114, 11.997, 12.640, 13.772, 16.478, 17.897, 19.671, 20.337, 21.422, 22.156, 23.228, 24.472, 25.882, 27.567, 28.277, 29.830, 31.160, 32.269 and 33.334.

The present disclosure provides an acetate of a compound of formula II.

In some embodiments, the acetate is a crystalline form having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 11.651, 12.495, 15.636, 15.965, 18.075 and 20.935.

Furthermore, the crystalline form of the acetate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 11.651, 12.495, 14.323, 15.121, 15.636, 15.965, 18.075, 19.247, 19.903 and 20.935.

Furthermore, the crystalline form of the acetate has an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 11.651, 12.495, 14.323, 15.121, 15.636, 15.965, 18.075, 19.247, 19.903, 20.935, 22.107, 22.998, 23.842, 24.733, 25.530, 26.843, 28.719, 29.750, 30.829, 32.142, 35.143 and 39.973.

The present disclosure further relates to a method for preparing benzoate, oxalate, methanesulfonate, maleate, hydrobromide, hydrochloride or acetate of a compound of formula II, comprising: mixing a certain amount of the compound of formula II with a proper amount of a solvent and benzoic acid, oxalic acid, methanesulfonic acid, maleic acid, hydrobromic acid, hydrochloric acid or acetic acid for reaction to obtain the salt of the compound of formula II with the corresponding acid, wherein the solvent is selected from the group consisting of one or more of a hydrocarbon solvent, an ether solvent, an alcohol solvent, an ester solvent, a ketone solvent, a nitrile solvent, a halogenated hydrocarbon solvent, a nitrogenous solvent, water and dimethyl sulfoxide,

the hydrocarbon solvent includes, but is not limited to, *n*-butane, *n*-pentane, *n*-hexane or *n*-heptane;

the ether solvent includes, but is not limited to, tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl *tert*-butyl ether, isopropyl ether or 1,4-dioxane;

the alcohol solvent includes, but is not limited to, methanol, ethanol, isopropanol, *n*-propanol, isoamyl alcohol or trifluoroethanol;

the ester solvent includes, but is not limited to, ethyl acetate, isopropyl acetate or butyl acetate;

the ketone solvent includes, but is not limited to, acetone, acetophenone or 4-methyl-2-

pentanone;

the nitrile solvent includes, but is not limited to, acetonitrile or propionitrile;

the halogenated hydrocarbon solvent includes, but is not limited to, chloromethane, dichloromethane, chloroform or carbon tetrachloride;

the nitrogenous solvent includes, but is not limited to, nitromethane, *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide.

In some embodiments, a method for preparing an amorphous form of a compound of formula II, comprises: taking a certain amount of the compound of formula II, adding a proper amount of a solvent, precipitating a solid, filtering and drying to obtain the amorphous form of the compound of formula II. In certain embodiments, the solvent may be selected from the group consisting of isopropyl ether, toluene and isopropyl acetate/*n*-hexane (v:v = 1:3).

In some embodiments, a method for preparing an amorphous form of a compound of formula II, comprises: purifying a certain amount of the compound of formula II by high performance liquid chromatography with an elution system of ammonium bicarbonate/water/acetonitrile to obtain the amorphous form of the compound of formula II.

In some embodiments, a method for preparing an amorphous form of a compound of formula II, comprises: taking a certain amount of the compound of formula II, adding a proper amount of a solvent, precipitating a solid, filtering and drying to obtain the amorphous form of the compound of formula II, wherein the solvent is selected from the group consisting of isopropyl ether, toluene and a mixed solvent of isopropyl acetate and *n*-hexane (v:v = 1:3), and the method for precipitating the amorphous form is selected from the group consisting of precipitation at room temperature, precipitation by cooling and precipitation by volatilizing the solvent.

In some embodiments, a method for preparing an amorphous form of a compound of formula II, comprises: taking a certain amount of the compound of formula II, adding a proper amount of isopropyl ether, toluene or a mixed solvent of isopropyl acetate and *n*-hexane (v:v = 1:3), heating until complete or incomplete dissolution, cooling to room temperature, stirring to precipitate a solid, filtering and drying to obtain the amorphous form of the compound of formula II.

The present disclosure further relates to a method for preparing an amorphous or crystalline form of a benzoate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and benzoic acid, precipitating a solid, filtering and drying to obtain the amorphous or crystalline form of the benzoate of the compound of

formula II. In certain embodiments, the solvent is *n*-hexane or methyl *tert*-butyl ether.

The present disclosure further relates to a method for preparing an amorphous or crystalline form of an oxalate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and oxalic acid, precipitating a solid, filtering and drying to obtain the amorphous or crystalline form of the oxalate of the compound of formula II. In certain embodiments, the solvent is *n*-hexane or methyl *tert*-butyl ether.

The present disclosure further relates to a method for preparing an amorphous form of a methanesulfonate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and methanesulfonic acid, precipitating a solid, filtering and drying to obtain the amorphous form of the methanesulfonate of the compound of formula II. In certain embodiments, the solvent is methyl *tert*-butyl ether.

The present disclosure further relates to a method for preparing crystalline forms B, C and D of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and maleic acid, precipitating a solid, filtering and drying to obtain the crystalline forms B, C and D of the maleate of the compound of formula II. In certain embodiments, the solvent is methyl *tert*-butyl ether.

The present disclosure further relates to a method for preparing a crystalline form I of a hydrobromide of a compound of formula II, comprising: precipitating a crystal by reacting the compound of formula II with hydrobromic acid in a proper amount of a solvent selected from the group consisting of one or more of a hydrocarbon solvent, an ether solvent, an alcohol solvent, an ester solvent, a ketone solvent, a nitrile solvent, a halogenated hydrocarbon solvent, a nitrogenous solvent, water and dimethyl sulfoxide, wherein

the hydrocarbon solvent includes, but is not limited to, *n*-butane, *n*-pentane, *n*-hexane or *n*-heptane;

the ether solvent includes, but is not limited to, tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl *tert*-butyl ether, isopropyl ether or 1,4-dioxane;

the alcohol solvent includes, but is not limited to, methanol, ethanol, isopropanol, *n*-propanol, isoamyl alcohol or trifluoroethanol;

the ester solvent includes, but is not limited to, ethyl acetate, isopropyl acetate or butyl acetate;

the ketone solvent includes, but is not limited to, acetone, acetophenone or 4-methyl-2-pentanone;

the nitrile solvent includes, but is not limited to, acetonitrile or propionitrile;

the halogenated hydrocarbon solvent includes, but is not limited to, chloromethane, dichloromethane, chloroform or carbon tetrachloride;

the nitrogenous solvent includes, but is not limited to, nitromethane, *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide.

In some embodiments, for the method for preparing the crystalline form I of the hydrobromide of the compound of formula II, the solvent is methyl *tert*-butyl ether and ethanol.

The present disclosure further relates to a method for preparing a crystalline form I of a hydrobromide of a compound of formula II, comprising: mixing a certain amount of the compound of formula II with a proper amount of a solvent and hydrobromic acid, precipitating a solid, filtering and drying to obtain the crystalline form I of the hydrobromide of the compound of formula II. In certain embodiments, the solvent is methyl *tert*-butyl ether and ethanol.

The present disclosure further relates to a method for preparing crystalline forms α, β and γ of a hydrochloride of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and hydrochloric acid, precipitating a solid, filtering and drying to obtain the crystalline forms α, β and γ of the hydrochloride of the compound of formula II. In certain embodiments, the solvent is methyl *tert*-butyl ether.

The present disclosure further relates to a method for preparing a crystalline form γ of a hydrochloride of a compound of formula II, comprising: loading a certain amount of the crystalline form β of the compound of formula II to a DVS system and running a process with parameters of dm/dt = 0.002, 50-95-0-95-50% RH, Max 360 min, 25 °C to obtain the crystalline form γ of the hydrochloride of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form of an acetate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of a solvent and acetic acid, precipitating a solid, filtering and drying to obtain the crystalline form of the acetate of the compound of formula II. In certain embodiments, the solvent is water and ethanol.

In certain embodiments, for the preparation process of the amorphous form of the compound of formula II, the benzoate, oxalate, methanesulfonate, maleate, hydrobromide, hydrochloride and acetate of the compound of formula II, and the crystalline form of the benzoate, the amorphous form of the benzoate, the crystalline form of the oxalate, the amorphous form of the oxalate, the

amorphous form of the methanesulfonate, the crystalline forms B, C and D of the maleate, the crystalline form I of the hydrobromide, the crystalline forms α, β and γ of the hydrochloride and the crystalline form of the acetate, the solvent is selected from the group consisting of one or more of a hydrocarbon solvent, an ether solvent, an alcohol solvent, an ester solvent, a ketone solvent, a nitrile solvent, a halogenated hydrocarbon solvent, a nitrogenous solvent, water and dimethyl sulfoxide. The hydrocarbon solvent includes, but is not limited to, *n*-butane, *n*-pentane, *n*-hexane or *n*-heptane; the ether solvent includes, but is not limited to, diethyl ether, propylene glycol methyl ether, methyl *tert*-butyl ether, isopropyl ether or 1,4-dioxane; the alcohol solvent includes, but is not limited to, methanol, ethanol, isopropanol, *n*-propanol, isoamyl alcohol or trifluoroethanol; the ester solvent includes, but is not limited to, ethyl acetate, isopropyl acetate or butyl acetate; the ketone solvent includes, but is not limited to, acetone, acetophenone or 4-methyl-2-pentanone; the nitrile solvent includes, but is not limited to, acetonitrile or propionitrile; the halogenated hydrocarbon solvent includes, but is not limited to, chloromethane, dichloromethane, 1,2-dichloroethane, chloroform or carbon tetrachloride; and the nitrogenous solvent includes, but is not limited to, nitromethane, *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide.

The method for precipitating a solid form of the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein is selected from the group consisting of precipitation at room temperature, precipitation by cooling and precipitation by volatilizing the solvent.

In certain embodiments, the solid form of the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein refers to the crystalline form of the benzoate, the amorphous form of the benzoate, the crystalline form of the oxalate, the amorphous form of the oxalate, the amorphous form of the methanesulfonate, the crystalline forms B, C and D of the maleate, the crystalline form I of the hydrobromide, the crystalline forms α, β and γ of the hydrochloride and the crystalline form of the acetate of the compound of formula II.

The method for crystallizing the crystalline form of the compound disclosed herein is selected from the group consisting of crystallization at room temperature, crystallization by cooling, crystallization by volatilization or induction crystallization by adding seed crystal, and the crystalline form of the compound is selected from the group consisting of the crystalline form of

the benzoate, the crystalline form of the oxalate, the crystalline forms B, C and D of the maleate, the crystalline form I of the hydrobromide, the crystalline forms α, β and γ of the hydrochloride and the crystalline form of the acetate of the compound of formula II.

The present disclosure further relates to a method for preparing an amorphous or crystalline form of a benzoate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of *n*-hexane or methyl *tert*-butyl ether and benzoic acid, stirring at 50 °C overnight, filtering and drying to obtain the amorphous or crystalline form of the benzoate of the compound of formula II.

The present disclosure further relates to a method for preparing an amorphous or crystalline form of an oxalate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether or *n*-hexane and oxalic acid, stirring at 50 °C overnight, filtering and drying to obtain the amorphous or crystalline form of the oxalate of the compound of formula II.

The present disclosure further relates to a method for preparing an amorphous form of a methanesulfonate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and methanesulfonic acid, stirring at 50 °C overnight, filtering and drying to obtain the amorphous form of the methanesulfonate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form B of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600 rpm for 10 min to 10 h, filtering and drying to obtain the crystalline form B of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form B of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600 rpm for 10 min, 20 min, 30 min, 1 h or 2 h, filtering and drying to obtain the crystalline form B of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form C of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600

rpm for 12 h to 36 h, filtering and drying to obtain the crystalline form C of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form C of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600 rpm for 1 d, filtering and drying to obtain the crystalline form C of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form D of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600 rpm for 48 h to 72 h, filtering and drying to obtain the crystalline form D of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form D of a maleate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and maleic acid, stirring at 50 °C at 600 rpm for 3 d, filtering and drying to obtain the crystalline form D of the maleate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form I of a hydrobromide of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and hydrobromic acid or a mixture of hydrobromic acid and ethanol, stirring at 25 °C at 600 rpm for 12 h to 72 h, filtering and drying to obtain the crystalline form I of the hydrobromide of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form I of a hydrobromide of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and hydrobromic acid, stirring at 25 °C at 600 rpm for 3 d, filtering and drying to obtain the crystalline form I of the hydrobromide of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form I of a hydrobromide of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and a mixture of

hydrobromic acid and ethanol (in a volume ratio selected from the group consisting of 1:1, 1:50 and 1:99), stirring at 25 °C at 600 rpm overnight and for 3 d, filtering and drying to obtain the crystalline form I of the hydrobromide of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form α of a hydrochloride of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and concentrated hydrochloric acid, stirring at 50 °C for 12 h to 48 h, filtering and drying to obtain the crystalline form α of the hydrochloride of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form α of a hydrochloride of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and concentrated hydrochloric acid, stirring at 50 °C for 2 d, filtering and drying to obtain the crystalline form α of the hydrochloride of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form β of a hydrochloride of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and a solution of hydrochloric acid in ethanol, precipitating a solid, filtering and drying to obtain the crystalline form β of the hydrochloride of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form β of a hydrochloride of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of methyl *tert*-butyl ether and a solution of hydrochloric acid in ethanol (concentrated hydrochloric acid:ethanol = 1:99, well mixed), stirring at 25 °C for 1 h and at 50 °C for 2 d, filtering and drying to obtain the crystalline form β of the hydrochloride of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form of an acetate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of water and a solution of acetic acid in ethanol, precipitating a solid, filtering and drying to obtain the crystalline form of the acetate of the compound of formula II.

The present disclosure further relates to a method for preparing a crystalline form of an acetate of a compound of formula II, comprising: taking a certain amount of the compound of formula II, adding a proper amount of water and a solution of acetic acid in ethanol (precisely transferring

0.1 mL of acetic acid, adding 9.9 mL of ethanol, mixing well), stirring at 50 °C overnight, filtering and drying to obtain the crystalline form of the acetate of the compound of formula II.

The present disclosure further relates to a pharmaceutical composition comprising an acid addition salt of a compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt or an amorphous form of the compound of formula II, and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present disclosure further relates to a pharmaceutical composition comprising a crystalline form I of a hydrobromide of a compound of formula II, and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present disclosure further relates to a pharmaceutical composition prepared from an amorphous form of a compound of formula II, an acid addition salt of the compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present disclosure further relates to a pharmaceutical composition prepared from a crystalline form I of a hydrobromide of a compound of formula II and one or more pharmaceutically acceptable carriers, diluents or excipients.

The present disclosure further relates to a pharmaceutical composition comprising an amorphous form of a compound of formula II or an acid addition salt of the compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, and optionally one or more pharmaceutically acceptable carriers and/or diluents. The pharmaceutical composition can be formulated into any pharmaceutically acceptable dosage form, for example, into tablet, capsule, pill, granule, solution, suspension, syrup, injection (the formulation is prepared from the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein, or the injection itself comprises the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein, including a solution for injection, a sterile powder for injection and a concentrated solution for injection), suppository, inhalant or spray.

The present disclosure further relates to a method for preparing a pharmaceutical composition, comprising: mixing the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition

salt disclosed herein with at least one pharmaceutically acceptable carrier, diluent or excipient. In addition, the pharmaceutical composition disclosed herein can be administered by any suitable route of administration, such as oral, parenteral, rectal, pulmonary or local administration, to a patient or subject in need. For oral administration, the pharmaceutical composition can be formulated into an oral formulation, for example, a solid oral formulation such as tablet, capsule, pill and granule, or a liquid oral formulation such as oral solution, oral suspension and syrup. When formulated into an oral formulation, the pharmaceutical formulation may further comprise a suitable filler, binder, disintegrant, lubricant and the like. For parenteral administration, the pharmaceutical composition can be formulated into an injection, including a solution for injection, a sterile powder for injection and a concentrated solution for injection. When formulated into an injection, the pharmaceutical composition may be manufactured by conventional methods in the prior art. When formulated into an injection, the pharmaceutical formulation may be free of additives, or contain proper additives according to the nature of the medicament. For rectal administration, the pharmaceutical formulation can be formulated into a suppository or the like. For pulmonary administration, the pharmaceutical formulation can be formulated into an inhalant or spray. In certain embodiments, the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein is present in the pharmaceutical composition or medicament in a therapeutically and/or prophylactically effective amount. In certain embodiments, the amorphous form of the compound of formula II or the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt disclosed herein is present in the pharmaceutical composition or medicament in a form of unit dose.

The present disclosure further relates to use of an amorphous form of a compound of formula II or an acid addition salt of the compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, or a pharmaceutical composition comprising or prepared from the same, in preparing a medicament for treating a disease or condition mediated by RORγ. The disease or condition mediated by RORγ includes, but is not limited to, inflammatory and autoimmune diseases and cancers, wherein the inflammatory and autoimmune diseases include, but are not limited to, arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis vulgaris, psoriatic arthritis, osteoarthritis, regional suppurative, ulcerative colitis, ankylosing spondylitis,

autoimmune diabetes, type I diabetes, autoimmune ocular disease, autoimmune thyroid disease, type I immune hypersecretion syndrome, type II autoimmune polycyrine syndrome, multiple sclerosis, inflammatory bowel disease, inflammatory bowel syndrome, juvenile idiopathic arthritis, Sjögren syndrome, Crohn's disease, asthma, Kawasaki's disease, Hashimoto's thyroiditis, infectious disease, ankylosing spondylitis, chronic obstructive pulmonary disease (COPD), pulmonary disease, glomerulonephritis, myocarditis, thyroiditis, dry eye, uveitis, Behcet's disease, asthma, atopic dermatitis, contact dermatitis, allograft rejection, polymyositis, GVHD, acne, ulcerative colitis, systemic lupus erythematosus, scleroderma, bronchitis, dermatomyositis and allergic rhinitis; the cancers include, but are not limited to, non-Hodgkin's lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, synovial sarcoma, breast cancer, cervical cancer, colon cancer, lung cancer, stomach cancer, rectal cancer, pancreatic cancer, brain cancer, skin cancer, mouth cancer, prostate cancer, bone cancer, kidney cancer, ovarian cancer, bladder cancer, liver cancer, fallopian tube tumor, ovarian tumor, peritoneal tumor, melanoma, solid tumor, glioma, glioblastoma, hepatocellular carcinoma, papillary renal tumor, head and neck tumor, leukemia, lymphoma, myeloma and non-small cell lung cancer.

SUMMARY

In the specification and claims of the present application, unless otherwise specified, the scientific and technological terms used herein have meanings generally understood by those skilled in the art. However, definitions and explanations for some of the related terms are provided below to better understand the present disclosure. In addition, if the definitions and explanations of the terms provided in the present application are not consistent with the meanings generally understood by those skilled in the art, the definitions and explanations of the terms provided in the present application shall prevail.

The "ether solvent" described herein includes, but is not limited to: tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl *tert*-butyl ether, isopropyl ether or 1,4-dioxane.

Specific examples of "alcohol solvent" described herein include, but are not limited to: methanol, ethanol, isopropanol, *n*-propanol, isoamyl alcohol or trifluoroethanol.

The "ester solvent" described herein includes, but is not limited to: ethyl acetate, isopropyl acetate or butyl acetate.

Specific examples of "ketone solvent" described herein include, but are not limited to: acetone, acetophenone or 4-methyl-2-pentanone.

Specific examples of "nitrile solvent" described herein include, but are not limited to: acetonitrile or propionitrile.

Specific examples of "halogenated hydrocarbon solvent" described herein include, but are not limited to: chloromethane, dichloromethane, chloroform or carbon tetrachloride.

Specific examples of "hydrocarbon solvent" described herein include, but are not limited to: *n*-butane, *n*-pentane, *n*-hexane or *n*-heptane.

The "X-ray powder diffraction pattern or XRPD" described herein is obtained by Cu-Kα ray diffraction.

The "differential scanning calorimetry or DSC" described herein refers to measurement of the temperature difference and heat flow difference between a sample and a reference substance during a process of increasing or holding the temperature of the sample to characterize all the physical changes and chemical changes related to the thermal effect, and to obtain the phase change information of the sample.

The "2θ or angle 2θ" described herein refers to diffraction angle. θ is Bragg angle in unit ° or degree. The error range of 2θ may be ±0.3, ±0.2 or ±0.1.

Beneficial Effects

The amorphous form of the compound of formula II, the benzoate, oxalate, methanesulfonate, maleate, hydrobromide, hydrochloride and acetate of the compound of formula II, and the crystalline form of the benzoate, the amorphous form of the benzoate, the crystalline form of the oxalate, the amorphous form of the oxalate, the amorphous form of the methanesulfonate, the crystalline forms B, C and D of the maleate, the crystalline form I of the hydrobromide, the crystalline forms α, β and γ of the hydrochloride and the crystalline form of the acetate of the compound of formula II provided herein provide alternative solid forms of the compound of formula II that can be used as RORγ regulators in drug development processes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an XRPD pattern of an amorphous form of a compound of formula II.

FIG. 2 is an XRPD pattern of an amorphous form of a benzoate of a compound of formula II.

FIG. 3 is an XRPD pattern of a crystalline form of a benzoate of a compound of formula II.

FIG. 4 is a DSC pattern of a crystalline form of a benzoate of a compound of formula II.

FIG. 5 is an XRPD pattern of an amorphous form of an oxalate of a compound of formula II.

FIG. 6 is an XRPD pattern of a crystalline form of an oxalate of a compound of formula II.

FIG. 7 is an XRPD pattern of an amorphous form of a methanesulfonate of a compound of formula II.

FIG. 8 is an XRPD pattern of a crystalline form B of a maleate of a compound of formula II.

FIG. 9 is a DSC pattern of a crystalline form B of a maleate of a compound of formula II.

FIG. 10 is a TGA pattern of a crystalline form B of a maleate of a compound of formula II.

FIG. 11 is a DVS vapor sorption plot of a crystalline form B of a maleate of a compound of formula II.

FIG. 12 is a comparison of XRPD patterns before and after DVS analysis of a crystalline form B of a maleate of a compound of formula II.

FIG. 13 is an XRPD pattern of a crystalline form C of a maleate of a compound of formula II.

FIG. 14 is a DSC pattern of a crystalline form C of a maleate of a compound of formula II.

FIG. 15 is a TGA pattern of a crystalline form C of a maleate of the compound of formula II.

FIG. 16 is an XRPD pattern of a crystalline form D of a maleate of a compound of formula II.

FIG. 17 is a DSC pattern of a crystalline form D of a maleate of a compound of formula II.

FIG. 18 is a TGA pattern of a crystalline form D of a maleate of a compound of formula II.

FIG. 19 is an XRPD pattern of a crystalline form I of a hydrobromide of a compound of formula II.

FIG. 20 is a DSC pattern of a crystalline form I of a hydrobromide of a compound of formula II.

FIG. 21 is a TGA pattern of a crystalline form I of a hydrobromide of a compound of formula II.

FIG. 22 is a DVS vapor sorption plot of a crystalline form I of a hydrobromide of a compound of formula II.

FIG. 23 is a comparison of XRPD patterns before and after DVS analysis of a crystalline form I of a hydrobromide of a compound of formula II.

FIG. 24 is an XRPD pattern of a crystalline form α of a hydrochloride of a compound of formula II.

FIG. 25 is a DSC pattern of a crystalline form α of a hydrochloride of a compound of formula II.

FIG. 26 is a TGA pattern of a crystalline form α of a hydrochloride of a compound of formula II.

FIG. 27 is a DVS vapor sorption plot of a crystalline form α of a hydrochloride of a compound

of formula II.

FIG. 28 is a comparison of XRPD patterns before and after DVS analysis of a crystalline form α of a hydrochloride of a compound of formula II.

FIG. 29 is an XRPD pattern of a crystalline form β of a hydrochloride of a compound of formula II.

FIG. 30 is a DSC pattern of a crystalline form β of a hydrochloride of a compound of formula II.

FIG. 31 is a TGA pattern of a crystalline form β of a hydrochloride of a compound of formula II.

FIG. 32 is a DVS vapor sorption plot of a crystalline form β of a hydrochloride of a compound of formula II.

FIG. 33 is a comparison of XRPD patterns before and after DVS analysis of a crystalline form β of a hydrochloride of a compound of formula II.

FIG. 34 is an XRPD pattern of a crystalline form γ of a hydrochloride of a compound of formula II.

FIG. 35 is an XRPD pattern of a crystalline form of an acetate of a compound of formula II.

FIG. 36 is a DSC pattern of a crystalline form of an acetate of a compound of formula II.

DETAILED DESCRIPTION

Hereinafter, the present disclosure will be explained in more details with reference to the examples. The examples are only used to illustrate the technical solutions of the present disclosure, rather than limit the essence and scope of the present disclosure.

Test conditions for the instruments used in the experiment:

The structure of the compounds was determined by nuclear magnetic resonance (NMR) analysis or/and mass spectrometry (MS). NMR shifts (δ) are given in a unit of 10^{-6} (ppm). NMR analysis was conducted with a Bruker AVANCE-400 system using deuterated dimethyl sulfoxide (DMSO-d_6), deuterated chloroform ($CDCl_3$) and deuterated methanol (CD_3OD) as solvents and tetramethylsilane (TMS) as internal standard.

MS was conducted with a FINNIGAN LCQAd (ESI) mass spectrometer (manufacturer: Thermo, model: Finnigan LCQ advantage MAX).

The HPLC was conducted with an Agilent 1200 DAD high pressure liquid chromatograph (Sunfire C18 150 × 4.6 mm chromatographic column) and a Waters 2695-2996 high pressure

liquid chromatograph (Gimini C18 150 × 4.6 mm chromatographic column).

XRPD refers to X-ray powder diffraction detection: The measurement was conducted using a BRUKER D8 X-ray diffractometer with a Cu anode (40 kV, 40 mA) and Cu-Kα radiation (λ = 1.5418 Å). Scanning mode: θ/2θ, scanning range: 10–48°.

DSC refers to differential scanning calorimetry: The measurement was conducted using a METTLER TOLEDO DSC 3+ differential scanning calorimeter with a temperature ramping rate of 10 °C/min, specific temperature ranges shown in corresponding patterns (mostly 25–300 or 25–350 °C) and a nitrogen purging speed of 50 mL/min.

TGA refers to thermogravimetric analysis: The measurement was conducted using a METTLER TOLEDO TGA 2 thermogravimetric analyzer with a temperature ramping rate of 10 °C/min, specific temperature ranges shown in corresponding patterns (mostly 25–300 °C) and a nitrogen purging speed of 20 mL/min.

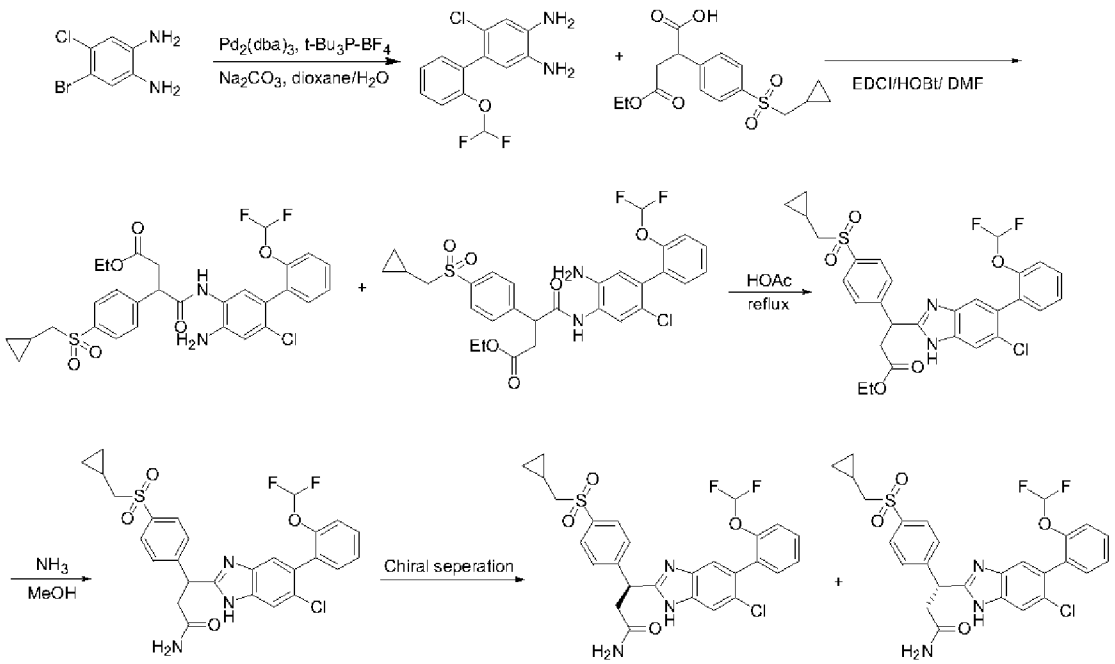
DVS refers to dynamic vapor sorption: The measurement was conducted with a Surface Measurement Systems advantage 2 at 25 °C, starting from 50% humidity in humidity range of 0%–95% with a step size of 10%. The judging criterion was that the mass change of each gradient dM/dT is less than 0.002 and TMAX is less than 360 min in two circles.

The monitoring of the reaction progress in the examples was conducted by thin layer chromatography (TLC). The developing solvent for reactions, the eluent system for column chromatography purification and the developing solvent system for thin layer chromatography included: A: *n*-hexane/ethyl acetate system. The volume ratio of the solvents was adjusted according to the polarity of the compound, or by adding a small amount of basic or acidic reagents such as triethylamine and acetic acid.

Comparative Example 1. Preparation example of compound of formula II (methods in Examples 152 and 153 of Patent Application No. PCT/US19/30526)

Preparation of (*S*)-3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanamide

Preparation of (*R*)-3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanamide



Step I. Preparation of 6-chloro-2'-(difluoromethoxy)-[1,1'-biphenyl]-3,4-diamine

A mixture of 4-bromo-5-chlorobenzene-1,2-diamine (1.5 g, 6.78 mmol), 2-(2-(difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.2 g, 8.15 mmol), tris(dibenzylideneacetone)dipalladium (620 mg), tri-*tert*-butylphosphonium tetrafluoroborate (393 mg), sodium carbonate (1.7 g, 13.7 mmol), 1,4-dioxane (50 mL) and water (10 mL) was deoxygenated, heated to 90 °C, and stirred for 3 h. The reaction solution was concentrated at reduced pressure. The residue was directly loaded on an ISCO solid column, and eluted with a mixed solvent of *n*-hexane/ethyl acetate to give a white solid product (1.0 g, 51.9% yield). MS (+) ES: 285 $(M+H)^+$.

Step II. Preparation of ethyl 4-((4-amino-6-chloro-2'-(dichloromethoxy)-[1,1'-biphenyl]-3-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate

Preparation of ethyl 4-((5-amino-2-chloro-2'-(dichloromethoxy)-[1,1'-biphenyl]-4-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate

EDCl (560 mg, 2.93 mmol), HOBT (447 mg, 2.93 mmol) and DIPEA (380 mg, 2.94 mmol) were added to a solution of 6-chloro-2'-(difluoromethoxy)-[1,1'-biphenyl]-3,4-diamine (543 mg, 1.9 mmol), 2-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-ethoxy-4-oxobutanoic acid (500 mg, 1.47 mmol) and DMF (5 mL), and the reaction system was stirred at room temperature for 2 h. The reaction solution was adsorbed on 5 g of silica gel, loaded onto a silica gel column, and eluted with 45% ethyl acetate in *n*-hexane to obtain a mixture of ethyl 4-((4-amino-6-chloro-2'-

(dichloromethoxy)-[1,1'-biphenyl]-3-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate and ethyl 4-((5-amino-2-chloro-2'-(dichloromethoxy)-[1,1'-biphenyl]-4-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate as a white solid (600 mg, 62.3% yield). MS (ESI): 607 $(M+H)^+$.

Step III. Preparation of ethyl 3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propionate

A solution of the mixture of ethyl 4-((4-amino-6-chloro-2'-(dichloromethoxy)-[1,1'-biphenyl]-3-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate and ethyl 4-((5-amino-2-chloro-2'-(dichloromethoxy)-[1,1'-biphenyl]-4-yl)amino)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)-4-oxobutanoate (800 mg) in acetic acid (15 mL) was heated to 80 °C and stirred for 2 h for reaction. The reaction solution was concentrated at reduced pressure, and the obtained residue was purified by column chromatography with an eluent of 60% ethyl acetate in *n*-hexane to obtain ethyl 3-(6-chloro-5-(2-(dichloromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propionate as an off-white solid (600 mg, 77.3% yield). MS (ESI): 589 $(M+H)^+$.

Step IV. Preparation of (*S*)-3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanamide

Preparation of (*R*)-3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanamide

A 7 N solution of ammonia in methanol (4.8 mL, 33.9 mmol) was added to a solution of ethyl 3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propionate (400 mg, 0.68 mmol) in methanol (5 mL). The reaction system was heated to 60 °C and stirred for 12 h for reaction. The reaction solution was concentrated at reduced pressure, and the resulting crude product was purified by column chromatography with a *n*-hexane/ethyl acetate eluent system to obtain 3-(6-chloro-5-(2-(difluoromethoxy)phenyl)-1*H*-benzo[*d*]imidazol-2-yl)-3-(4-((cyclopropylmethyl)sulfonyl)phenyl)propanamide (177 mg).

The resulting product was subjected to chiral resolution (conditions: CHIRALCEL OZ-H (OZH00CD-VC005), 0.46 cm I.D. × 15 cm L; mobile phase: 100% methanol; flow rate: 1.0 mL/min). The corresponding fractions were collected and concentrated at reduced pressure to obtain the target compound (67 mg, 60 mg).

Single-component compounds (shorter retention time)

MS (+) ES: 560 $(M+H)^+$

Chiral analysis methodology: retention time: 3.919 min, chiral purity: 100% (column: OD Phenomenex Lux Cellulose-1 150 × 4.6 mm, 5 μm; mobile phase: ethanol/*n*-hexane = 80:20 (v:v)).

1H NMR (400 mHz, CD_3OD): 7.92 (d, 8.0Hz, 2H), 7.51-7.49 (s, 1H), 7.65 (d, 8.0 Hz, 2 H), 7.56-7.54 (m, 1H), 7.48-7.44 (m, 1H), 7.33-7.32 (m, 2H), 7.28-7.26 (d, 8.0Hz, 1H), 6.86 (d, 8.0Hz, 1H), 4.96-4.92 (t, 8.0Hz, 1H), 3.41-3.35 (dd, 8.0Hz, 1H), 3.13-3.11 (d, 8.0Hz, 2H), 3.12-3.06 (dd, 8.0Hz, 1H), 0.93-0.91 (m, 1H), 0.52-0.50 (d, 8.0Hz, 2H), 0.13-0.11 (d, 8.0Hz, 2H).

Single-component compound (longer retention time, compound of formula II)

MS (+) ES: 560 $(M+H)^+$

Chiral analysis methodology: retention time: 8.942 min, chiral purity: 100% (column: OD Phenomenex Lux Cellulose-1 150 × 4.6 mm, 5 μm; mobile phase: ethanol/*n*-hexane = 80:20 (v:v)).

1H NMR (400 mHz, CD_3OD): 7.92 (d, 8.0Hz, 2H), 7.51-7.49 (s, 1H), 7.65 (d, 8.0 Hz, 2 H), 7.56-7.54 (m, 1H), 7.48-7.44 (m, 1H), 7.33-7.32 (m, 2H), 7.28-7.26 (d, 8.0Hz, 1H), 6.86 (d, 8.0Hz, 1H), 4.96-4.92 (t, 8.0Hz, 1H), 3.41-3.35 (dd, 8.0Hz, 1H), 3.13-3.11 (d, 8.0Hz, 2H), 3.12-3.06 (dd, 8.0Hz, 1H), 0.93-0.91 (m, 1H), 0.52-0.50 (d, 8.0Hz, 2H), 0.13-0.11 (d, 8.0Hz, 2H).

Test Example 1. Biochemical assay of LanthaScreen TR-FRET RORγ-LBD and co-activation peptide

Materials and reagents

1. RORγ LBD-GST tagged (Cat No. RORC-114H, Creative Biomart)
2. Fluorescein-D22 coactivator (Cat No. PV4386, Invitrogen)
3. LanthaScreen™ Tb anti-GST antibody (Cat No. PV3550, Invitrogen)
4. TR-FRET coregulatory buffer D (Cat No. PV4420, Invitrogen)
5. DTT (Cat No. P2325, Fisher)
6. 384 well assay plate (Cat No. 6008280, Perkin Elmer)
7. Tecan Infinite M1000 plate reader (Tecan)

Procedures

Complete TR-FRET Coregulator Buffer D was prepared by diluting 1 M DTT with TR-FRET Coregulator Buffer D to a final concentration of 5 mM DTT. The compounds were diluted in

Complete TR-FRET Coregulator Buffer D. The solutions were serially 7-fold diluted from an initial concentration of 3 μM to the 7th concentration. 10 μL of the dilutions was added to each well of the 384-well plate. For negative and positive controls, 10 μL of Complete TR-FRET Coregulator Buffer D was added.

A RORγ LBD solution was prepared using Complete TR-FRET Coregulator Buffer D. The final concentration of the RORγ LBD solution in each reaction was 25 ng. Other than the negative wells receiving 5 μL of Complete TR-FRET Coregulator Buffer D, 5 μL of the RORγ LBD solution was added to the remaining wells of the 384-well assay plate.

Complete TR-FRET Coregulator Buffer D was used to prepare a solution containing 0.6 μM Fluorescein-D22 and 8 nM Tbanti-GST antibody, and 5 μL of the prepared solution was added to all wells of the 384-well assay plate.

The 384-well plate was mixed gently on a plate shaker and let stand at room temperature for 1 h away from light. The 384-well plate was sealed with a plastic film to avoid evaporation.

The plate was measured on a Tecan Infinite M1000 plate reader at wavelengths of 520 nm and 495 nm. IC_{50} values were calculated using GraphPad Prism by plotting log compound concentration versus percentage inhibition. The IC_{50} values for the compounds are shown in Table 1.

Test Example 2. Assay for inhibiting cytokine IL-17A production in human peripheral blood mononuclear cells

Materials and instruments

1. Human PBMC (Stemcell, Cat No. 70025.1)
2. Lymphocyte medium (Zenbio, Cat No. LYMPH-1)
3. TexMACS (Miltenyi Biotec, Cat No. 130-097-196)
4. Human Cytostim (Miltenyi Biotec, Cat No. 130-092-173)
5. Human IL-17 ELISA, human IL-17 enzyme-linked immunosorbent assay kit (R&D Systems, D1700)
6. 96-well cell culture plate (Fisher Scientific, Cat No. 07-200-80)
7. Tecan SPARK plate reader (Tecan)

Procedures

Frozen human peripheral blood mononuclear cells (PBMCs) were rapidly thawed in a pre-warmed lymphocyte medium and centrifuged at 1000 rpm for 10 min. The cell culture

supernatant was discarded, and the cells were gently suspended in the TexMACS medium and counted. T cell activating reagent cytostim (10 μL/mL) was added to the cell suspension in certain proportions, and then the cells were seeded in a 96-well cell culture plate at a density of 1×10^5 PBMCs/well. Test compounds were diluted in gradient using TexMACS medium and added to the treatment wells in 2–3 replicates. Negative control wells containing cells only without cytostim were prepared to obtain background readings. The cell culture plate was incubated in a 5% carbon dioxide/37 °C incubator for 3 days. Cell culture supernatant was collected 3 days after treatment and centrifuged to remove the suspended matter. IL-17A in the supernatant was then quantified using an IL-17A enzyme-linked immunosorbent assay kit. The log(inhibitor) vs. response -- Variable slope (four parameters) algorithm in GraphPad Prism 6.0 was used to plot the curve for calculating the IC_{50} values of the compounds. The calculation equation of inhibition is as follows:

$$\text{Inhibition\%} = [100 - \frac{\text{OD(Compound)} - \text{OD(NC)}}{\text{OD(PC)} - \text{OD(NC)}} \times 100]/-1$$

In the calculation equation, inhibition% is inhibition rate; OD(NC) is the reading of cells in negative control groups with no cytostim and no compound; OD(PC) is the reading of cells in positive control groups with cytostim but no compound; OD(compound) is the reading of cells with cytostim and compound.

Table 1. Binding of compounds of formula II to RORγ and IL-17 production in human peripheral blood mononuclear cells

Compound	RORγ coactivation assay (IC_{50}, μM)	IL-17 production (IC_{50}, μM)
Those with longer retention time in Examples 152 and 153 (compound of formula II)	0.013	0.010

Example 1. Preparation of amorphous form of compound of formula II

The compound of formula II (30 mg, 53.57 μmol) was added to isopropyl ether (1.5 mL). The mixture was heated to 70 °C to obtain an opaque white suspension. The suspension was slowly cooled to room temperature, stirred for 16 h and filtered. The filter cake was collected and dried *in vacuo* to obtain a product (20 mg, 66% yield). The product was in an amorphous form with XRPD pattern shown in FIG. 1.

Example 2. Preparation of amorphous form of compound of formula II

The compound of formula II (30 mg, 53.57 μmol) was added to toluene (1.5 mL). The mixture was heated to 70 °C and stirred to obtain a clarified solution. The solution was slowly cooled to room temperature and a solid was precipitated on the inner wall of the container. The mixture was stirred for 16 h at room temperature and filtered. The filter cake was collected and dried *in vacuo* to obtain a product (20 mg, 66% yield). The product was in an amorphous form as determined by X-ray powder diffraction.

Example 3. Preparation of amorphous form of compound of formula II

The compound of formula II (30 mg, 53.57 μmol) was added to a 1.5 mL mixture of isopropyl acetate/*n*-hexane (v:v = 1:3). The mixture was heated to 70 °C and a viscous solid was precipitated. The solution was slowly cooled to room temperature and a solid was precipitated. The mixture was stirred for 16 h at room temperature and filtered. The filter cake was collected and dried *in vacuo* to obtain a product (20 mg, 66% yield). The product was in an amorphous form as determined by X-ray powder diffraction.

Example 4. Preparation of amorphous form of compound of formula II

The compound of formula II (5 g, 8.93 mmol) was purified by high performance liquid chromatography (Waters-2767, eluent system: ammonium bicarbonate, water and acetonitrile) to obtain a product (2.5 g, 50% yield). The product was in an amorphous form as determined by X-ray powder diffraction.

Example 5. Influencing factor study of amorphous form of compound of formula II

A sample of the amorphous form of the compound of formula II (Example 4) was let stand open to examine the stability of the sample in conditions of heating (40 °C and 60 °C), illumination (4500 Lux) and high humidity (RH 75% and RH 90%) in a period of 30 days.

Results:

Table 2. Results of influencing factor study

		Amorphous form			
Conditions	Time (days)	Color and appearance	Purity (%)	Weight gain (%)	Chiral purity
Initial	0	White solid	99.91	/	99.4
4500 Lux	5	White solid	99.91	/	/
	10	White solid	99.91	/	99.3

	30	White solid	99.93	/	99.3
	5	White solid	99.93	/	/
40°C	10	White solid	99.90	/	99.4
	30	White solid	99.92	/	99.5
	5	White solid	99.95	/	/
60°C	10	White solid	99.95	/	99.4
	30	White solid	99.95	/	99.4
	5	White solid	99.92	10.42	/
RH 75%	10	White solid	99.90	13.2	99.3
	30	White solid	99.90	23.24	99.4
	5	White solid	99.91	21.67	/
RH 90%	10	White solid	99.92	26.49	99.4
	30	White solid	99.89	37.24	99.4

Conclusion:

The results of influencing factor study in Table 2 showed that: the amorphous form of the compound of the formula II has good chemical stability after standing for 30 days in conditions of illumination, high temperature of 40 °C, high temperature of 60 °C, high humidity of 75% and high humidity of 90%.

Example 6. Long-term/accelerated stability study of amorphous form of compound of formula II

The amorphous form of the compound of formula II (Example 4) was subjected to a long-term (25 °C, 60% RH)/accelerated (40 °C, 75% RH) stability study with a period of 3 months.

Results

Table 3. Result of long-term/accelerated stability study of amorphous form of compound of formula II

Sample	Condition of standing	Purity/chiral purity Initial	Purity (%) Month 1	Purity (%) Month 2	Purity (%) Month 3	Chiral purity (%) Month 3
Amorphous form	25℃, 60%RH	99.87/99.2	99.86	99.86	99.85	99.2
	40℃, 75%RH	99.87/99.2	99.87	99.86	99.88	99.1

5°C	99.87/99.2	99.86	99.86	99.85	99.1

The results of the long-term/accelerated stability study in Table 3 showed that: the amorphous form of the compound of formula II has good chemical stability in conditions of a long term (25 °C, 60% RH) and acceleration (40 °C, 75% RH) in a period of 3 months.

Example 7. Preparation of amorphous form of benzoate of compound of formula II

0.5 mL of *n*-hexane was added to 10 mg of the compound of formula II before 2.3 mg of benzoic acid was added. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as an amorphous form of the benzoate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 2.

Example 8. Preparation of crystalline form of benzoate of compound of formula II

0.5 mL of methyl *tert*-butyl ether was added to 10 mg of the compound of formula II before 2.3 mg of benzoic acid was added. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form of the benzoate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 3. The DSC pattern is shown in FIG. 4, with a first endothermic peak value at 178.46 °C and a second endothermic peak value at 237.42 °C.

Table 4. Characteristic peaks of crystalline form of benzoate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	5.305	16.64444	100.0
Peak 2	7.411	11.91828	43.6
Peak 3	19.140	4.63321	1.3
Peak 4	22.031	4.03134	23.9

Example 9. Preparation of amorphous form of oxalate of compound of formula II

0.5 mL of methyl *tert*-butyl ether was added to 10 mg of the compound of formula II before 2 mg of oxalic acid was added. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as an amorphous form of the oxalate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 5.

Example 10. Preparation of crystalline form of oxalate of compound of formula II

0.5 mL of *n*-hexane was added to 10 mg of the compound of formula II before 2 mg of oxalic acid was added. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form of the oxalate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 6.

Table 5. Characteristic peaks of crystalline form of oxalate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	14.378	6.15525	100.0
Peak 2	18.463	4.80158	51.5
Peak 3	21.670	4.09779	70.9
Peak 4	23.075	3.85126	50.6
Peak 5	28.127	3.17003	21.6

Example 11. Preparation of amorphous form of methanesulfonate of compound of formula II

0.5 mL of methyl *tert*-butyl ether was added to 10 mg of the compound of formula II before 1.8 μL of methanesulfonic acid was added. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as an amorphous form of the methanesulfonate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 7.

Example 12. Preparation of crystalline form B of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 30 min to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form B of the maleate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 8. The DSC pattern is shown in FIG. 9, with a first endothermic peak value at 138.04 °C; the TGA pattern is shown in FIG. 10.

DVS characterization: the vapor sorption of the crystalline form B of the maleate at 25 °C increased along with the increase of humidity in a range of 20.0% RH to 80.0% RH, with a weight change of 1.731%, less than 2% but not less than 0.2%, indicating that the sample is slightly hygroscopic. In a normal storage condition (i.e., 60% humidity/25 °C), the vapor

sorption was about 1.438%; in an accelerated test condition (i.e., 70% humidity), the vapor sorption was about 1.809%; in an extreme condition (i.e., 90% humidity), the vapor sorption was about 3.077%.

The comparison of X-ray powder diffraction patterns before and after DVS showed that crystalline form did not change during DVS. The DVS pattern is shown in FIG. 11, and the comparison of X-ray powder diffraction patterns before and after DVS is shown in FIG. 12.

Table 6. Characteristic peaks of crystalline form B of maleate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	7.624	11.58707	74.9
Peak 2	9.659	9.14922	40.7
Peak 3	13.815	6.40503	41.2
Peak 4	15.844	5.58882	56.9
Peak 5	17.391	5.09522	100.0
Peak 6	18.619	4.76186	31.5
Peak 7	21.802	4.07319	76.4
Peak 8	23.667	3.75633	49.8
Peak 9	26.441	3.36816	13.2

Example 13. Preparation of crystalline form B of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 10 min to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form B of the maleate of the compound of formula II as determined by X-ray powder diffraction.

Example 14. Preparation of crystalline form B of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 20 min to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form B of the maleate of the compound of formula II as determined by X-ray powder diffraction.

Example 15. Preparation of crystalline form B of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 1 h to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form B of the maleate of the compound of formula II as determined by X-ray powder diffraction.

Example 16. Preparation of crystalline form B of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 2 h to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form B of the maleate of the compound of formula II as determined by X-ray powder diffraction.

Example 17. Preparation of crystalline form C of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 1 d to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form C of the maleate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 13. The DSC pattern is shown in FIG. 14, with a first endothermic peak value at 154.58 °C; the TGA pattern is shown in FIG. 15.

Table 7. Characteristic peaks of crystalline form C of maleate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	7.325	12.05902	24.9
Peak 2	8.635	10.23231	46.0
Peak 3	9.809	9.00970	38.0
Peak 4	11.661	7.58265	14.6
Peak 5	13.649	6.48261	27.1
Peak 6	16.133	5.48950	23.5
Peak 7	16.765	5.28383	27.8
Peak 8	18.346	4.83192	100.0
Peak 9	21.689	4.09421	37.3
Peak 10	23.586	3.76901	31.9

Peak 11	25.303	3.51708	15.5

Example 18. Preparation of crystalline form D of maleate of compound of formula II

100 mg of the compound of formula II and 22 mg of maleic acid were added to 5 mL of methyl *tert*-butyl ether. The mixture was stirred at 600 rpm at 50 °C for 3 d to obtain a suspension. The suspension was filtered *in vacuo* and the residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form D of the maleate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 16. The DSC pattern is shown in FIG. 17, with a first endothermic peak value at 159.27 °C; the TGA pattern is shown in FIG. 18.

Table 8. Characteristic peaks of crystalline form D of maleate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	4.486	19.68368	65.1
Peak 2	5.998	14.72391	35.9
Peak 3	7.288	12.12061	48.6
Peak 4	9.067	9.74591	49.9
Peak 5	10.001	8.83770	50.9
Peak 6	13.914	6.35938	59.0
Peak 7	15.026	5.89121	34.9
Peak 8	16.227	5.45786	27.0
Peak 9	18.229	4.86287	100.0
Peak 10	18.940	4.68174	84.8
Peak 11	23.076	3.85108	58.0
Peak 12	25.612	3.47535	60.6
Peak 13	28.102	3.17274	12.9

Example 19. Preparation of crystalline form I of hydrobromide of compound of formula II

5 mL of methyl *tert*-butyl ether was added to 100 mg of the compound of formula II before 20 μL of hydrobromic acid was added. The mixture was stirred at 600 rpm at 25 °C for 3 days and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form I of the hydrobromide of the compound of formula II by X-ray

powder diffraction, with an XRPD pattern shown in FIG. 19. The DSC pattern is shown in FIG. 20, with a first endothermic peak value at 201.73 °C; the TGA pattern is shown in FIG. 21.

DVS characterization: the vapor sorption of the crystalline form I of the hydrobromide at 25 °C increased along with the increase of humidity in a range of 20.0% RH to 80.0% RH, with a weight change of 0.636%, less than 2% but not less than 0.2%, indicating that the sample is slightly hygroscopic. In a normal storage condition (i.e., 60% humidity/25 °C), the vapor sorption was about 0.589%; in an accelerated test condition (i.e., 70% humidity), the vapor sorption was about 0.702%; in an extreme condition (i.e., 90% humidity), the vapor sorption was about 1.094%.

The desorption process and the sorption process of the sample basically overlapped in the process of 0–95% humidity change; the comparison of X-ray powder diffraction patterns before and after DVS showed that crystalline form did not change during DVS. The DVS pattern is shown in FIG. 22, and the comparison of X-ray powder diffraction patterns before and after DVS is shown in FIG. 23.

Table 9. Characteristic peaks of crystalline form I of hydrobromide of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	8.128	10.86905	68.5
Peak 2	11.918	7.41964	7.5
Peak 3	12.579	7.03116	19.0
Peak 4	16.414	5.39626	54.1
Peak 5	17.075	5.18879	15.6
Peak 6	17.780	4.98456	39.3
Peak 7	18.750	4.72892	7.8
Peak 8	19.675	4.50851	9.9
Peak 9	20.733	4.28082	27.1
Peak 10	21.262	4.17552	100.0
Peak 11	23.113	3.84512	36.8
Peak 12	23.906	3.71929	15.0
Peak 13	24.391	3.64645	67.5
Peak 14	26.550	3.35455	14.5
Peak 15	28.445	3.13522	29.4

Peak 16	28.930	3.08378	26.0
Peak 17	29.547	3.02077	55.8
Peak 18	30.958	2.88630	27.7
Peak 19	32.236	2.77471	19.3
Peak 20	33.382	2.68204	1.4
Peak 21	38.670	2.32653	2.4
Peak 22	39.640	2.27183	3.3
Peak 23	40.830	2.20832	12.6
Peak 24	42.064	2.14635	5.4
Peak 25	43.342	2.08597	5.2
Peak 26	46.824	1.93865	4.0
Peak 27	48.190	1.88683	6.2
Peak 28	48.983	1.85811	4.1
Peak 29	50.746	1.79762	9.3

Example 20. Preparation of crystalline form I of hydrobromide of compound of formula II

5 mL of methyl *tert*-butyl ether was added to 100 mg of the compound of formula II before a 500 μL mixture of hydrobromic acid/ethanol (v:v = 1:50) was added. The mixture was stirred at 600 rpm at 25 °C for 3 days and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form I of the hydrobromide of the compound of formula II as determined by X-ray powder diffraction.

Example 21. Preparation of crystalline form I of hydrobromide of compound of formula II

5 mL of methyl *tert*-butyl ether was added to 100 mg of the compound of formula II before a 40 μL mixture of hydrobromic acid/ethanol (v:v = 1:1) was added. The mixture was stirred at 600 rpm at 25 °C for 3 days and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form I of the hydrobromide of the compound of formula II as determined by X-ray powder diffraction.

Example 22. Preparation of crystalline form I of hydrobromide of compound of formula II

15 mL of methyl *tert*-butyl ether was added to 100 mg of the compound of formula II before a 1000 μL mixture of hydrobromic acid/ethanol (v:v = 1:99) was added. The mixture was stirred at 600 rpm at 25 °C overnight and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to

obtain a product. The product was a crystalline form I of the hydrobromide of the compound of formula II as determined by X-ray powder diffraction.

Example 23. Preparation of crystalline form I of hydrobromide of compound of formula II

5 mL of methyl *tert*-butyl ether was added to 100 mg of the compound of formula II before a 1000 μL mixture of hydrobromic acid/ethanol (v:v = 1:99) was added. The mixture was stirred at 600 rpm at 25 °C overnight and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was a crystalline form I of the hydrobromide of the compound of formula II as determined by X-ray powder diffraction.

Example 24. Preparation of crystalline form α of hydrochloride of compound of formula II

5 mL of methyl *tert*-butyl ether and 15.6 μL of concentrated hydrochloric acid were added to 100 mg of the compound of formula II. The mixture was stirred at 50 °C for 2 d and dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form α of the hydrochloride of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 24. The DSC pattern is shown in FIG. 25, with a first endothermic peak value at 192.13 °C; the TGA pattern is shown in FIG. 26.

DVS characterization: the vapor sorption of the sample at 25 °C increased along with the increase of humidity in a range of 20.0% RH to 80.0% RH, with a weight change of 0.549%, less than 2% but not less than 0.2%, indicating that the sample is slightly hygroscopic. In a normal storage condition (i.e., 60% humidity/25 °C), the vapor sorption was about 0.463%; in an accelerated test condition (i.e., 70% humidity), the vapor sorption was about 0.574%; in an extreme condition (i.e., 90% humidity), the vapor sorption was about 1.040%.

The desorption process and the sorption process of the sample basically overlapped in the process of 0–95% humidity change; the comparison of X-ray powder diffraction patterns before and after DVS showed that crystalline form did not change during DVS. The DVS pattern is shown in FIG. 27, and the comparison of X-ray powder diffraction patterns before and after DVS is shown in FIG. 28.

Table 10. Characteristic peaks of crystalline form α of hydrochloride of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	7.931	11.13829	53.4
Peak 2	10.115	8.73832	19.9

Peak 3	12.166	7.26910	15.4
Peak 4	13.920	6.35673	24.2
Peak 5	15.224	5.81523	33.9
Peak 6	16.041	5.52078	13.9
Peak 7	16.315	5.42854	12.6
Peak 8	16.748	5.28930	12.2
Peak 9	17.425	5.08526	21.3
Peak 10	18.309	4.84177	64.7
Peak 11	19.624	4.52003	15.9
Peak 12	20.235	4.38496	19.6
Peak 13	21.491	4.13138	36.6
Peak 14	22.340	3.97642	67.3
Peak 15	23.359	3.80507	65.0
Peak 16	23.905	3.71950	48.0
Peak 17	24.570	3.62032	100.0
Peak 18	25.320	3.51464	20.1
Peak 19	25.811	3.44896	13.9
Peak 20	26.096	3.41194	10.5
Peak 21	27.624	3.22652	24.8
Peak 22	28.213	3.16057	24.6
Peak 23	29.190	3.05697	5.1
Peak 24	29.760	2.99971	2.4
Peak 25	31.266	2.85855	10.1
Peak 26	31.795	2.81217	5.5
Peak 27	32.324	2.76732	8.1
Peak 28	35.906	2.49902	3.7
Peak 29	37.291	2.40939	8.3

Example 25. Preparation of crystalline form β of hydrochloride of compound of formula II

5 mL of methyl *tert*-butyl ether and a 0.6 mL solution of concentrated hydrochloric acid in ethanol (0.1 mL of concentrated hydrochloric acid was added to 9.9 mL of ethanol and the

mixture was well mixed) were added to 100 mg of the compound of formula II. The mixture was stirred at 25 °C for 1 h and at 50 °C for 2 d, and filtered *in vacuo*. The residue was dried for 2 h at 40 °C to obtain a product. The product was identified as a crystalline form β of the hydrochloride of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 29. The DSC pattern is shown in FIG. 30, with a first endothermic peak value at 194.04 °C; the TGA pattern is shown in FIG. 31.

DVS characterization: the vapor sorption of the sample at 25 °C increased along with the increase of humidity in a range of 20.0% RH to 80.0% RH, with a weight change of 1.235%, less than 2% but not less than 0.2%, indicating that the sample is slightly hygroscopic. In a normal storage condition (i.e., 60% humidity/25 °C), the vapor sorption was about 1.755%; in an accelerated test condition (i.e., 70% humidity), the vapor sorption was about 1.954%; in an extreme condition (i.e., 90% humidity), the vapor sorption was about 2.534%.

The desorption process and the sorption process of the sample basically overlapped in individual processes of 0–95% humidity change, but the desorption process and the sorption process of the first and second cycles could not overlap; the comparison of X-ray powder diffraction patterns before and after DVS showed that crystalline form changed during DVS. The DVS pattern is shown in FIG. 32, and the comparison of X-ray powder diffraction patterns before and after DVS is shown in FIG. 33.

Table 11. Characteristic peaks of crystalline form β of hydrochloride of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	5.386	16.39621	39.0
Peak 2	8.191	10.78576	77.6
Peak 3	10.818	8.17156	29.1
Peak 4	12.688	6.97098	42.8
Peak 5	13.980	6.32982	20.9
Peak 6	14.915	5.93499	26.6
Peak 7	16.607	5.33388	19.7
Peak 8	18.076	4.90345	12.8
Peak 9	19.056	4.65352	12.9
Peak 10	20.036	4.42814	20.8

Peak 11	21.372	4.15427	100.0
Peak 12	22.040	4.02986	35.2
Peak 13	23.465	3.78826	25.0
Peak 14	24.355	3.65171	28.5
Peak 15	25.869	3.44132	36.7
Peak 16	26.582	3.35068	21.8
Peak 17	27.383	3.25440	12.0
Peak 18	29.253	3.05045	29.5
Peak 19	29.832	2.99256	39.9
Peak 20	30.946	2.88740	22.9
Peak 21	31.480	2.83959	41.4
Peak 22	32.504	2.75242	7.6
Peak 23	33.439	2.67755	8.5

Example 26. Preparation of crystalline form γ of hydrochloride of compound of formula II

A small amount of the crystalline form β of the hydrochloride of the compound of formula II was loaded on a DVS system and subjected to a detection with parameters of dm/dt=0.002, 50-95-0-95-50% RH, Max 360 min, 25 °C. The product was identified as a crystalline form β of the hydrochloride of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 34.

Table 12. Characteristic peaks of crystalline form γ of hydrochloride of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	8.114	10.88737	89.0
Peak 2	11.997	7.37097	42.5
Peak 3	12.640	6.99748	77.7
Peak 4	13.772	6.42501	45.7
Peak 5	16.478	5.37549	25.8
Peak 6	17.897	4.95221	45.6
Peak 7	19.671	4.50933	9.7
Peak 8	20.337	4.36327	52.8

Peak 9	21.422	4.14464	79.1
Peak 10	22.156	4.00903	62.3
Peak 11	23.228	3.82632	79.1
Peak 12	24.472	3.63450	100.0
Peak 13	25.882	3.43968	26.9
Peak 14	27.567	3.23307	27.4
Peak 15	28.277	3.15351	14.1
Peak 16	29.830	2.99281	38.1
Peak 17	31.160	2.86797	15.9
Peak 18	32.269	2.77189	17.0
Peak 19	33.334	2.68576	13.6

Example 27. Preparation of crystalline form of acetate of compound of formula II

1 mL of water was added to 20 mg of the compound of formula II before a solution of acetic acid in ethanol (0.1 mL of acetic acid was added to 9.9 mL of ethanol and the mixture was well mixed) was added in a molar ratio of 1:1. The mixture was stirred overnight at 50 °C and filtered *in vacuo*. The residue was dried for 1 h at 40 °C to obtain a product. The product was identified as a crystalline form of the acetate of the compound of formula II by X-ray powder diffraction, with an XRPD pattern shown in FIG. 35. The DSC pattern is shown in FIG. 36, with a first endothermic peak value at 206.96 °C, a first exothermic peak value at 213.49 °C and a second endothermic peak value at 246.30 °C.

Table 13. Characteristic peaks of crystalline form of acetate of compound of formula II

No.	2-Theta	d(A)	I%
Peak 1	11.651	7.58948	96.9
Peak 2	12.495	7.07863	38.2
Peak 3	14.323	6.17872	29.8
Peak 4	15.121	5.85472	28.9
Peak 5	15.636	5.66274	100.0
Peak 6	15.965	5.54704	66.5
Peak 7	18.075	4.90394	58.9
Peak 8	19.247	4.60782	20.4
Peak 9	19.903	4.45730	25.1

Peak 10	20.935	4.23993	38.5
Peak 11	22.107	4.01768	29.1
Peak 12	22.998	3.86402	47.4
Peak 13	23.842	3.72910	52.3
Peak 14	24.733	3.59676	59.9
Peak 15	25.530	3.48623	35.2
Peak 16	26.843	3.31862	11.7
Peak 17	28.719	3.10600	12.9
Peak 18	29.750	3.00061	6.1
Peak 19	30.829	2.89805	18.2
Peak 20	32.142	2.78260	14.6
Peak 21	35.143	2.55155	3.6
Peak 22	39.973	2.25369	2.6

Example 28. Influencing factor study of crystalline form α of hydrochloride and crystalline form I of hydrobromide of compound of formula II

Sample of the crystalline form α of the hydrochloride and the crystalline form I of the hydrobromide of the compound of formula II were let stand open to examine the stability of the samples in conditions of illumination (4500 Lux), high temperature (40 °C and 60 °C) and high humidity (RH 75% and RH 92.5%) in a period of 30 days.

Table 14. Stability data of the influencing factor study

		Crystalline form α of hydrochloride of compound of formula II				
Conditions	Time (days)	Color and appearance	Main peak purity (%)	Chiral purity (%)	Chloride ion content (%)	Crystalline form
Initial	0	White solid	96.925	99.14	5.75	Crystalline form α
40°C	7	White solid	96.915	99.131	/	Not changed
	14	White solid	96.921	99.115	/	Not changed
	30	White solid	96.824	99.207	5.75	Not changed

	7	White solid	96.884	99.136	/	Not changed
60°C	14	White solid	96.907	99.106	/	Not changed
	30	White solid	96.814	99.232	5.65	Not changed
	7	White solid	96.916	99.138	/	Not changed
75% RH	14	White solid	96.908	99.130	/	Not changed
	30	White solid	96.903	99.220	5.68	Not changed
	7	White solid	96.912	99.132	/	Not changed
92.5% RH	14	White solid	96.908	99.111	/	Not changed
	30	White solid	96.880	99.211	5.67	Not changed
	7	White solid	96.911	99.137	/	Not changed
4500 Lux	14	White solid	96.911	99.139	/	Not changed
	30	White solid	96.810	99.216	5.71	Not changed

Crystalline form I of hydrobromide of compound of formula II

Conditions	Time (days)	Color and appearance	Main peak purity (%)	Chiral purity (%)	Bromide ion content (%)	Crystalline form
Initial	0	White solid	97.689	99.298	11.75	Crystalline form I
	7	White solid	97.716	99.293	/	Not changed
40°C	14	White solid	97.727	99.165	/	Not changed
	30	White solid	97.644	99.251	11.73	Not changed
	7	White solid	97.645	99.299	/	Not changed
60°C	14	White solid	97.671	99.187	/	Not changed
	30	White solid	97.630	99.263	11.50	Not changed
	7	White solid	97.687	99.293	/	Not changed
75% RH	14	White solid	97.705	99.179	/	Not changed
	30	White solid	97.676	99.274	11.73	Not changed
	7	White solid	97.706	99.294	/	Not changed
92.5% RH	14	White solid	97.701	99.175	/	Not changed
	30	White solid	97.653	99.268	11.55	Not changed

	7	White solid	97.683	99.297	/	Not changed
4500 Lux	14	White solid	97.660	99.152	/	Not changed
	30	White solid	97.626	99.243	11.18	Not changed

Conclusions: the influencing factor study showed that: the crystalline form α of the hydrochloride and the crystalline form I of the hydrobromide of the compound of formula II have good physical and chemical stabilities in conditions of illumination, high temperatures of 40 °C and 60 °C and high humidities of 75% and 92.5%.

Example 29. Long-term/accelerated stability study of crystalline form α of hydrochloride and crystalline form I of hydrobromide of compound of formula II

The crystalline form α of the hydrochloride of the compound of formula II was let stand in conditions of 25 °C/60% RH and 40 °C/75% RH to examine its stability.

Table 15. Long term/accelerated stability study data for the crystalline form α of the hydrochloride of the compound of formula II

Conditions	Time	Crystalline form α of hydrochloride of compound of formula II				
		Color and appearance	Main peak purity (%)	Chiral purity (%)	Chloride ion content (%)	Crystalline form
Initial	0	White solid	96.925	99.14	5.75	Crystalline form α
25℃, 60%RH	Day 7	White solid	96.915	99.131	/	Not changed
	Day 14	White solid	96.831	99.111	/	Not changed
	Month 1	White solid	96.906	99.225	5.75	Not changed
	Month 2	White solid	96.883	99.332	5.74	Not changed
	Month 3	White solid	96.749	99.239	/	Not changed
	Month 6	White solid	96.170	99.187	5.85	Not changed
40℃, 75%RH	Day 7	White solid	96.906	99.137	/	Not changed
	Day 14	White solid	96.902	99.104	/	Not changed
	Month 1	White solid	96.846	99.206	5.44	Not changed
	Month 2	White solid	96.780	99.292	5.86	Not changed
	Month 3	White solid	96.664	99.149	/	Not changed
	Month 6	White solid	95.990	98.972	5.98	Not changed

The long-term/accelerated stability study showed that: the crystalline form α of the hydrochloride of the compound of formula II has good physical and chemical stability in conditions of a long term and acceleration in a period of 6 months.

The crystalline form I of the hydrobromide of the compound of formula II was let stand in conditions of 25 °C/60% RH and 40 °C/75% RH to examine its stability.

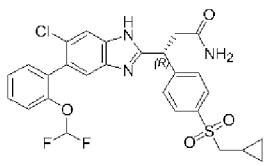
Table 16. Long term/accelerated stability study data for the crystalline form I of the hydrobromide of the compound of formula II

Conditions	Time	Crystalline form I of hydrobromide of compound of formula II				
		Color and appearance	Main peak purity (%)	Chiral purity (%)	Bromide ion content (%)	Crystalline form
Initial	0	White solid	97.689	99.298	11.75	Crystalline form I
25℃, 60%RH	Day 7	White solid	97.689	99.297	/	Not changed
	Day 14	White solid	97.697	99.198	/	Not changed
	Month 1	White solid	97.649	99.255	11.20	Not changed
	Month 2	White solid	97.661	99.363	11.05	Not changed
	Month 3	White solid	97.552	99.283	/	Not changed
	Month 6	White solid	96.981	99.228	11.82	Not changed
40℃, 75%RH	Day 7	White solid	97.661	99.295	/	Not changed
	Day 14	White solid	97.660	99.174	/	Not changed
	Month 1	White solid	97.558	99.262	11.49	Not changed
	Month 2	White solid	97.561	99.328	10.93	Not changed
	Month 3	White solid	97.259	99.275	/	Not changed
	Month 6	White solid	96.412	99.199	11.91	Not changed

The long-term/accelerated stability study showed that: the crystalline form I of the hydrobromide of the compound of formula II has good physical and chemical stability in conditions of a long term and acceleration in a period of 6 months.

CLAIMS

1. An acid addition salt of a compound of formula II or a pharmaceutically acceptable solvate of the acid addition salt, wherein the acid addition salt is an organic acid addition salt or an inorganic acid addition salt,



formula II.

2. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 1, wherein the organic acid addition salt is selected from the group consisting of benzoate, oxalate, methanesulfonate, maleate and acetate, and the inorganic acid addition salt is selected from the group consisting of hydrobromide and hydrochloride.

3. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the benzoate, oxalate and methanesulfonate are amorphous.

4. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the benzoate is a crystalline form having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.305 and 7.411.

5. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the oxalate is a crystalline form having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 14.378, 18.463 and 21.670.

6. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the maleate is a crystalline form B having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.624, 9.659, 13.815, 15.844 and 17.391.

7. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the maleate is a crystalline form

C having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.325, 8.635, 9.809, 13.649, 16.133, 16.765 and 18.346.

8. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the maleate is a crystalline form D having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 4.486, 7.288, 9.067, 10.001, 13.914, 18.229 and 18.940.

9. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrobromide is a crystalline form I having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 12.579, 16.414, 17.075, 17.780 and 20.733.

10. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrobromide is a crystalline form I having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 12.579, 16.414, 17.075, 17.780, 19.675, 20.733, 21.262, 23.113, 23.906, 24.391, 26.550, 28.445, 28.930 and 29.547.

11. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrobromide is a crystalline form I having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.128, 11.918, 12.579, 16.414, 17.075, 17.780, 18.750, 19.675, 20.733, 21.262, 23.113, 23.906, 24.391, 26.550, 28.445, 28.930, 29.547, 30.958, 32.236, 33.382, 38.670, 39.640, 40.830, 42.064, 43.342, 46.824, 48.190, 48.983 and 50.746.

12. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrochloride is a crystalline form α having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 7.931, 10.115, 13.920, 15.224, 17.425 and 18.309.

13. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrochloride is a crystalline form β having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 5.386, 8.191, 12.688, 16.607 and 20.036.

14. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the hydrochloride is a crystalline

form γ having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 8.114, 11.997, 12.640, 13.772, 16.478, 17.897 and 20.337.

15. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to claim 2, wherein the acetate is a crystalline form having an X-ray powder diffraction pattern with characteristic peaks at diffraction angles 2θ of 11.651, 12.495, 15.636, 15.965, 18.075 and 20.935.

16. The acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to any of claims 4 to 15, wherein the 2θ values of the crystalline forms have an error range of ±0.2.

17. A method for preparing the crystalline form I of the hydrobromide of the compound of formula II according to any of claims 9 to 11, comprising: precipitating a crystal by reacting the compound of formula II with hydrobromic acid in a proper amount of a solvent selected from the group consisting of one or more of a hydrocarbon solvent, an ether solvent, an alcohol solvent, an ester solvent, a ketone solvent, a nitrile solvent, a halogenated hydrocarbon solvent, a nitrogenous solvent, water and dimethyl sulfoxide, wherein

the hydrocarbon solvent includes, but is not limited to, *n*-butane, *n*-pentane, *n*-hexane or *n*-heptane;

the ether solvent includes, but is not limited to, tetrahydrofuran, diethyl ether, propylene glycol methyl ether, methyl *tert*-butyl ether, isopropyl ether or 1,4-dioxane;

the alcohol solvent includes, but is not limited to, methanol, ethanol, isopropanol, *n*-propanol, isoamyl alcohol or trifluoroethanol;

the ester solvent includes, but is not limited to, ethyl acetate, isopropyl acetate or butyl acetate;

the ketone solvent includes, but is not limited to, acetone, acetophenone or 4-methyl-2-pentanone;

the nitrile solvent includes, but is not limited to, acetonitrile or propionitrile;

the halogenated hydrocarbon solvent includes, but is not limited to, chloromethane, dichloromethane, chloroform or carbon tetrachloride;

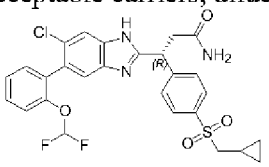
the nitrogenous solvent includes, but is not limited to, nitromethane, *N*,*N*-dimethylformamide or *N*,*N*-dimethylacetamide.

18. The method according to claim 17, wherein the solvent is methyl *tert*-butyl ether and ethanol.

19. A pharmaceutical composition comprising the acid addition salt or the pharmaceutically

acceptable solvate of the acid addition salt according to any of claims 1 to 16, and one or more pharmaceutically acceptable carriers, diluents or excipients.

20. A pharmaceutical composition comprising an amorphous form of a compound of formula II, and one or more pharmaceutically acceptable carriers, diluents or excipients,

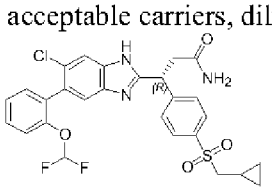


formula II.

21. A pharmaceutical composition comprising the crystalline form I of the hydrobromide according to any of claims 9 to 11, and one or more pharmaceutically acceptable carriers, diluents or excipients.

22. A pharmaceutical composition prepared from the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to any of claims 1 to 16 and one or more pharmaceutically acceptable carriers, diluents or excipients.

23. A pharmaceutical composition prepared from an amorphous form of a compound of formula II and one or more pharmaceutically acceptable carriers, diluents or excipients,

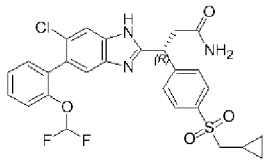


formula II.

24. A pharmaceutical composition prepared from the crystalline form I of the hydrobromide according to any of claims 9 to 11 and one or more pharmaceutically acceptable carriers, diluents or excipients.

25. A method for preparing a pharmaceutical composition, comprising: mixing the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to any of claims 1 to 16 with at least one pharmaceutically acceptable carrier, diluent or excipient.

26. A method for preparing a pharmaceutical composition, comprising: mixing an amorphous form of a compound of formula II with at least one pharmaceutically acceptable carrier, diluent or excipient,



formula II.

27. Use of the acid addition salt of the compound of formula II or the pharmaceutically acceptable solvate of the acid addition salt according to any of claims 1 to 16 or the pharmaceutical composition according to any of claims 19 to 24 in preparing a medicament for treating a disease or disorder mediated by RORγ.

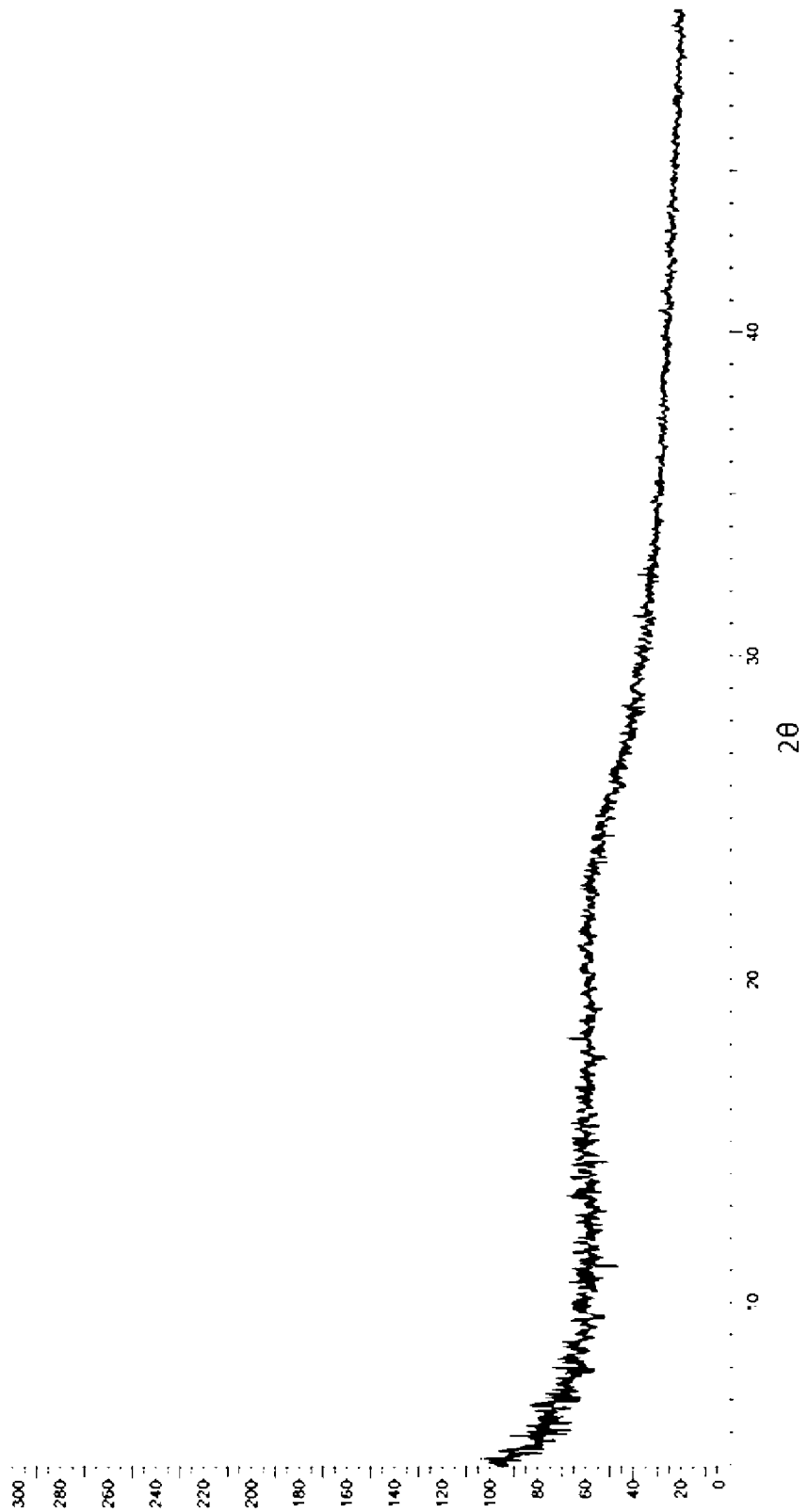


FIG. 1

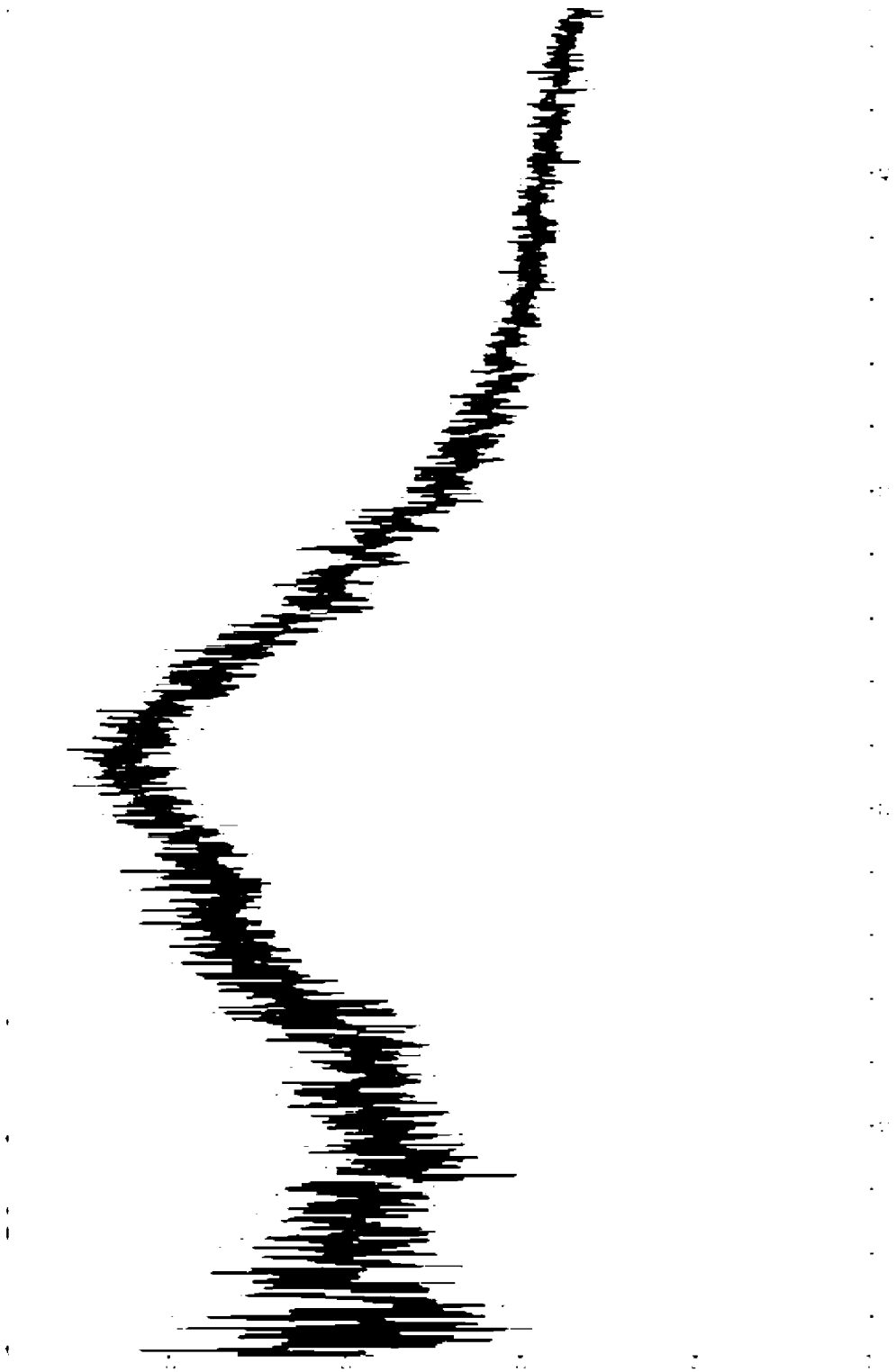


FIG. 2

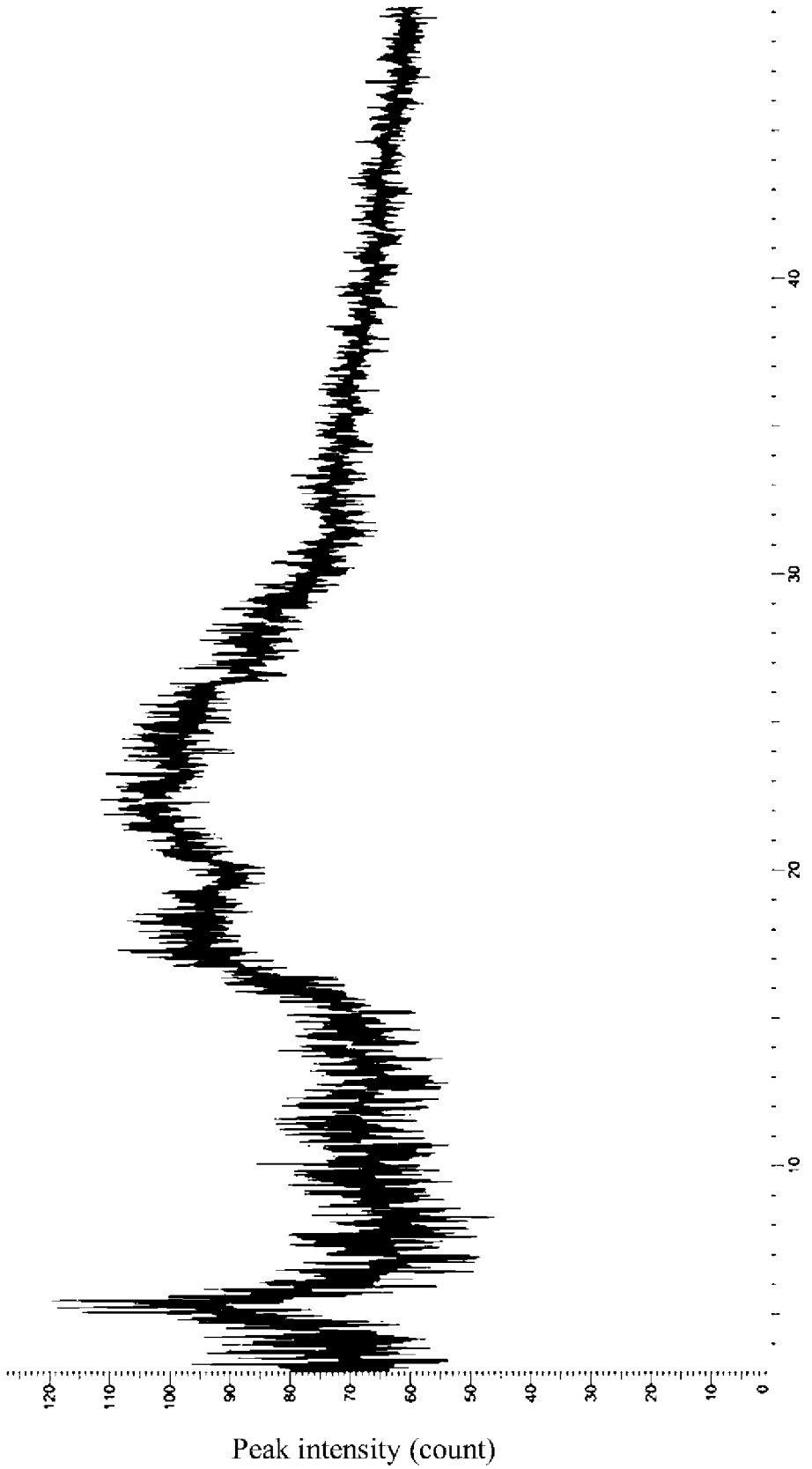


FIG. 3

CA 03156332 2022-4-27

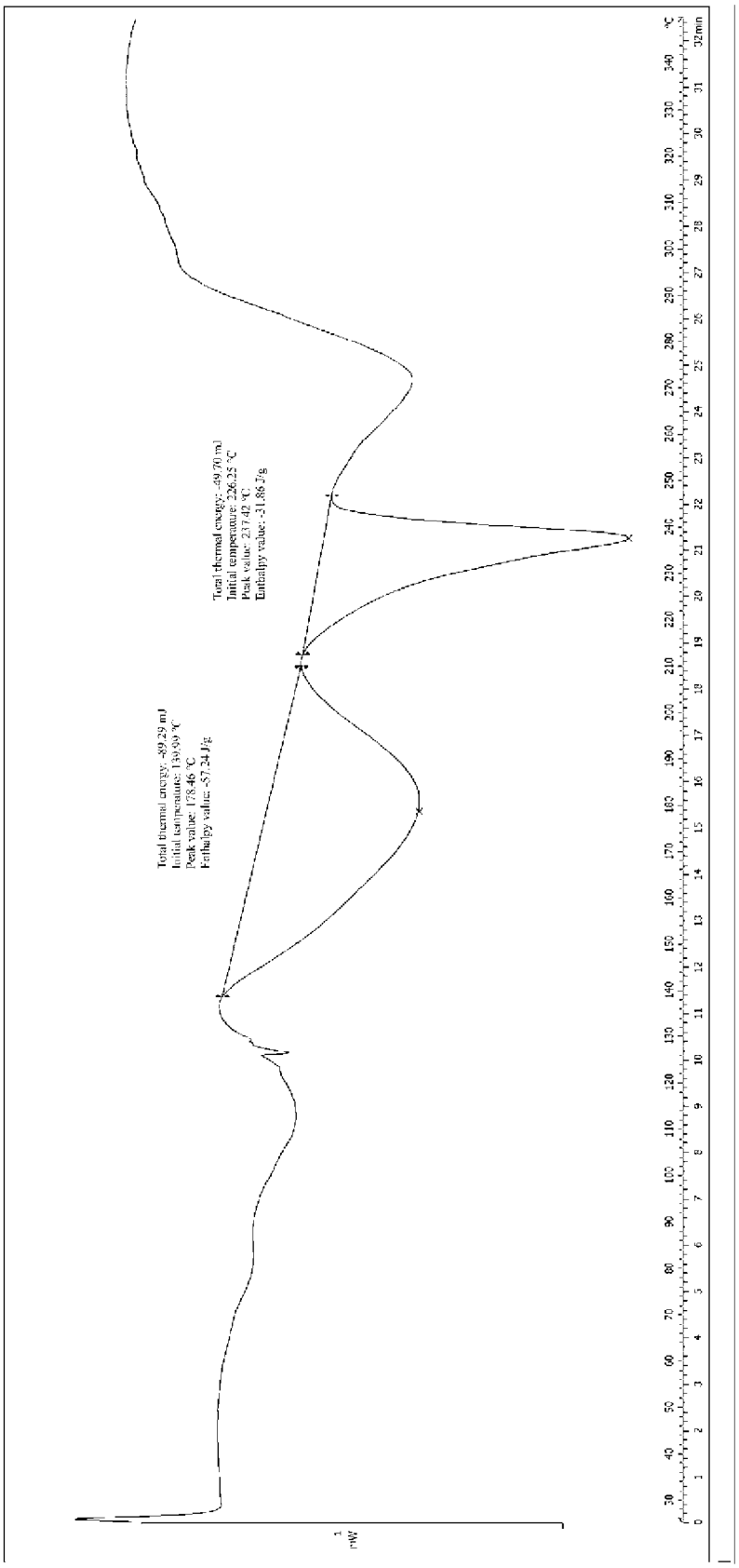


FIG. 4

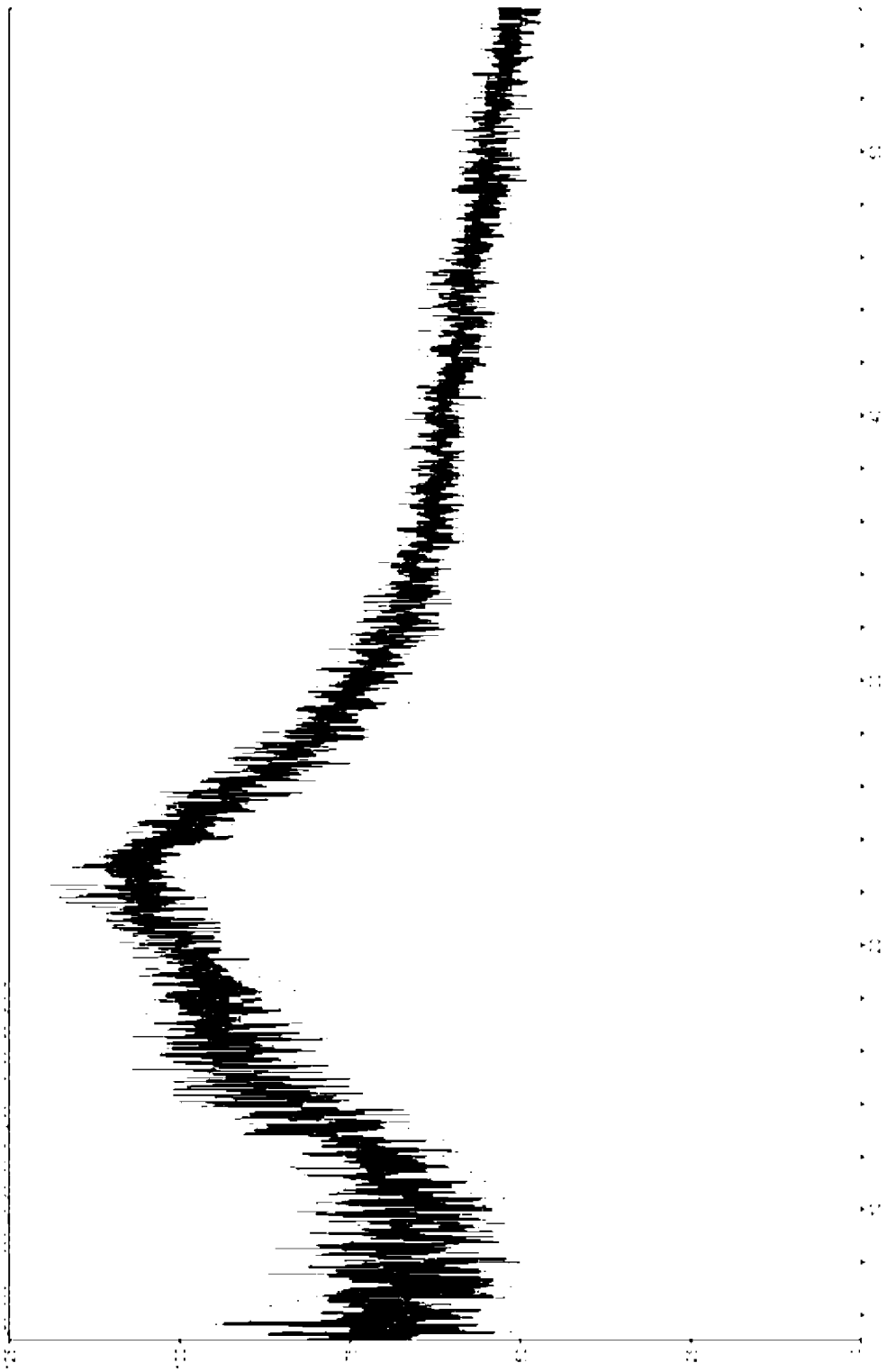


FIG. 5

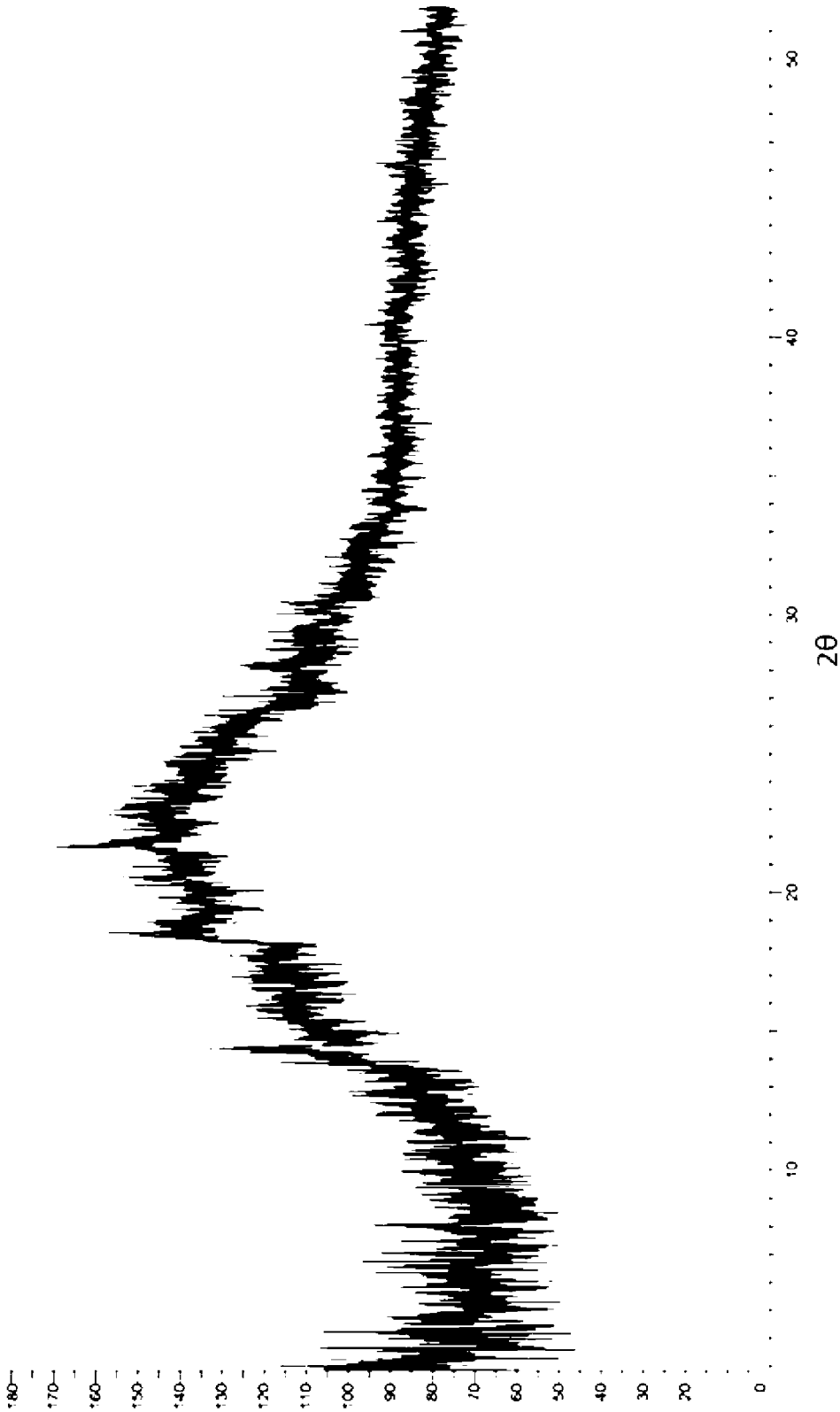


FIG. 6

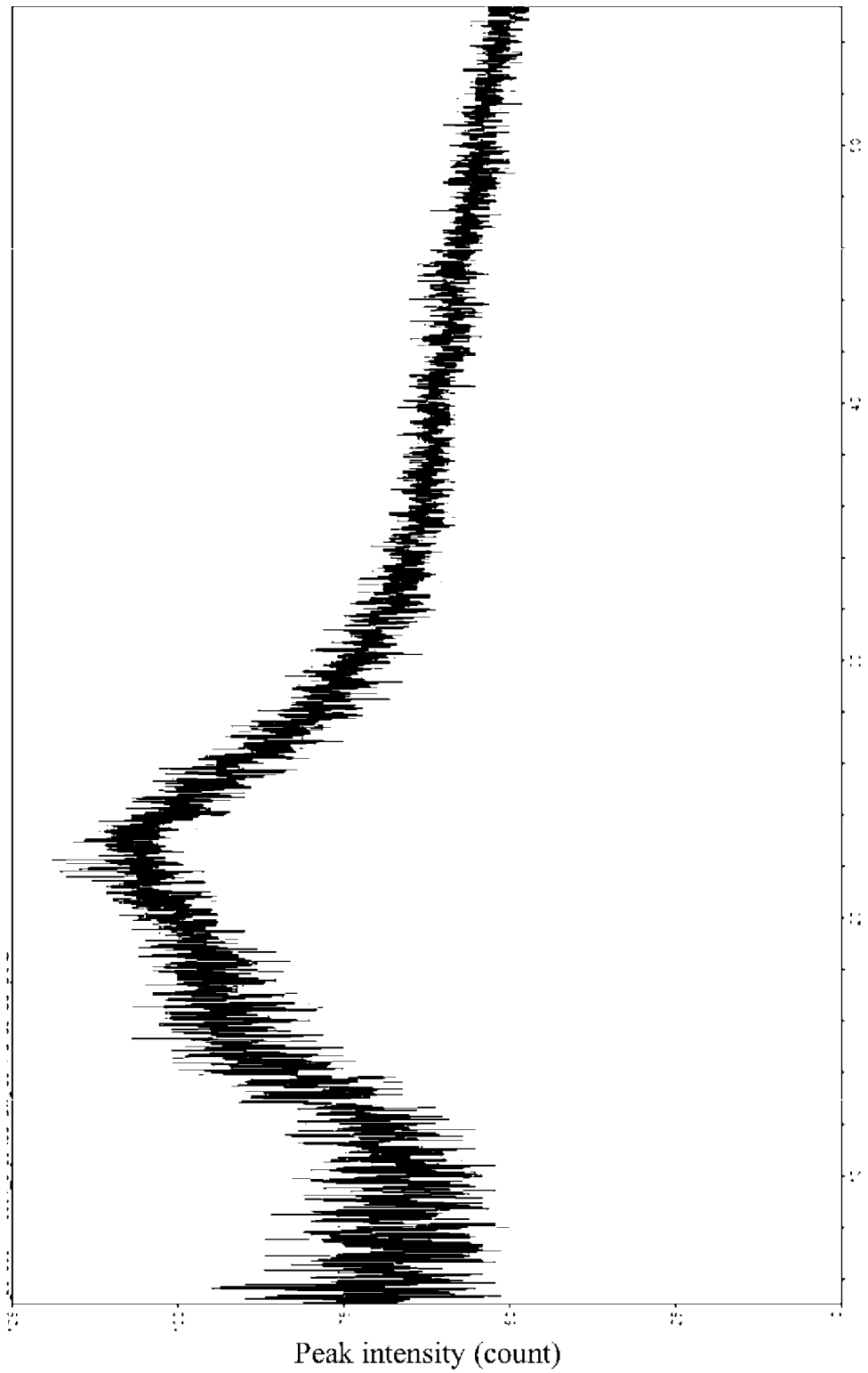


FIG. 7

CA 03156332 2022-4-27

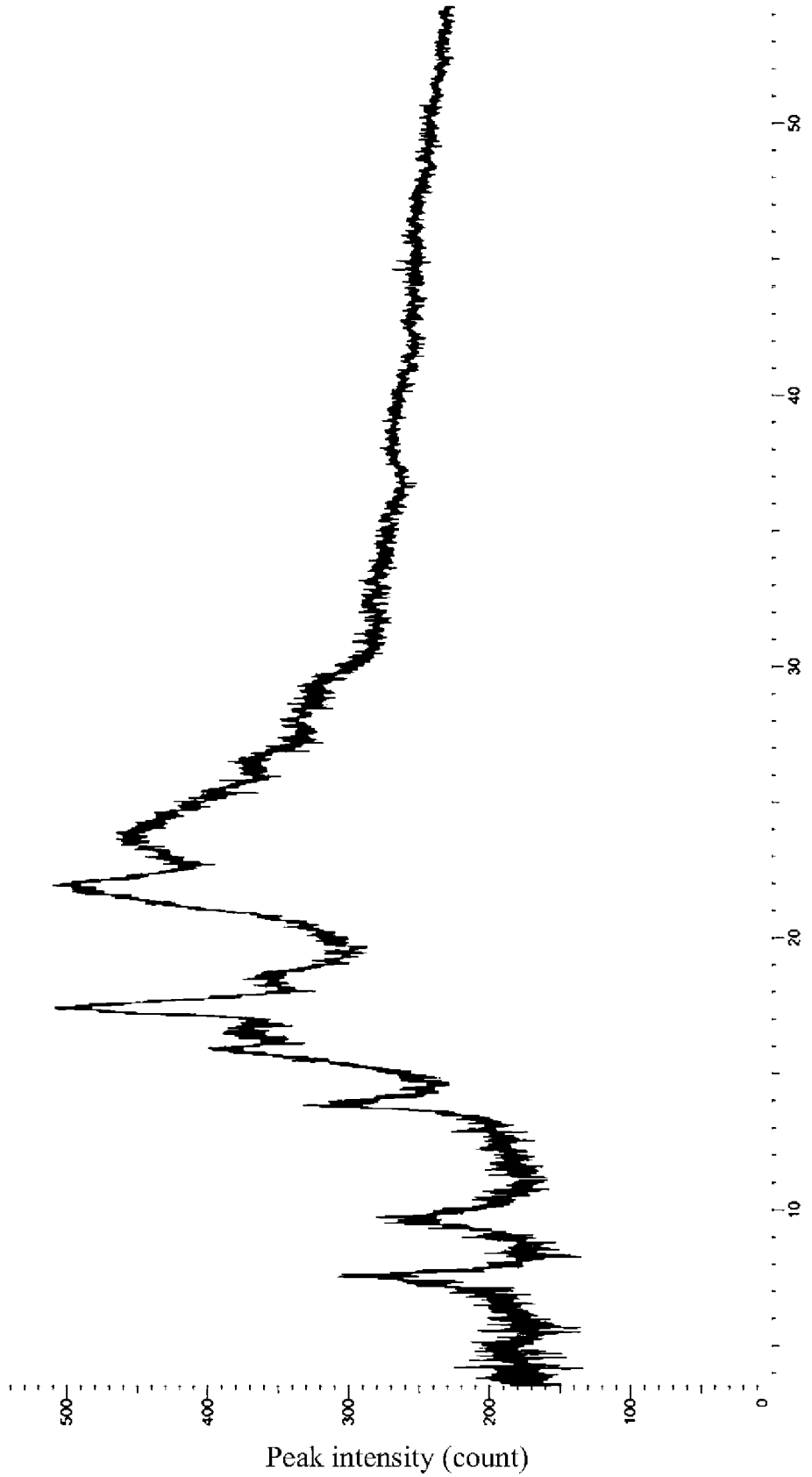


FIG. 8

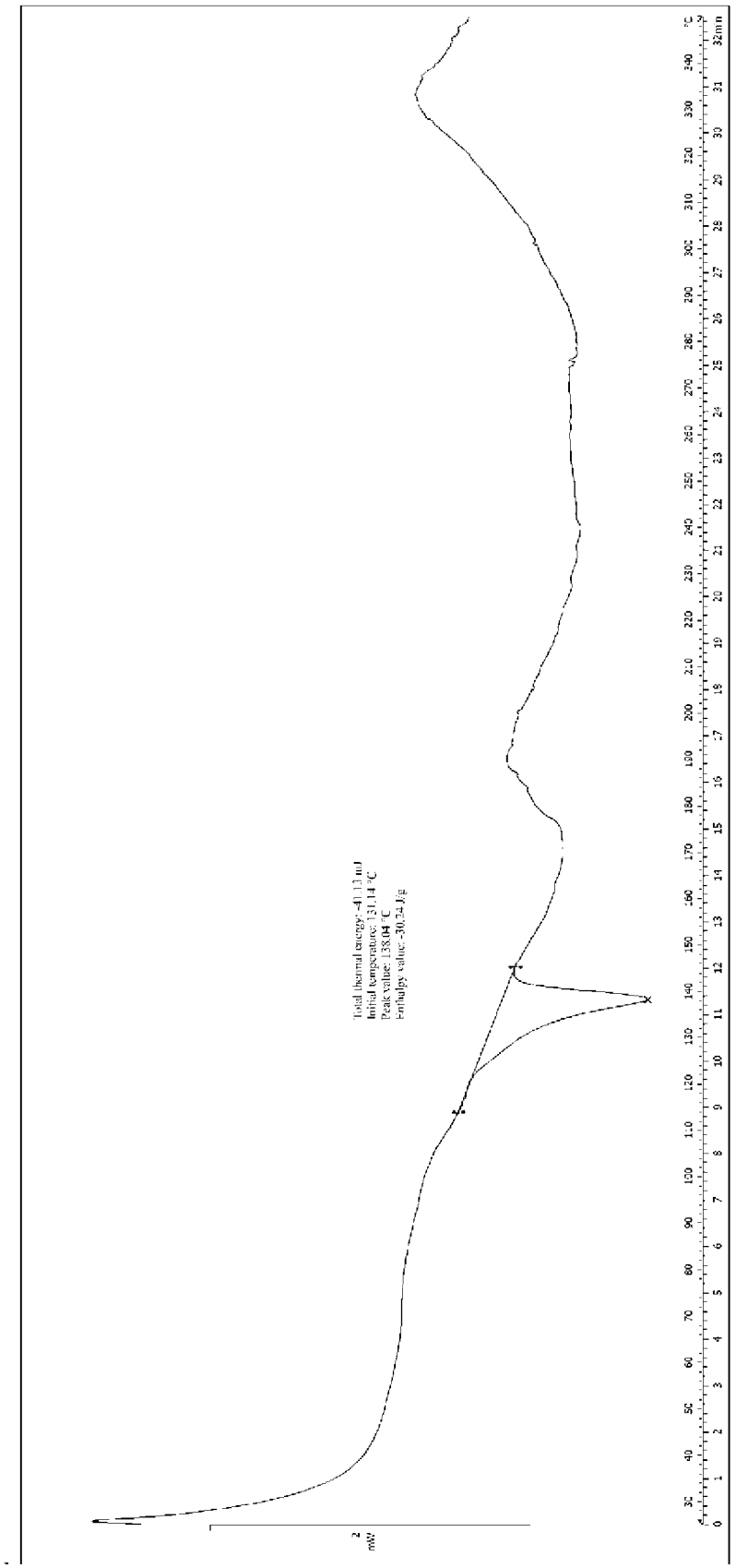


FIG. 9

CA 03156332 2022-4-27

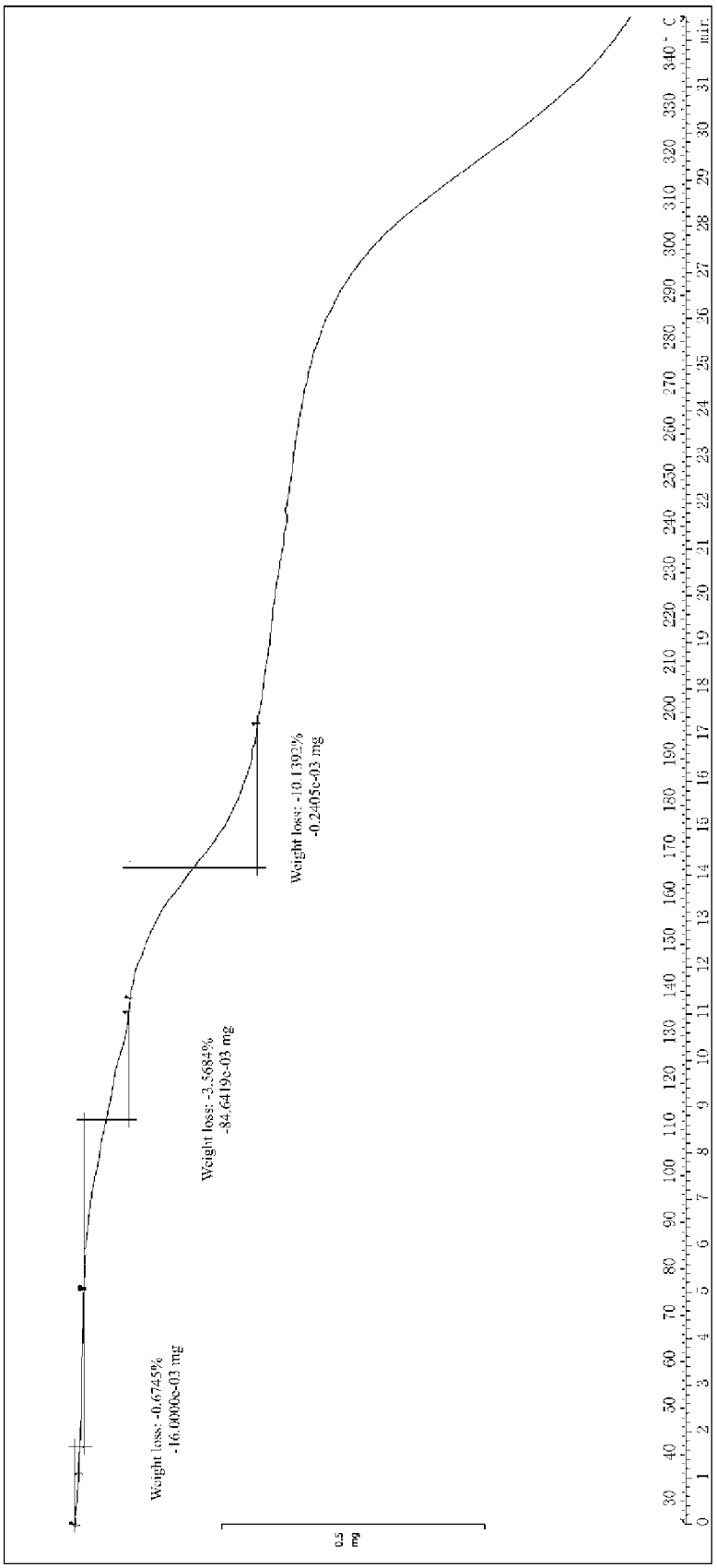


FIG. 10

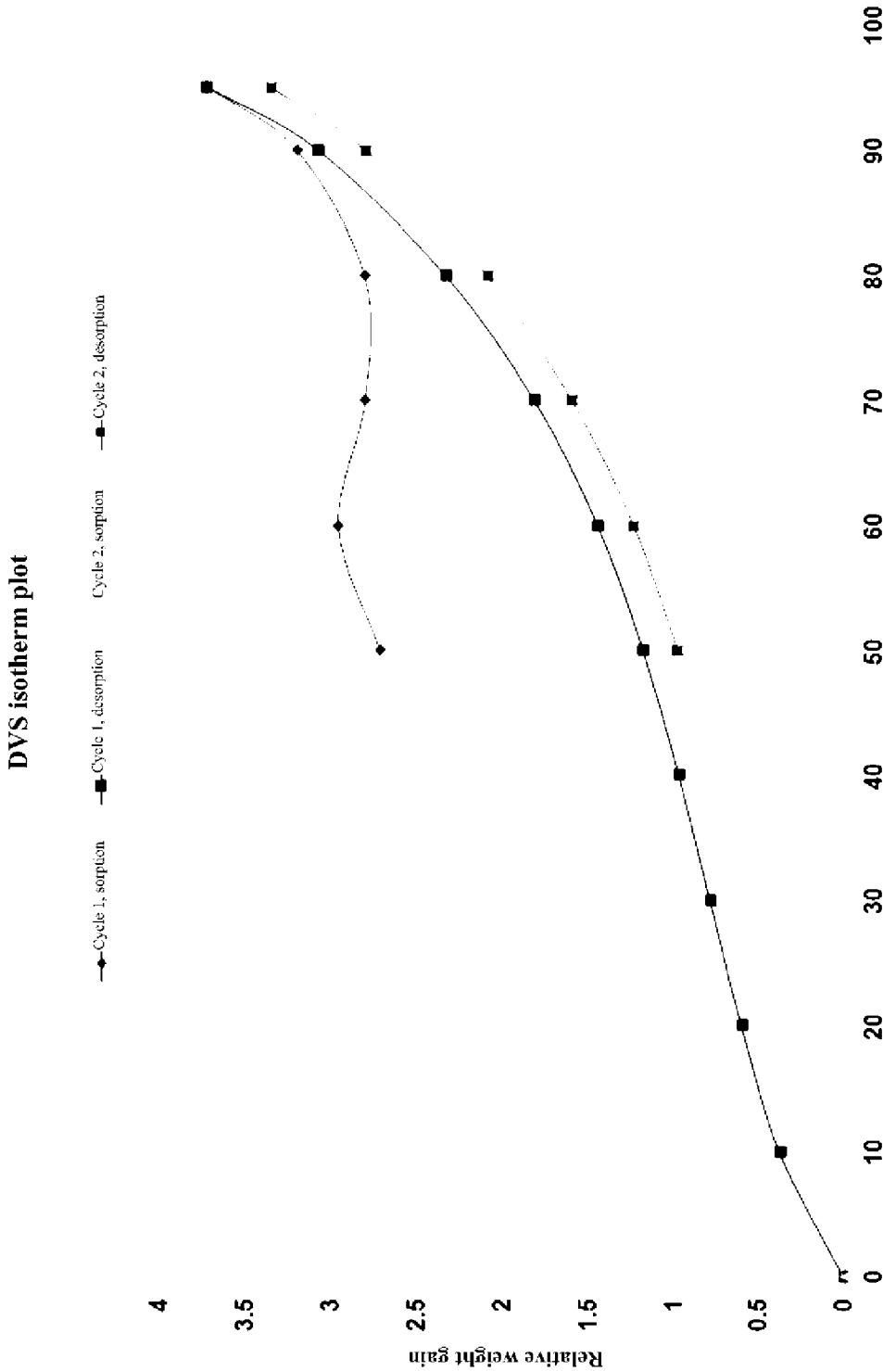


FIG. 11

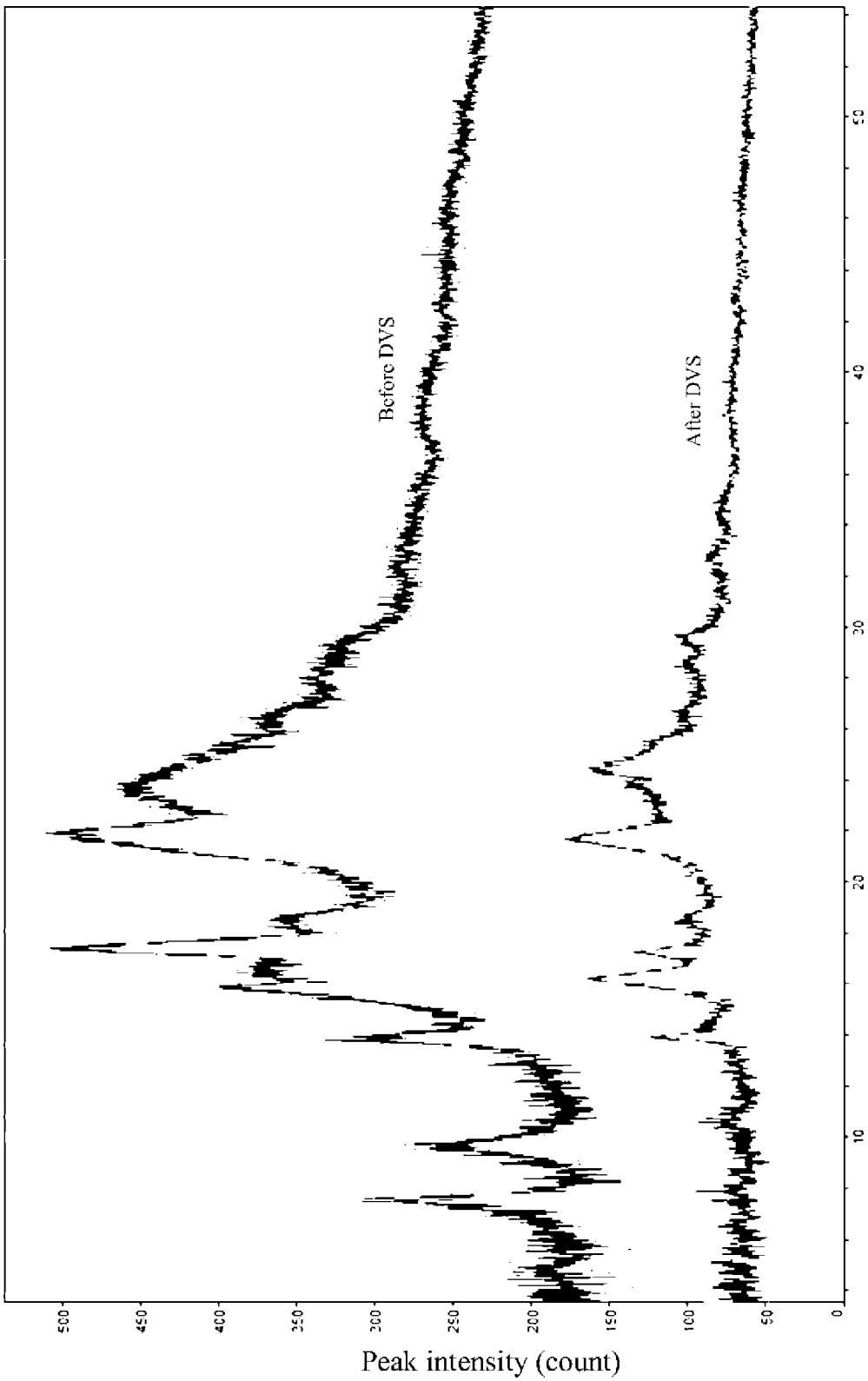


FIG. 12

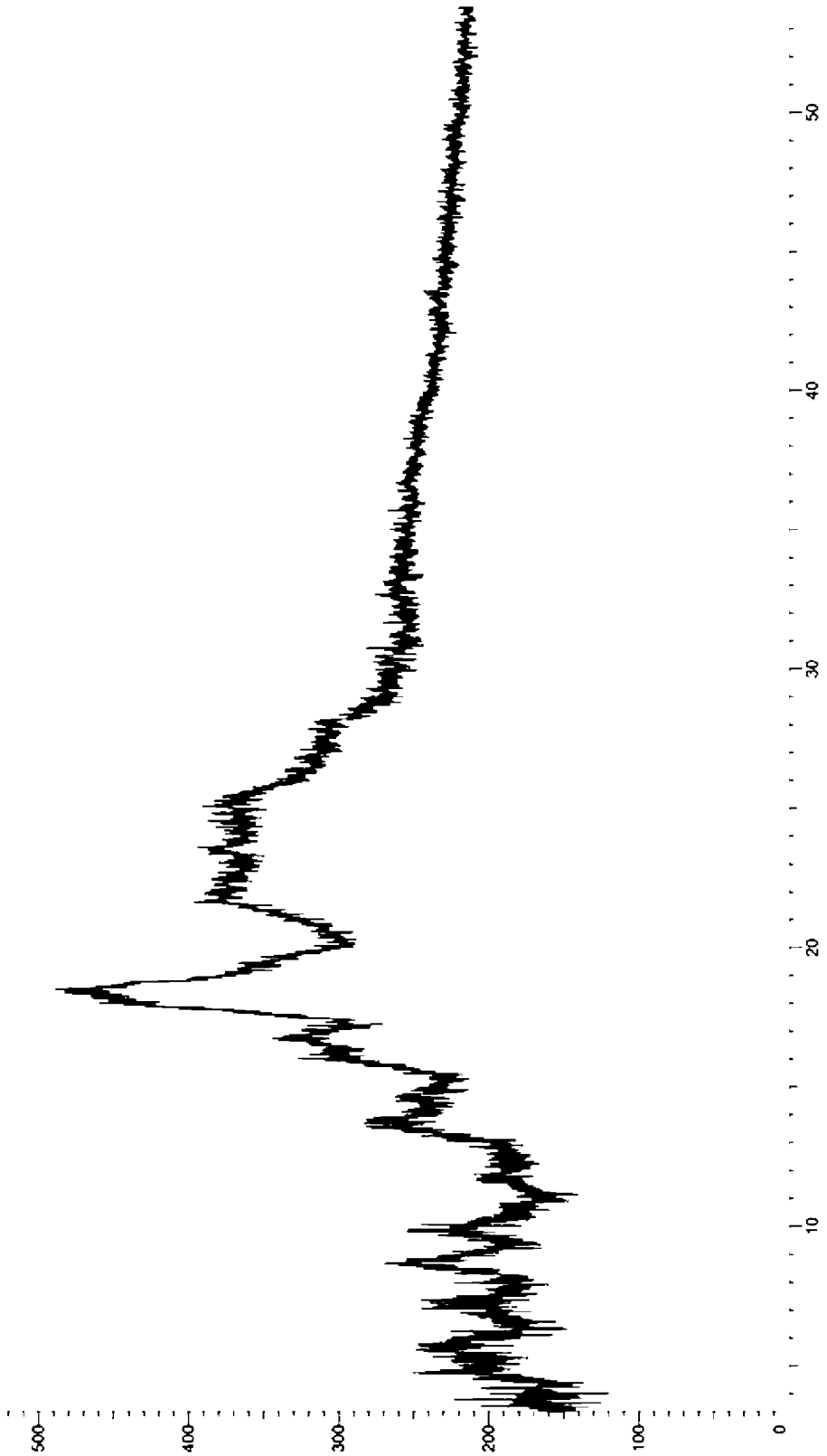


FIG. 13

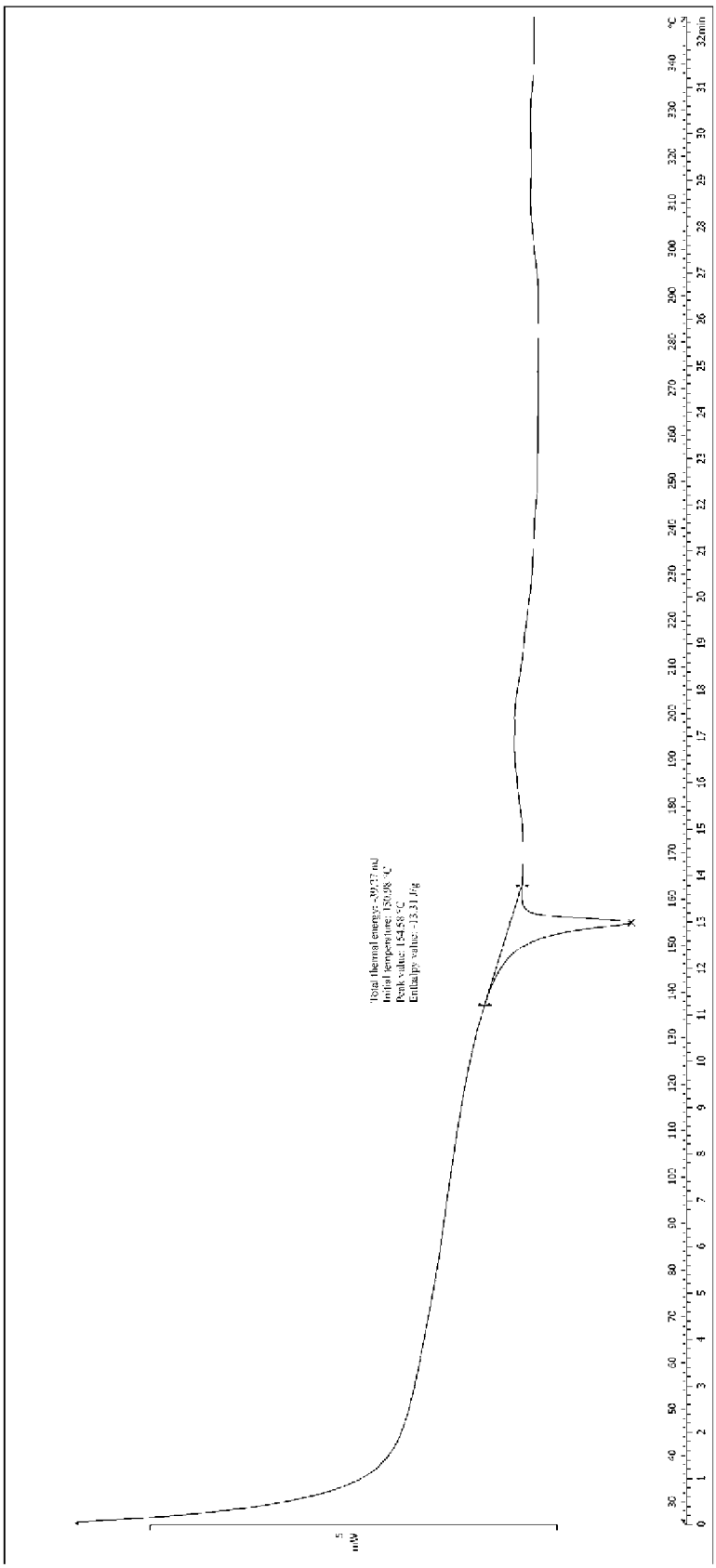

Total thermal energy: -39.27 mJ
Initial temperature: 150.98 °C
Peak value: 154.58 °C
Enthalpy value: -13.31 J/g
mW
°C
32min

FIG. 14

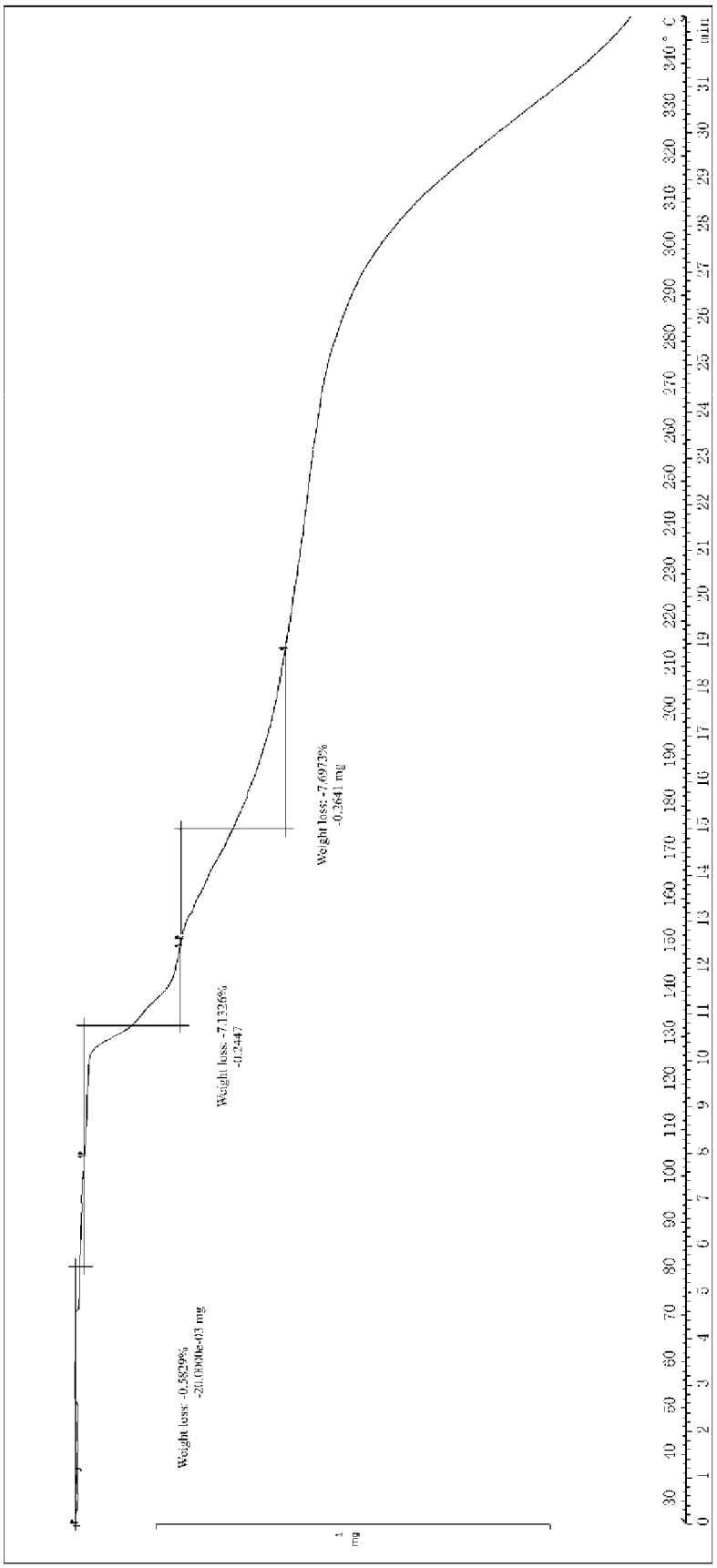


FIG. 15

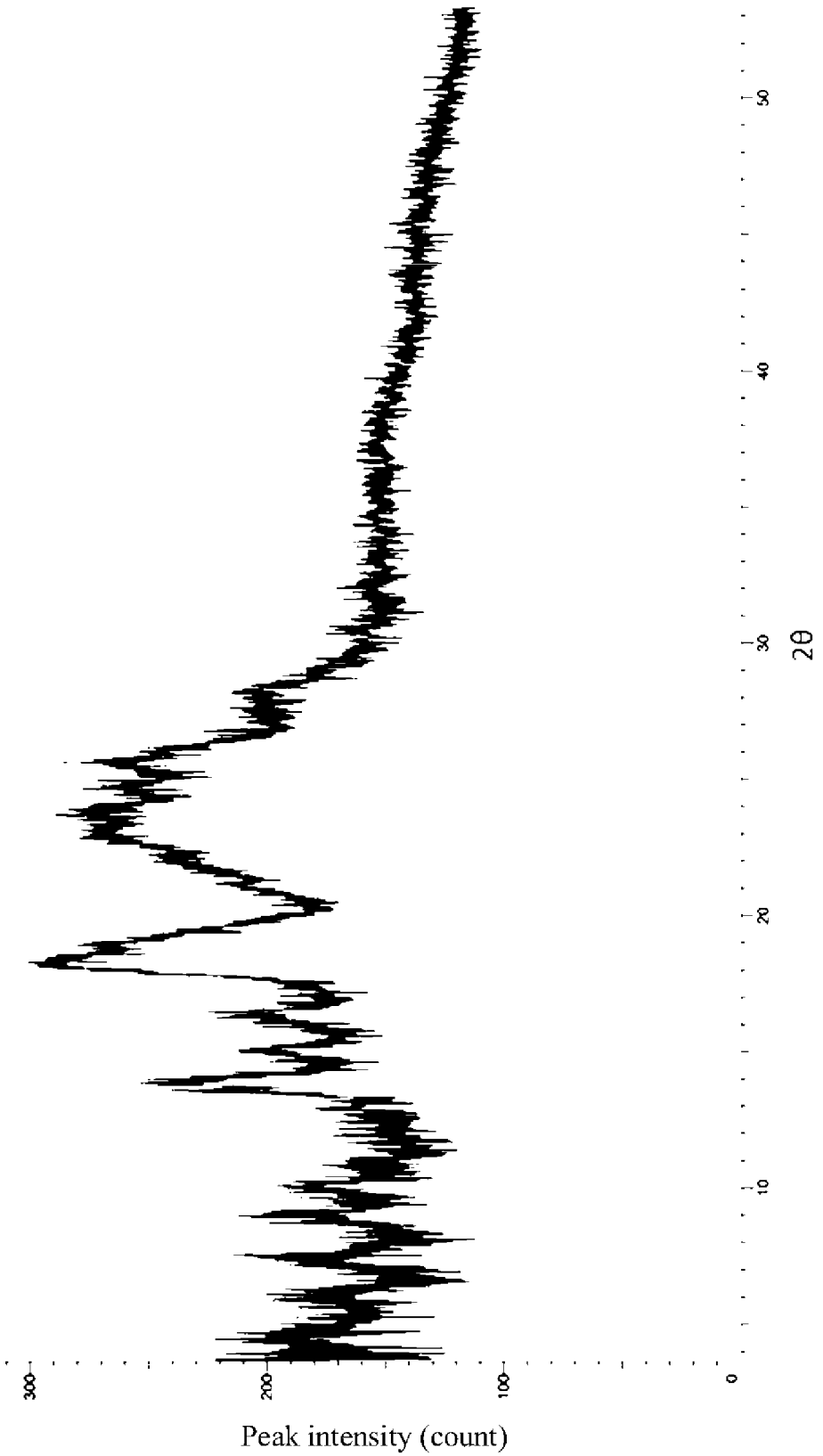


FIG. 16

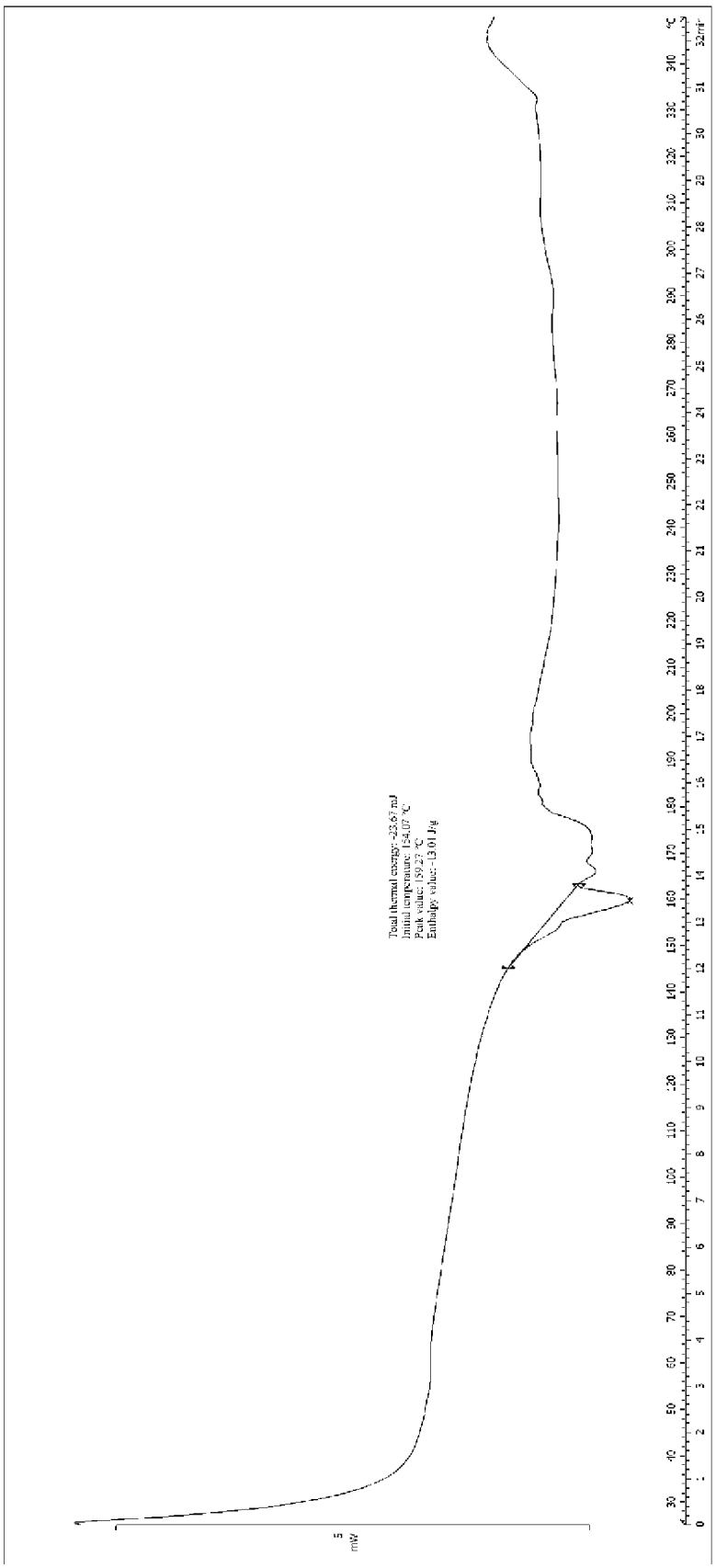

Total thermal energy: -23.67 mJ
Initial temperature: 154.07 °C
Peak value: 159.27 °C
Enthalpy value: -13.01 J/g
5
mW
°C

FIG. 17

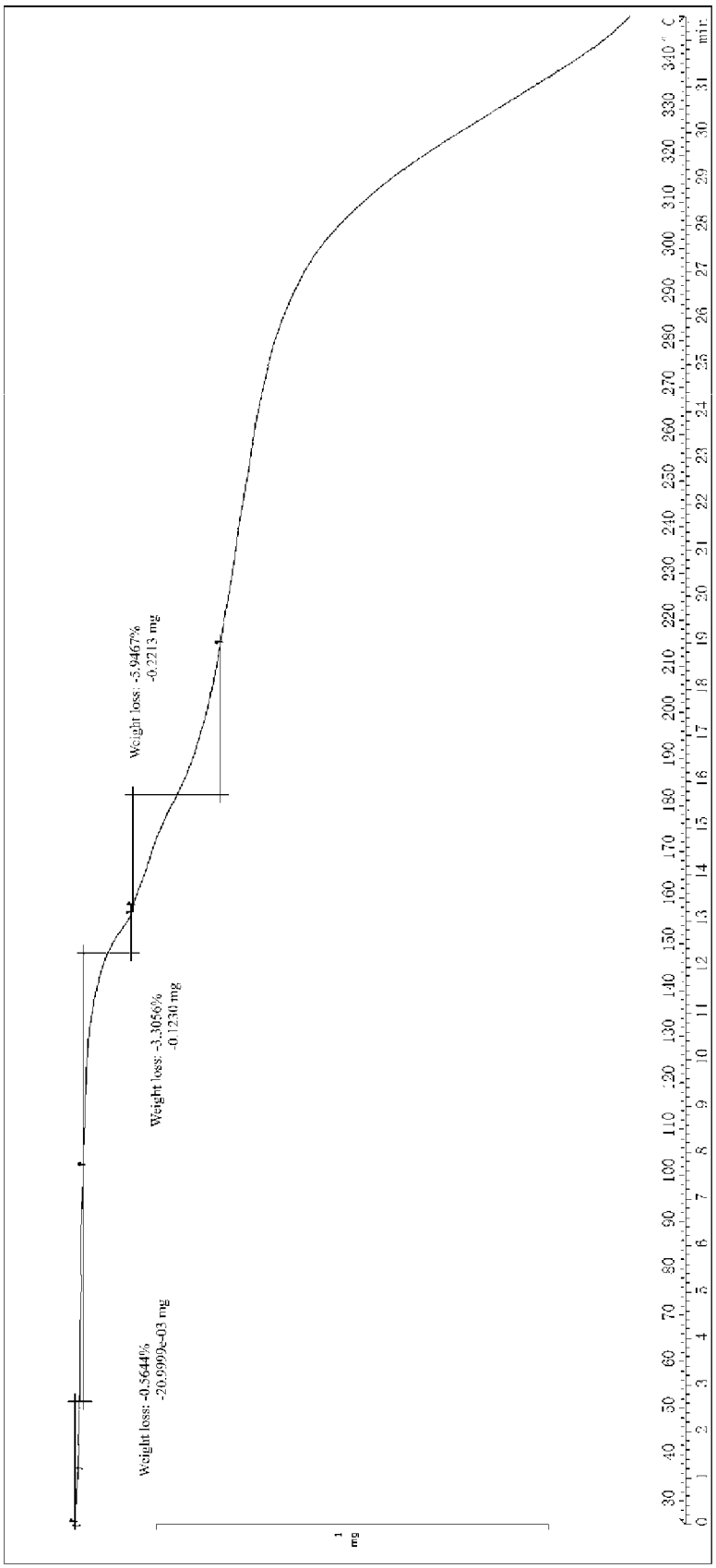


FIG. 18

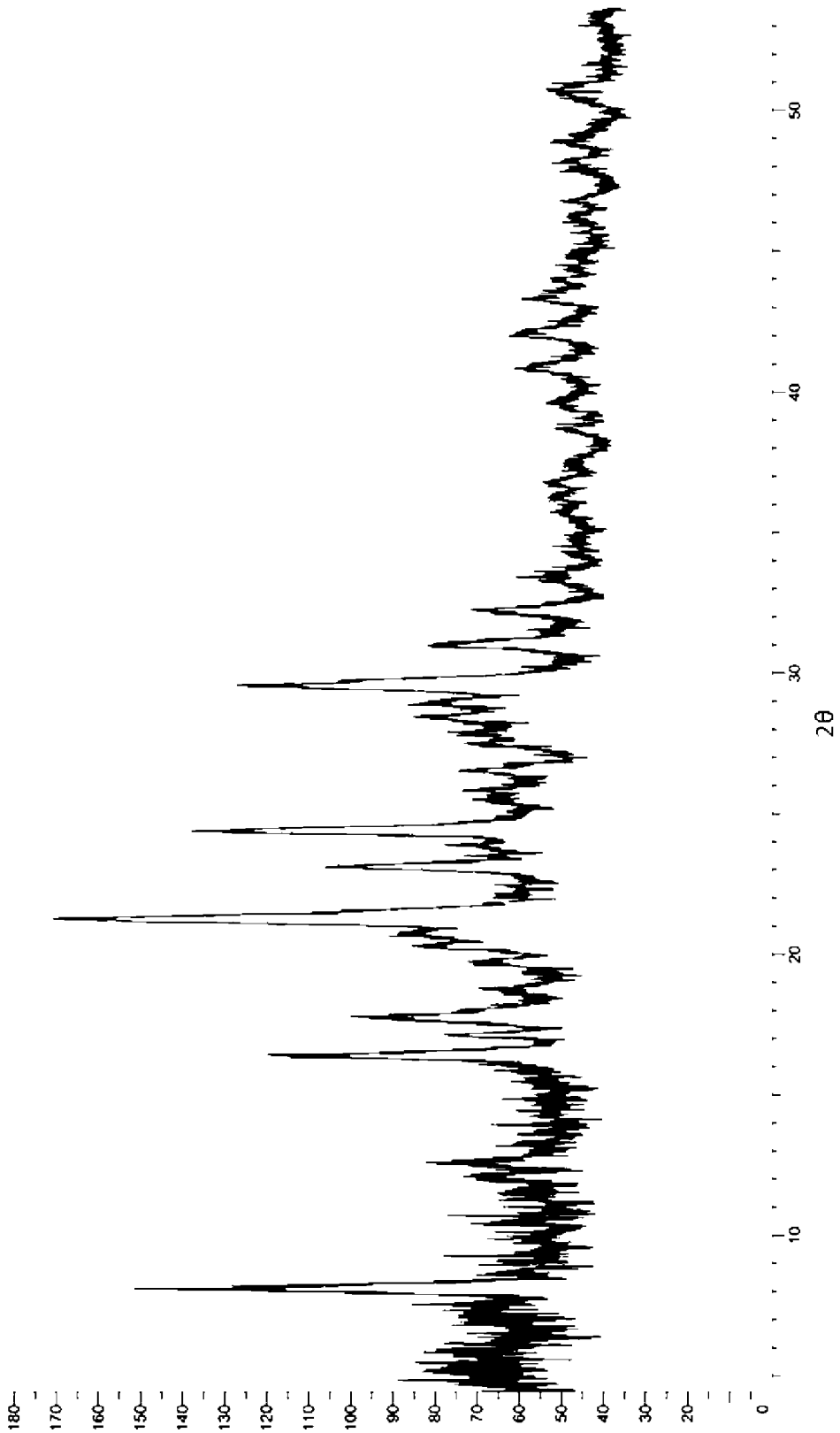


FIG. 19

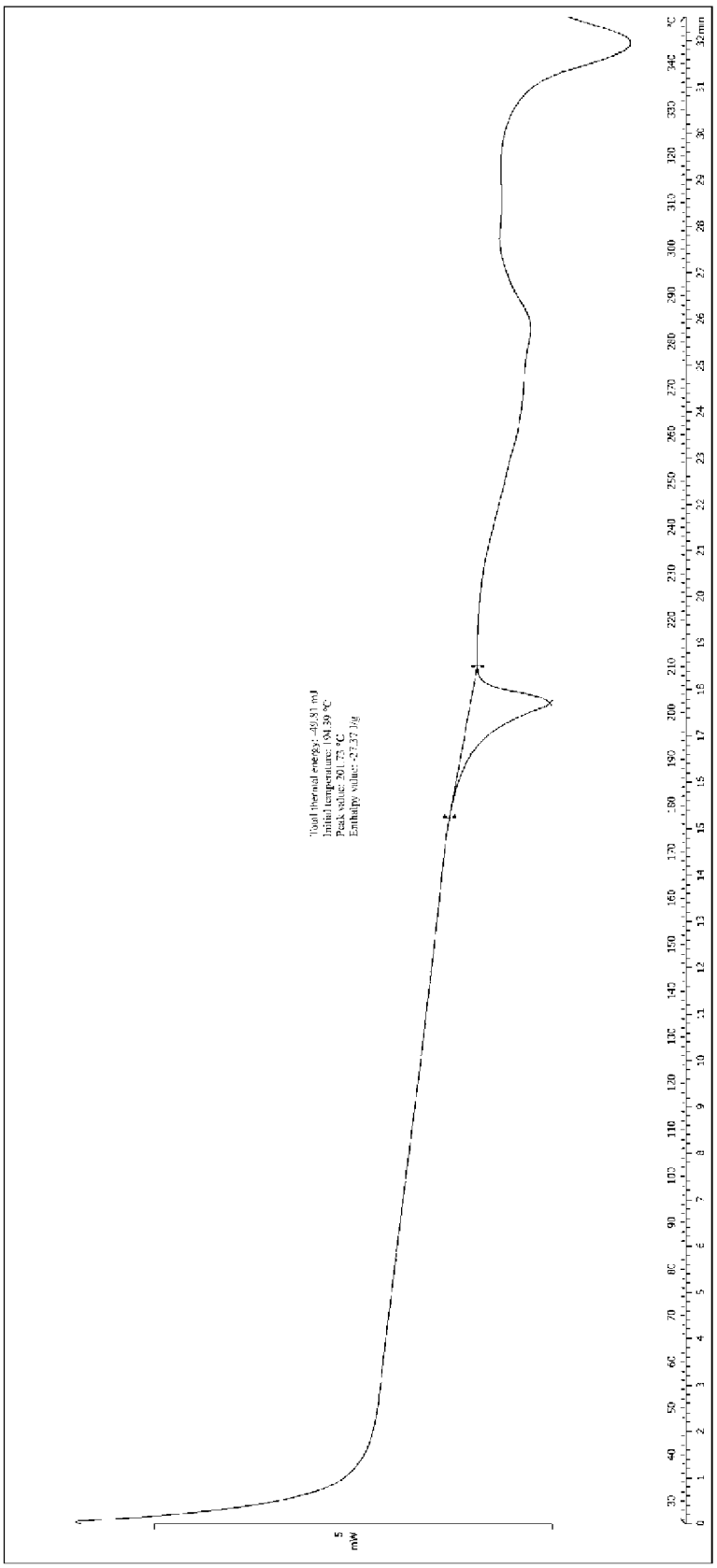

Total thermal energy: -46.81 mJ
Initial temperature: 194.39 °C
Peak value: 201.77 °C
Enthalpy value: -27.37 J/g
5
mW
32mm

FIG. 20

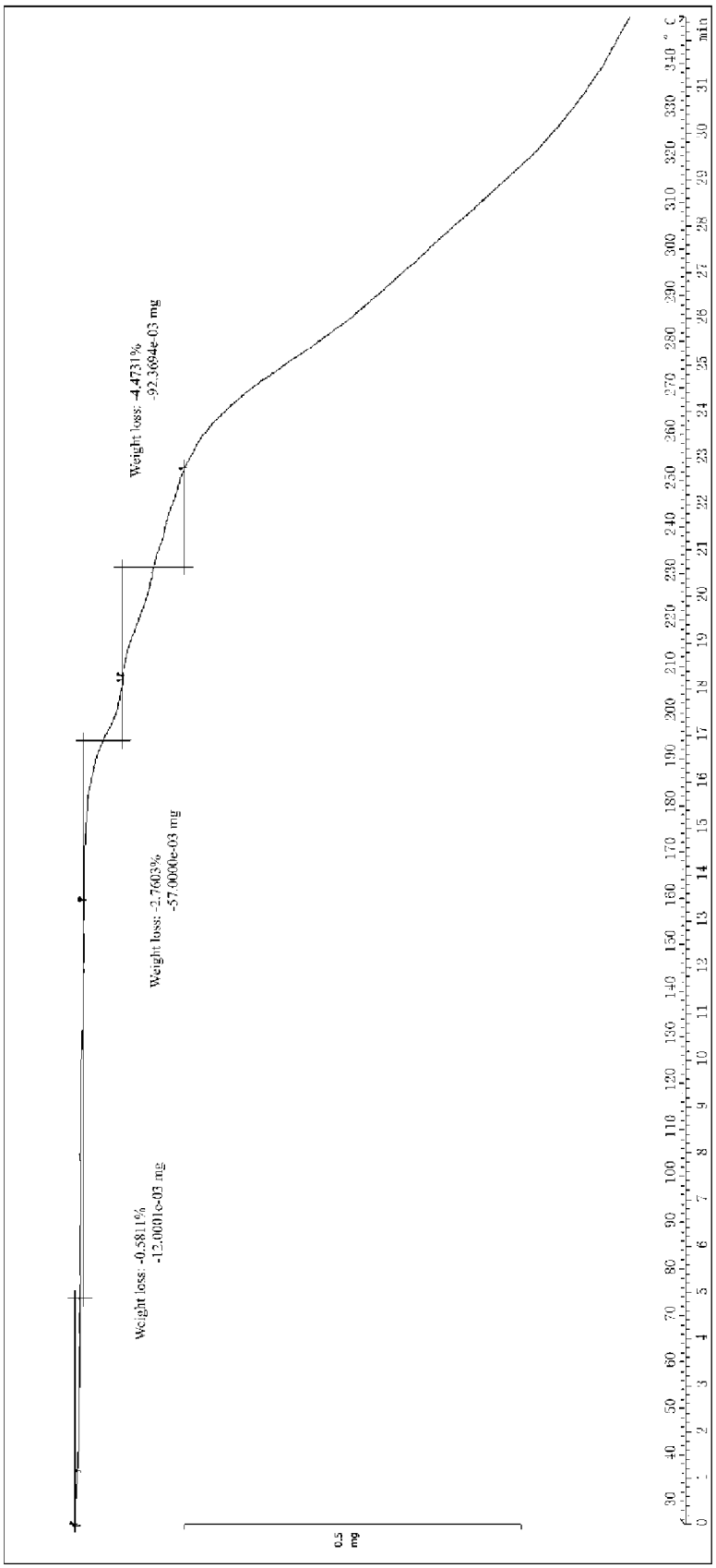


FIG. 21

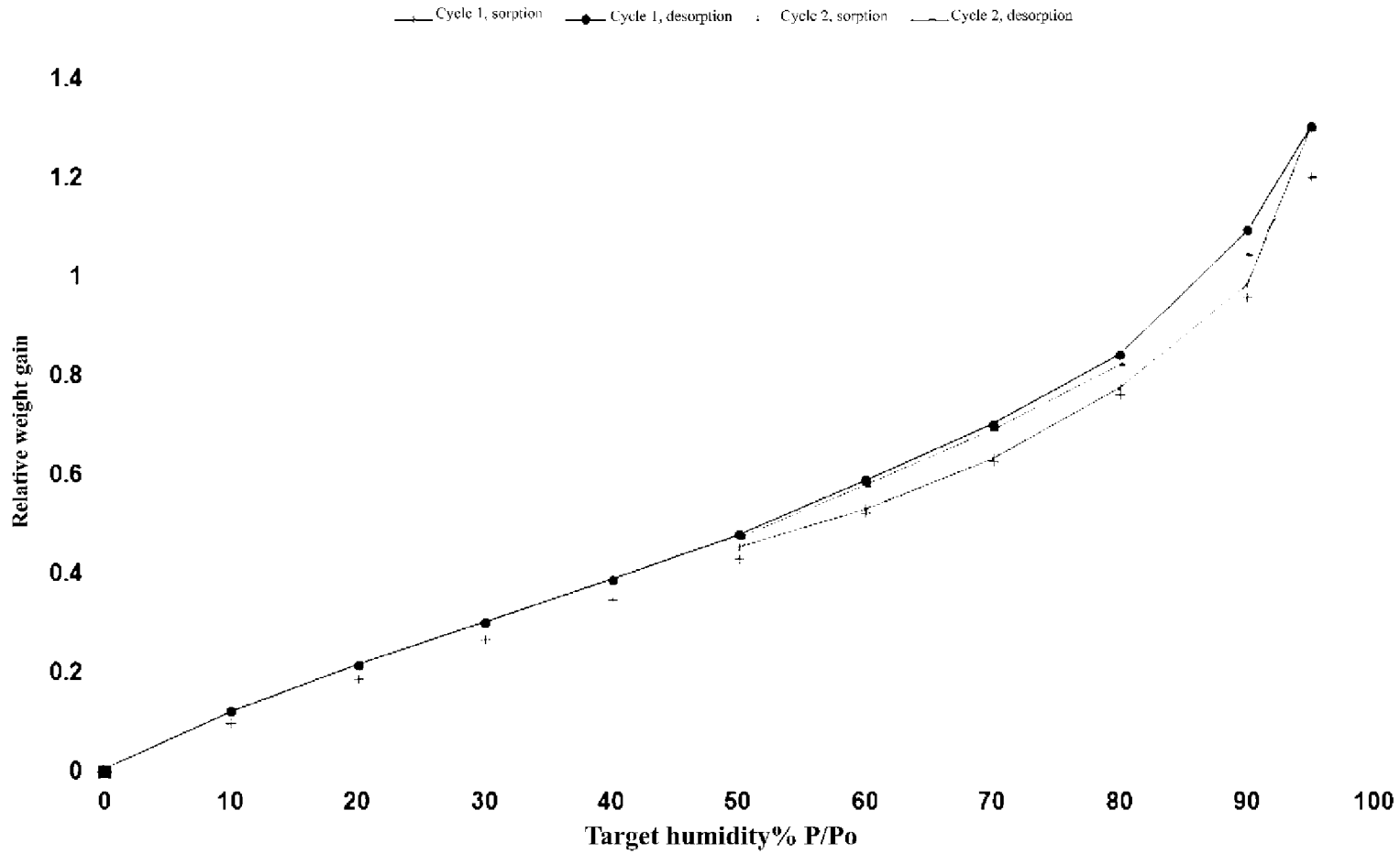

DVS isotherm plot
Cycle 1, sorption
Cycle 1, desorption
Cycle 2, sorption
Cycle 2, desorption
Relative weight gain
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
100
Target humidity% P/Po

FIG. 22

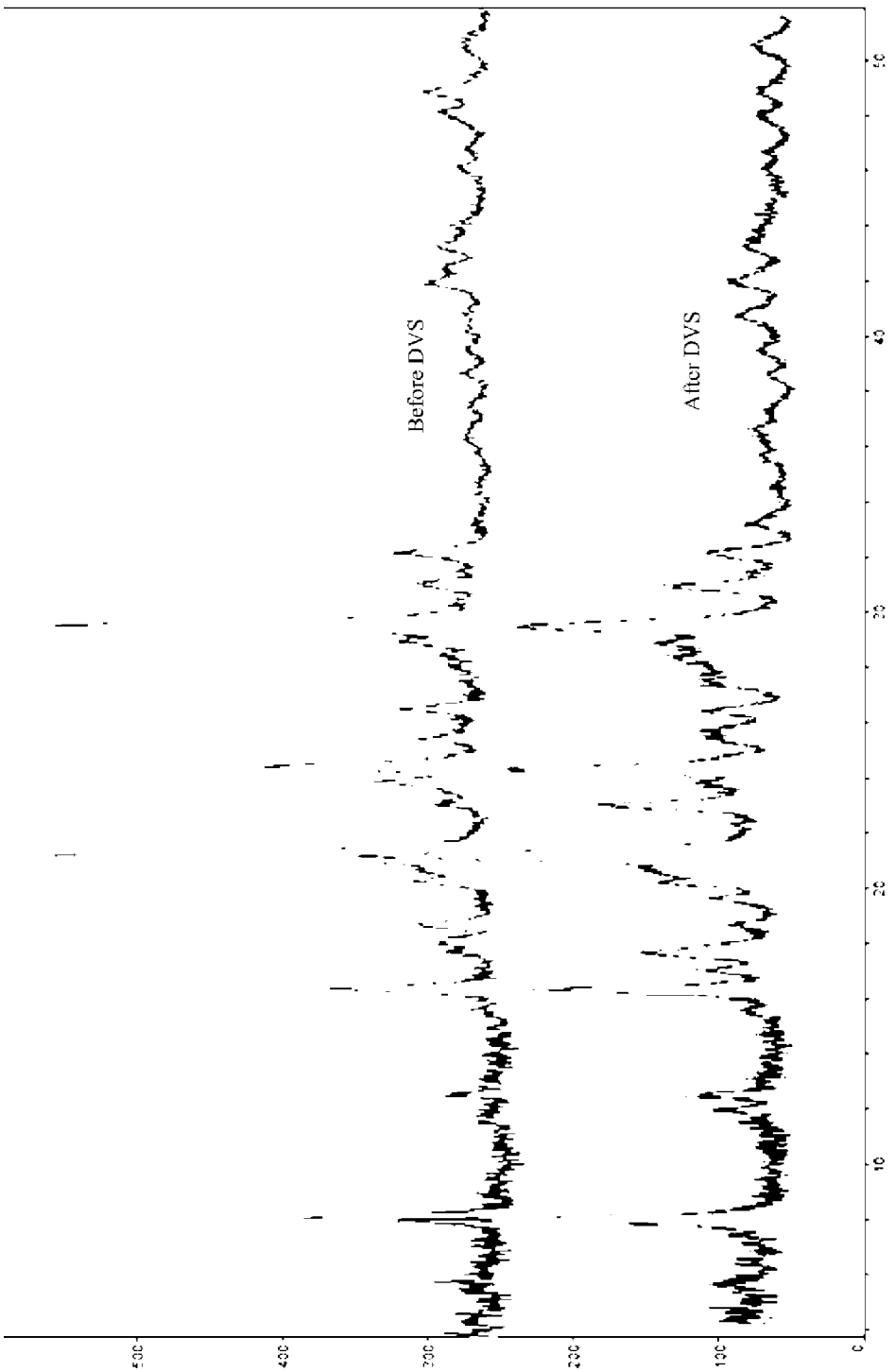


FIG. 23

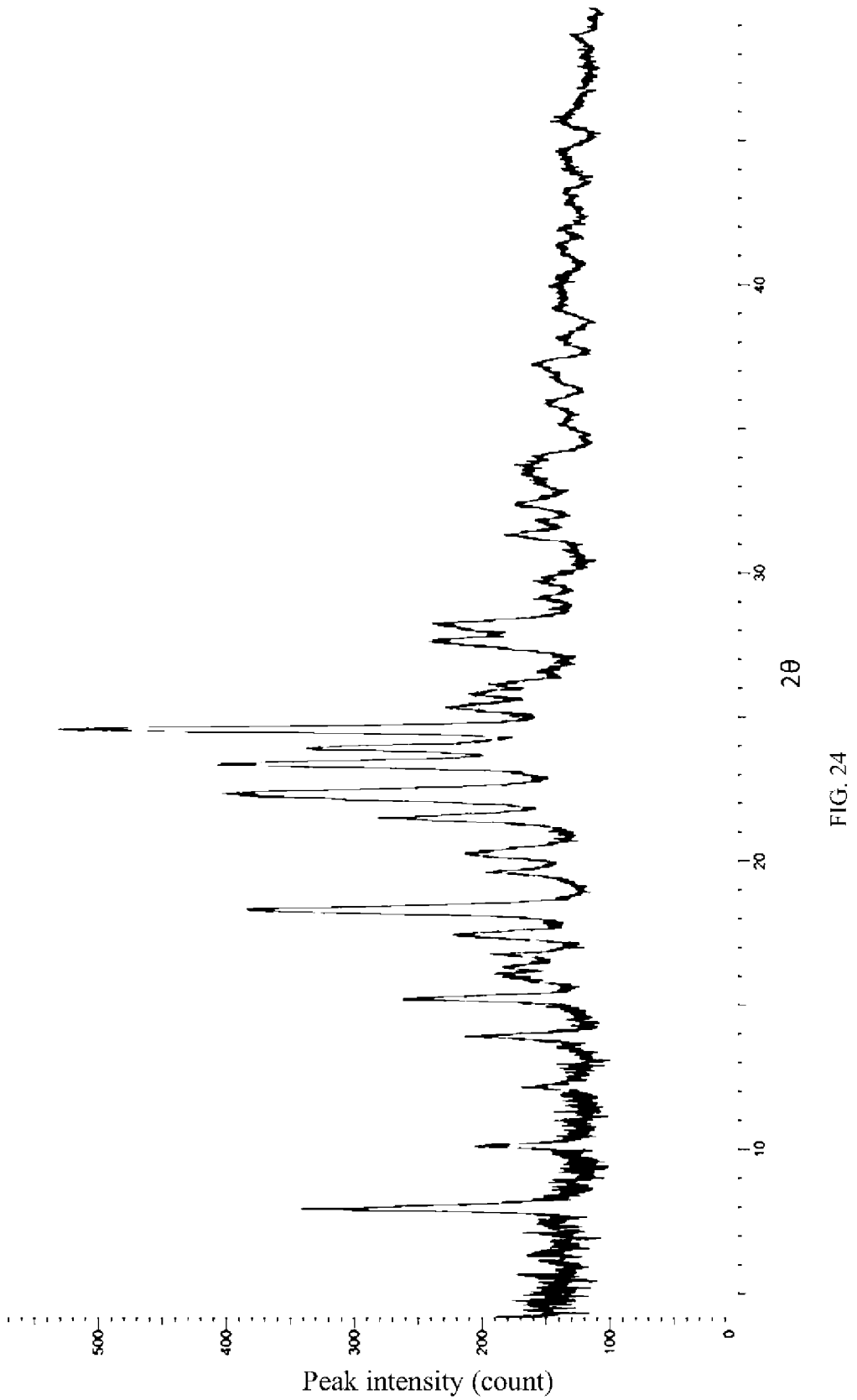


FIG. 24

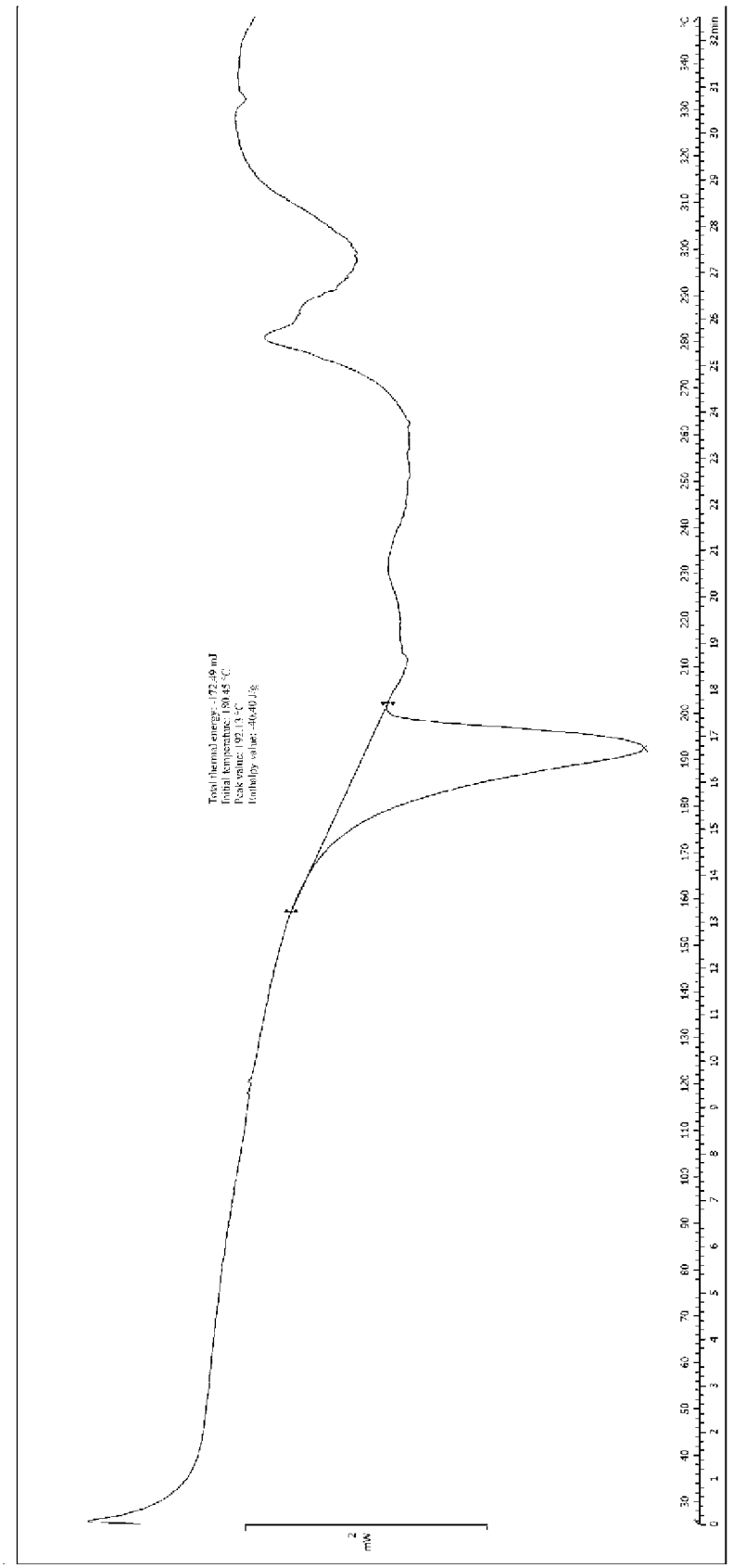

Total thermal energy: -172.49 mJ
Initial temperature: 180.45 °C
Peak value: 192.13 °C
Enthalpy value: -46.40 J/g
mW
°C
min

FIG. 25

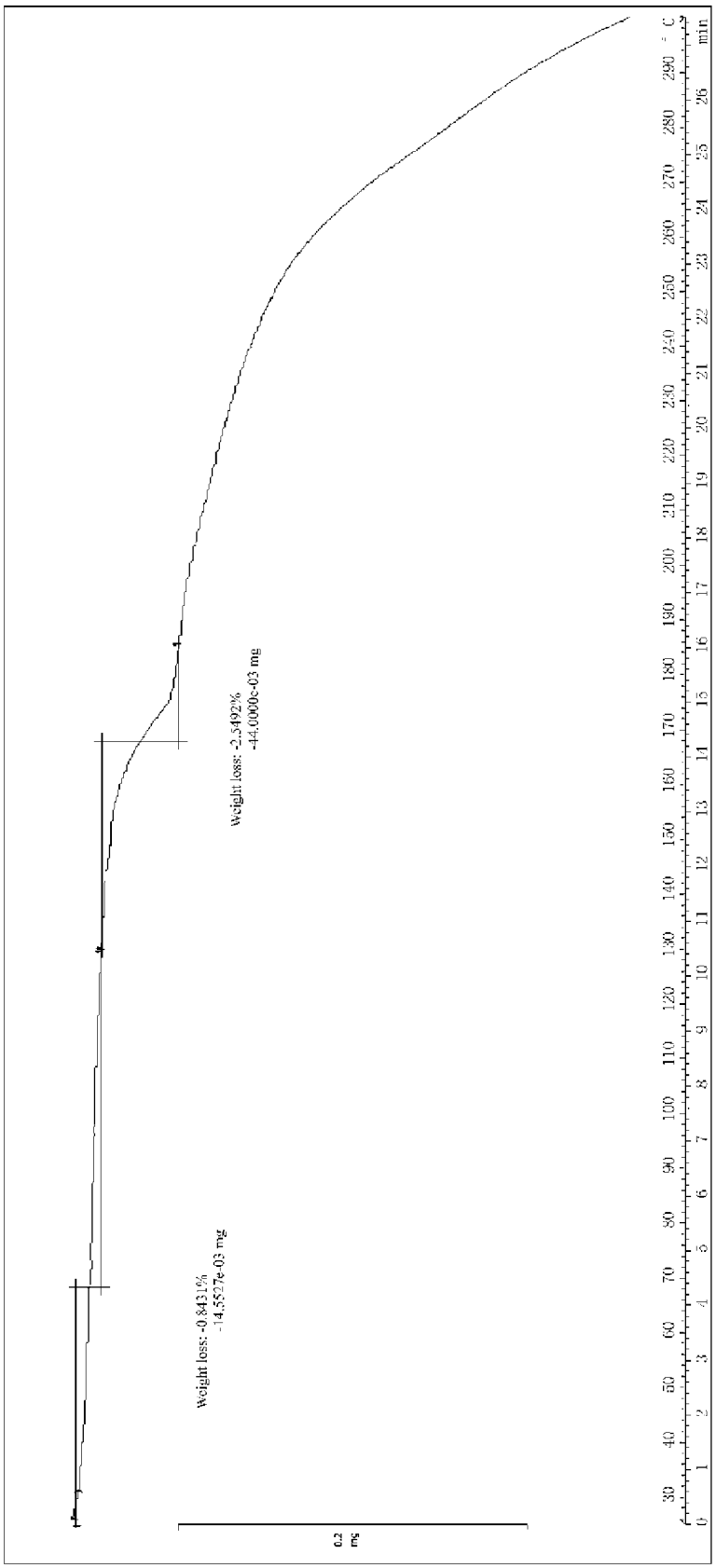


FIG. 26

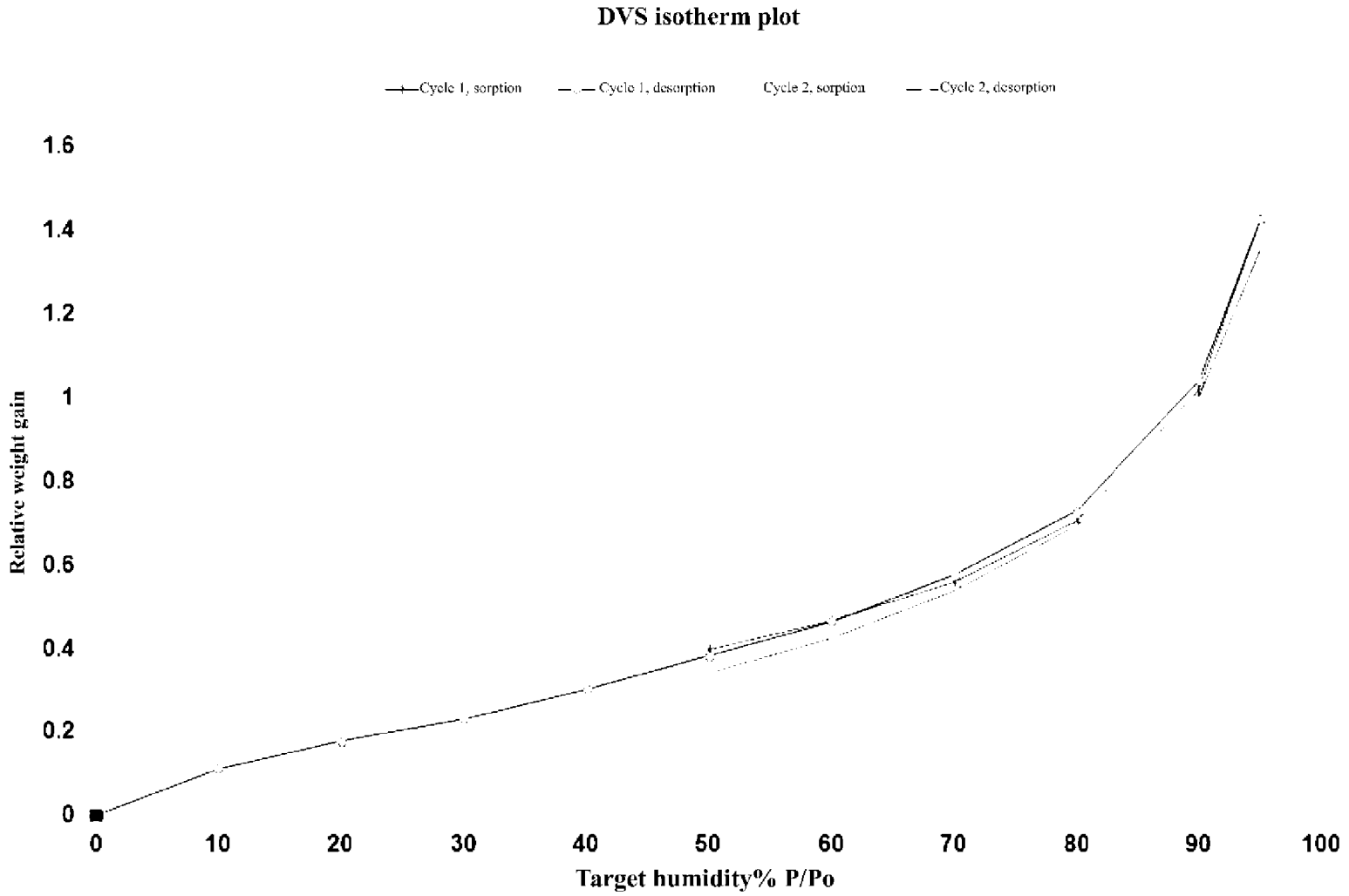

DVS isotherm plot
Cycle 1, sorption
Cycle 1, desorption
Cycle 2, sorption
Cycle 2, desorption
Relative weight gain
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
60
70
80
90
100
Target humidity% P/Po

FIG. 27

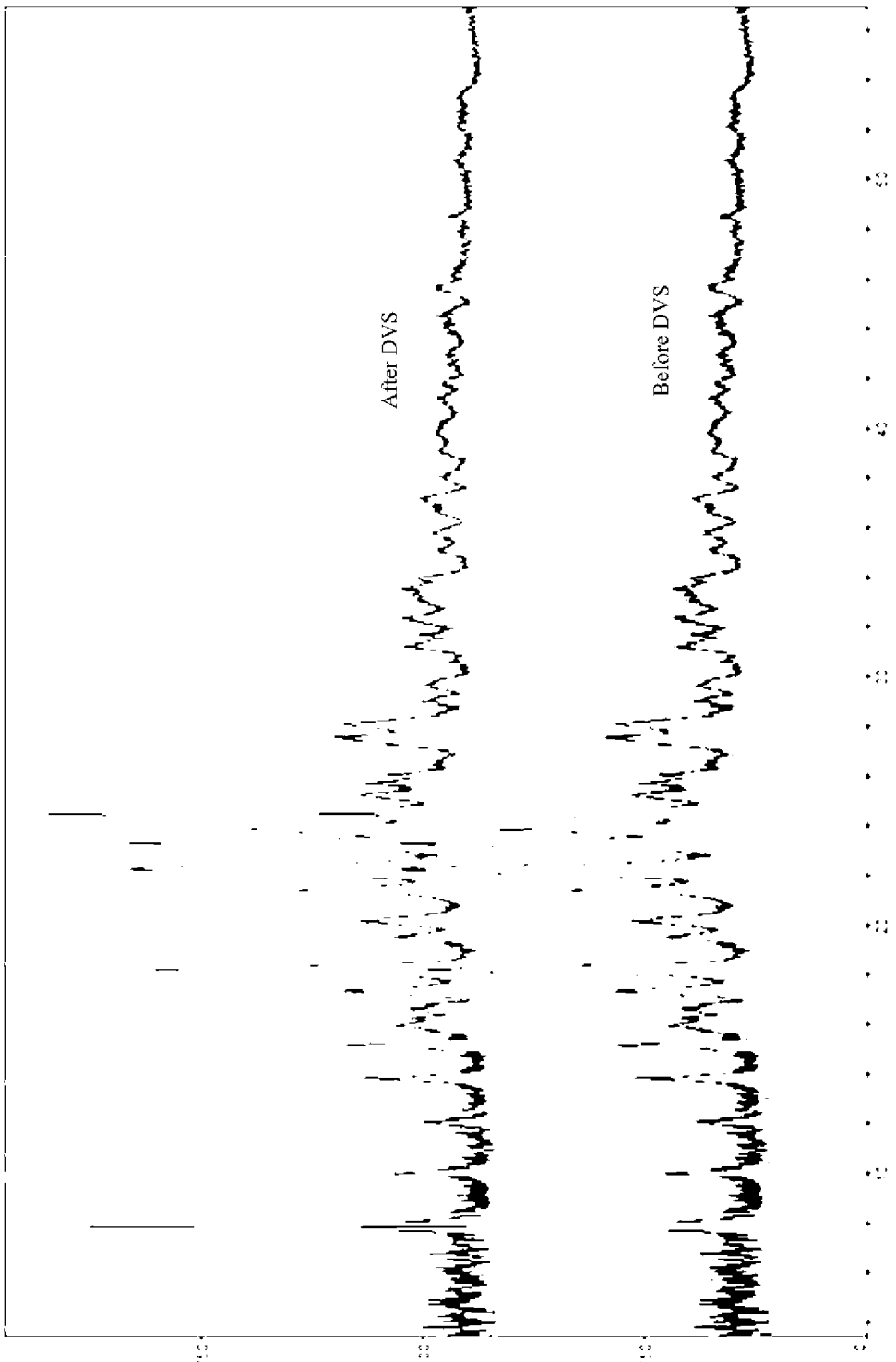


FIG. 28

CA 03156332 2022-4-27

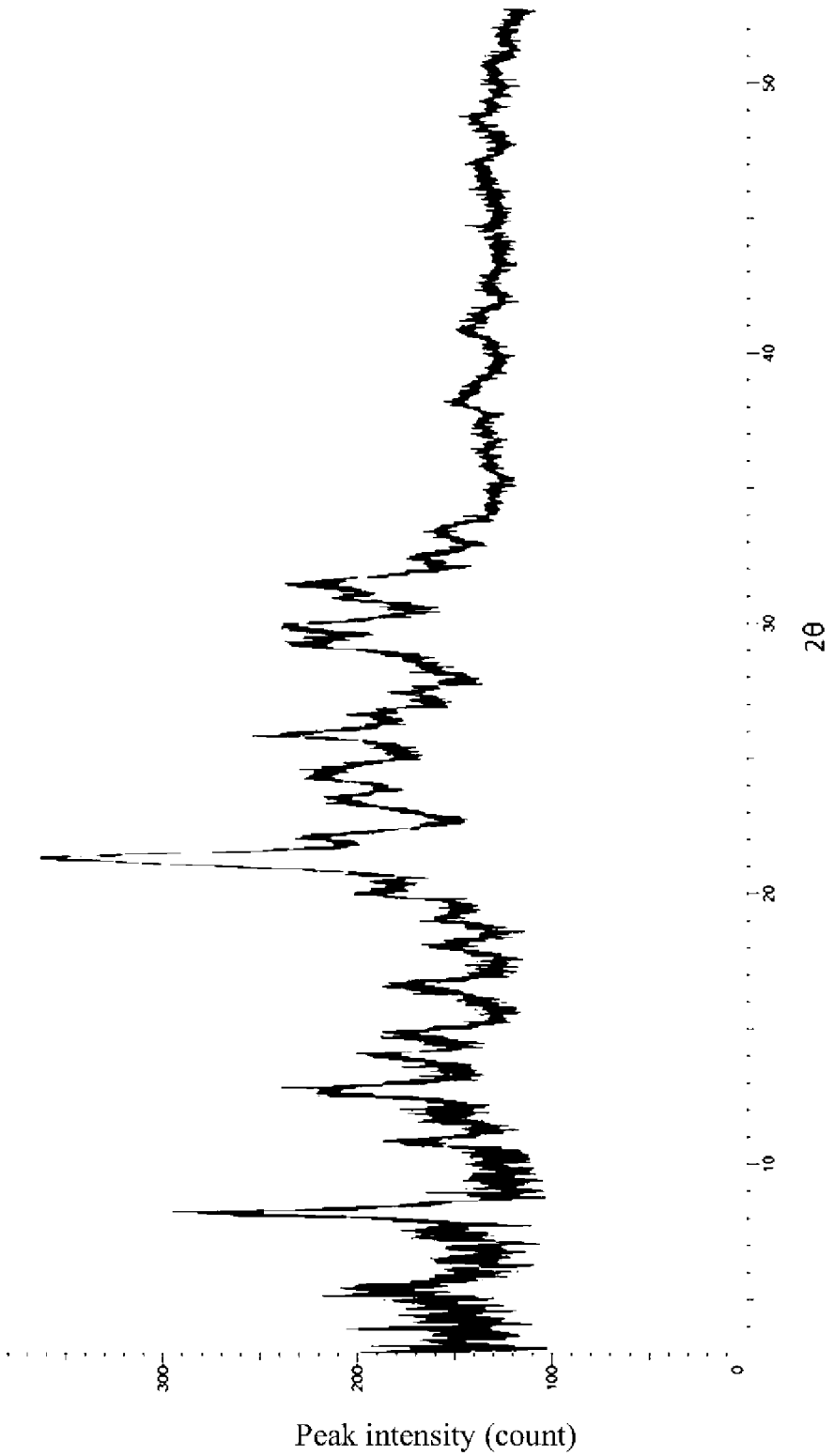


FIG. 29

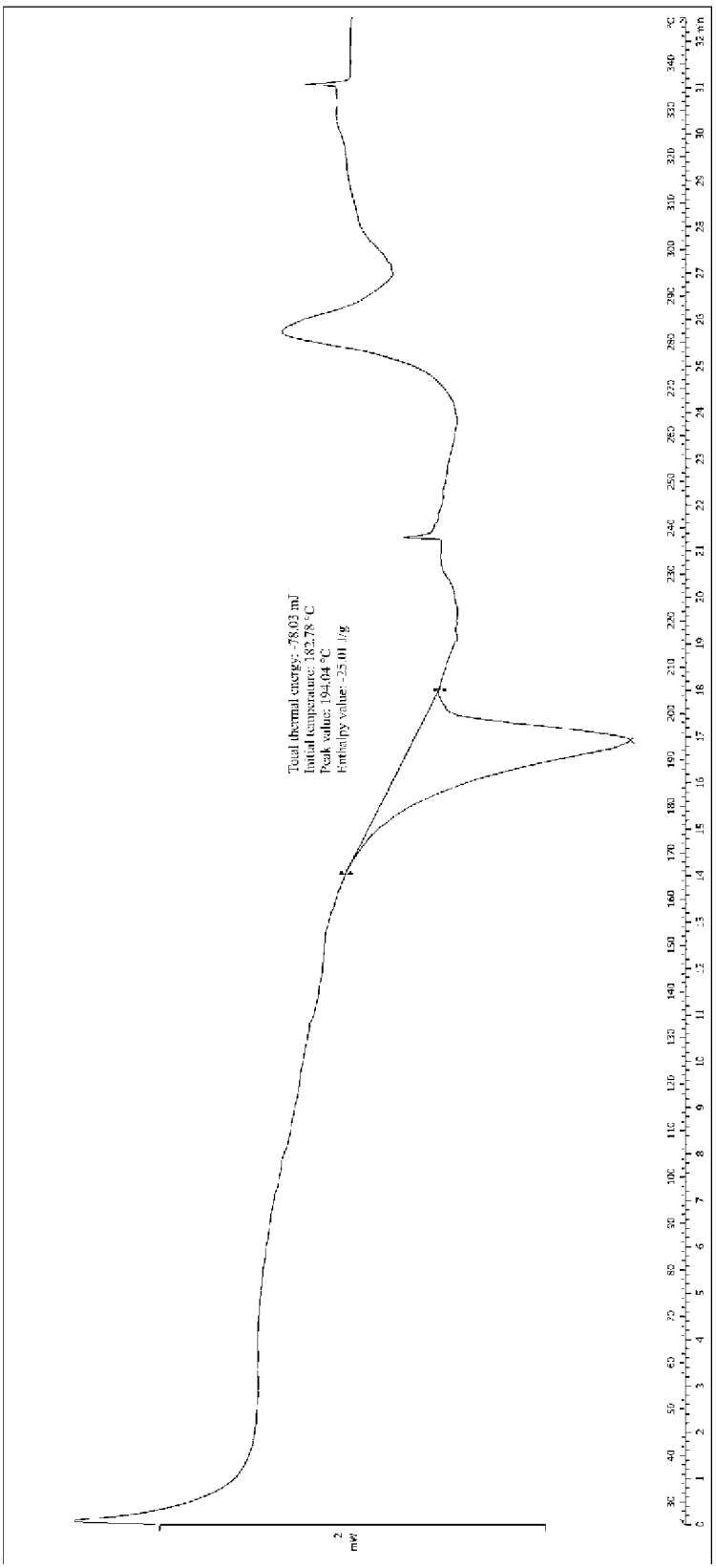

Total thermal energy: -78.03 mJ
Initial temperature: 182.78 °C
Peak value: 194.04 °C
Enthalpy value: -25.01 J/g
2
mW
min

FIG. 30

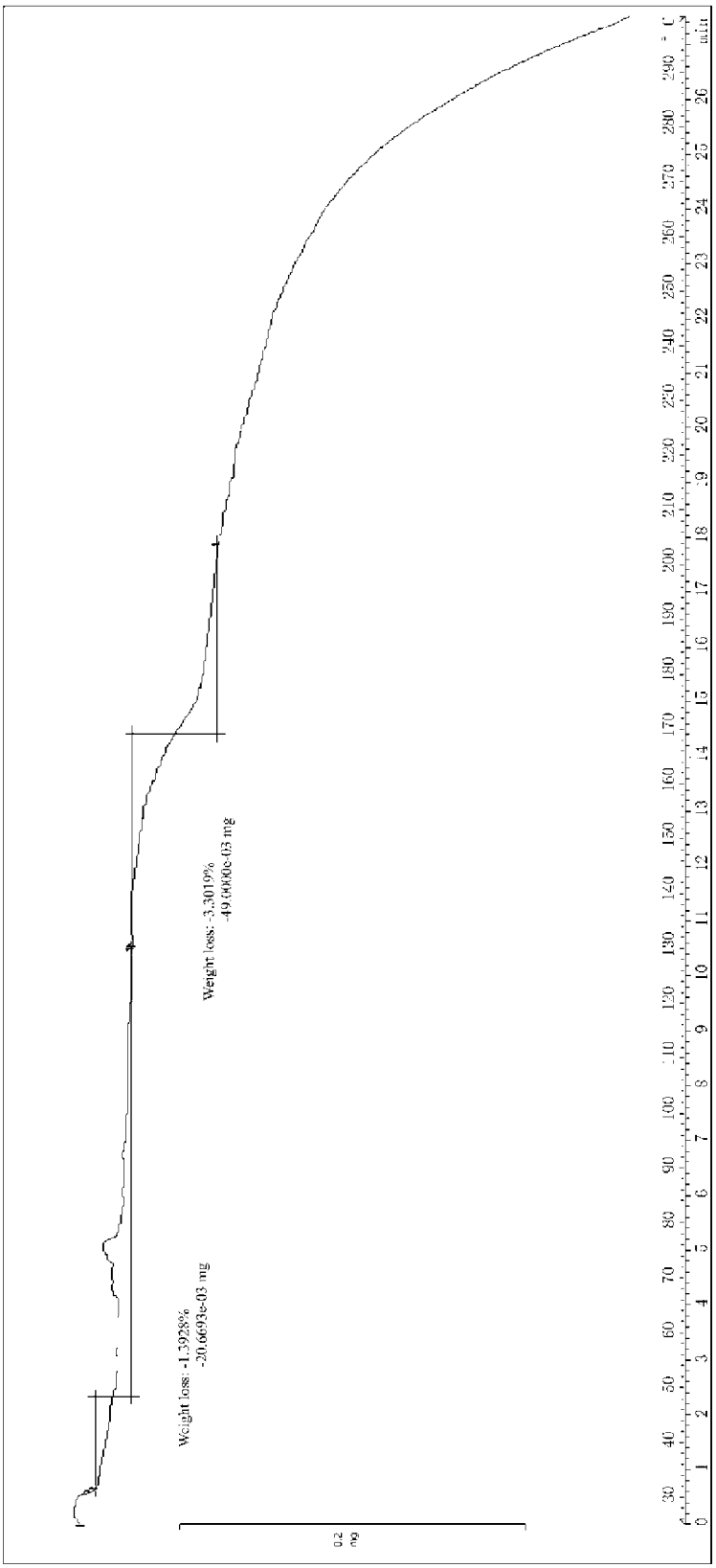

Weight loss: -1.3928%
-20.6693e-03 mg
Weight loss: -3.3019%
-49.0000e-03 mg
0.2
mg
°C

FIG. 31

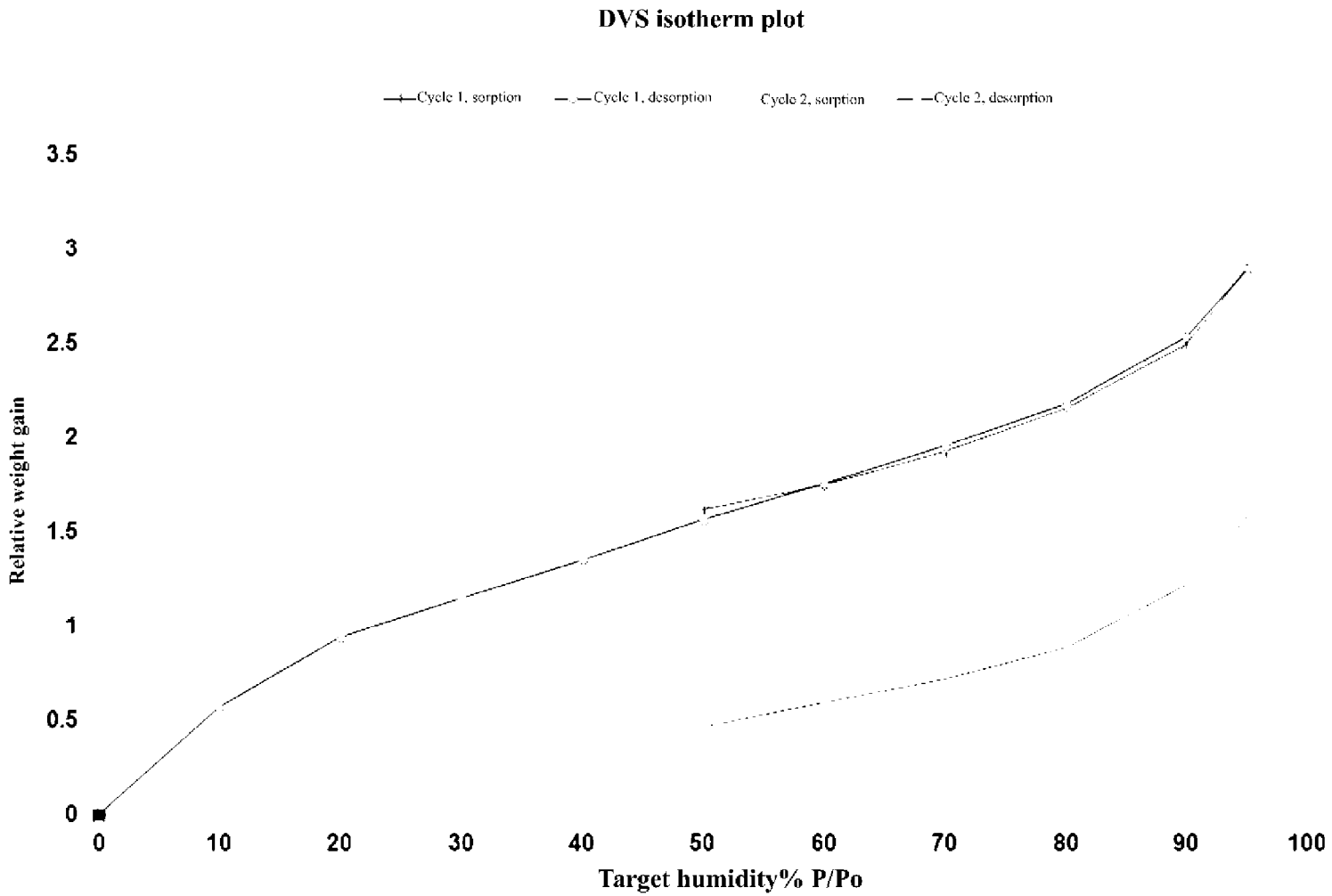

DVS isotherm plot
Cycle 1, sorption
Cycle 1, desorption
Cycle 2, sorption
Cycle 2, desorption
Relative weight gain
3.5
3
2.5
2
1.5
1
0.5
0
0
10
20
30
40
50
60
70
80
90
100
Target humidity% P/Po

FIG. 32

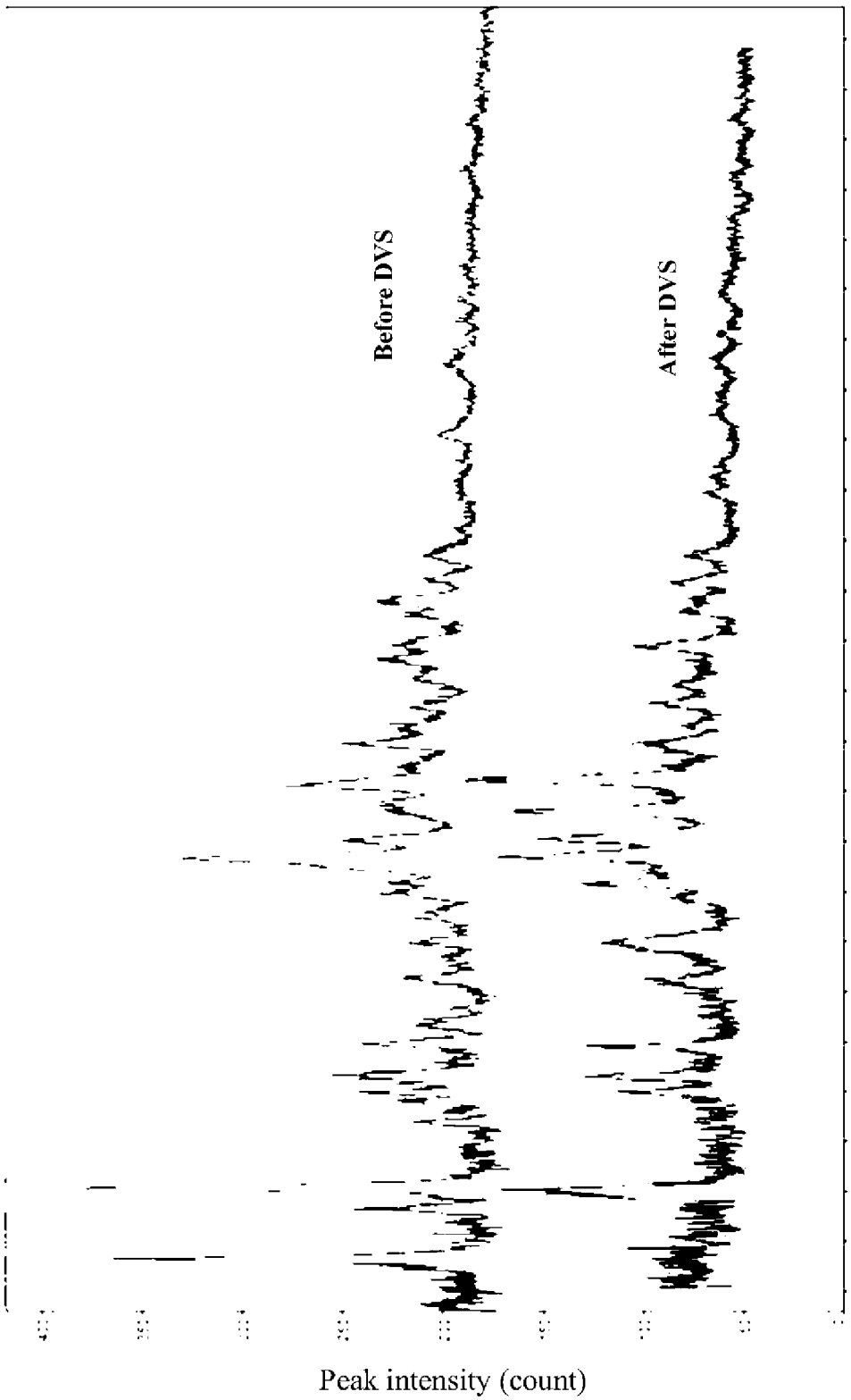


FIG. 33

CA 03156332 2022-4-27

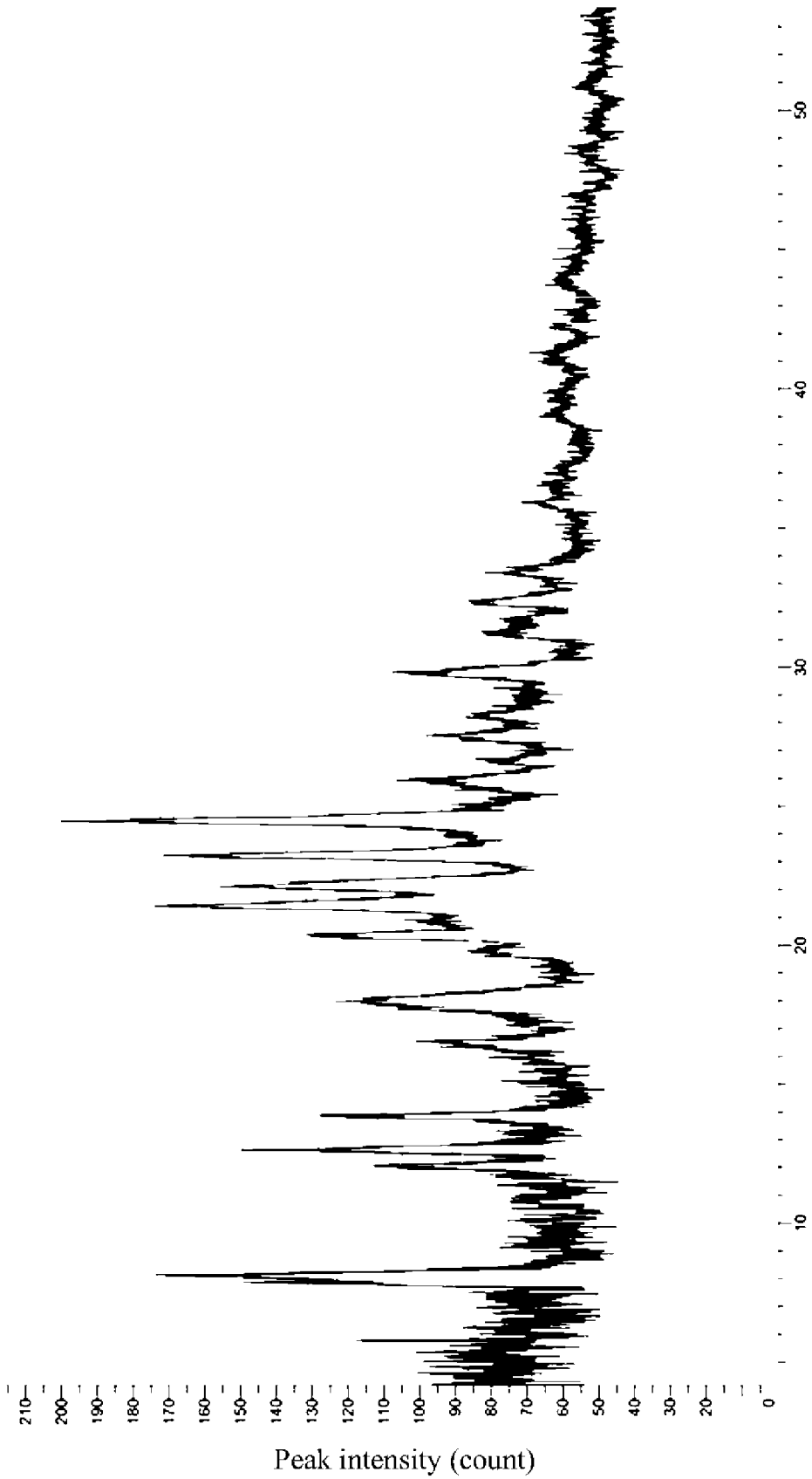


FIG. 34

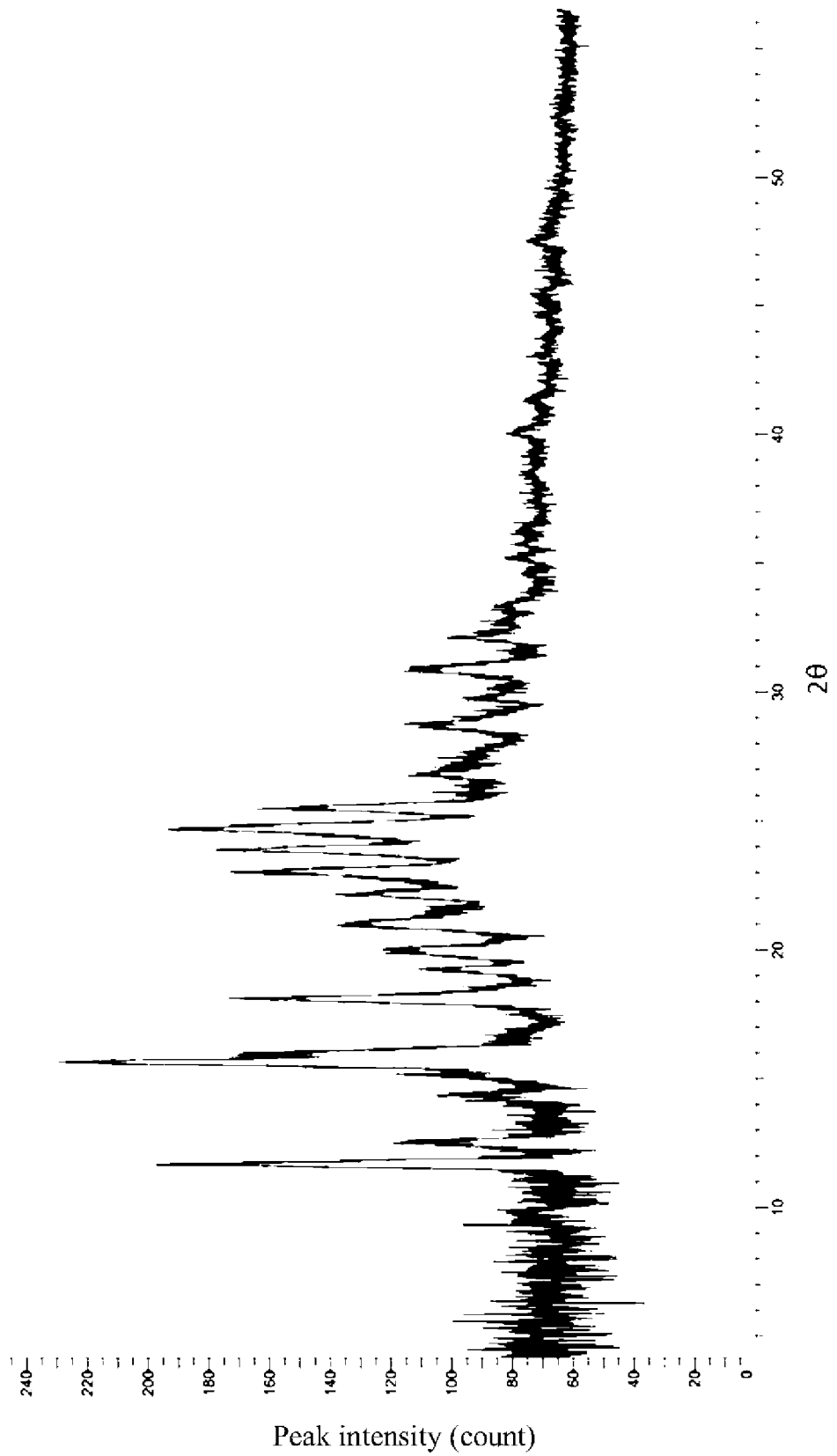


FIG. 35

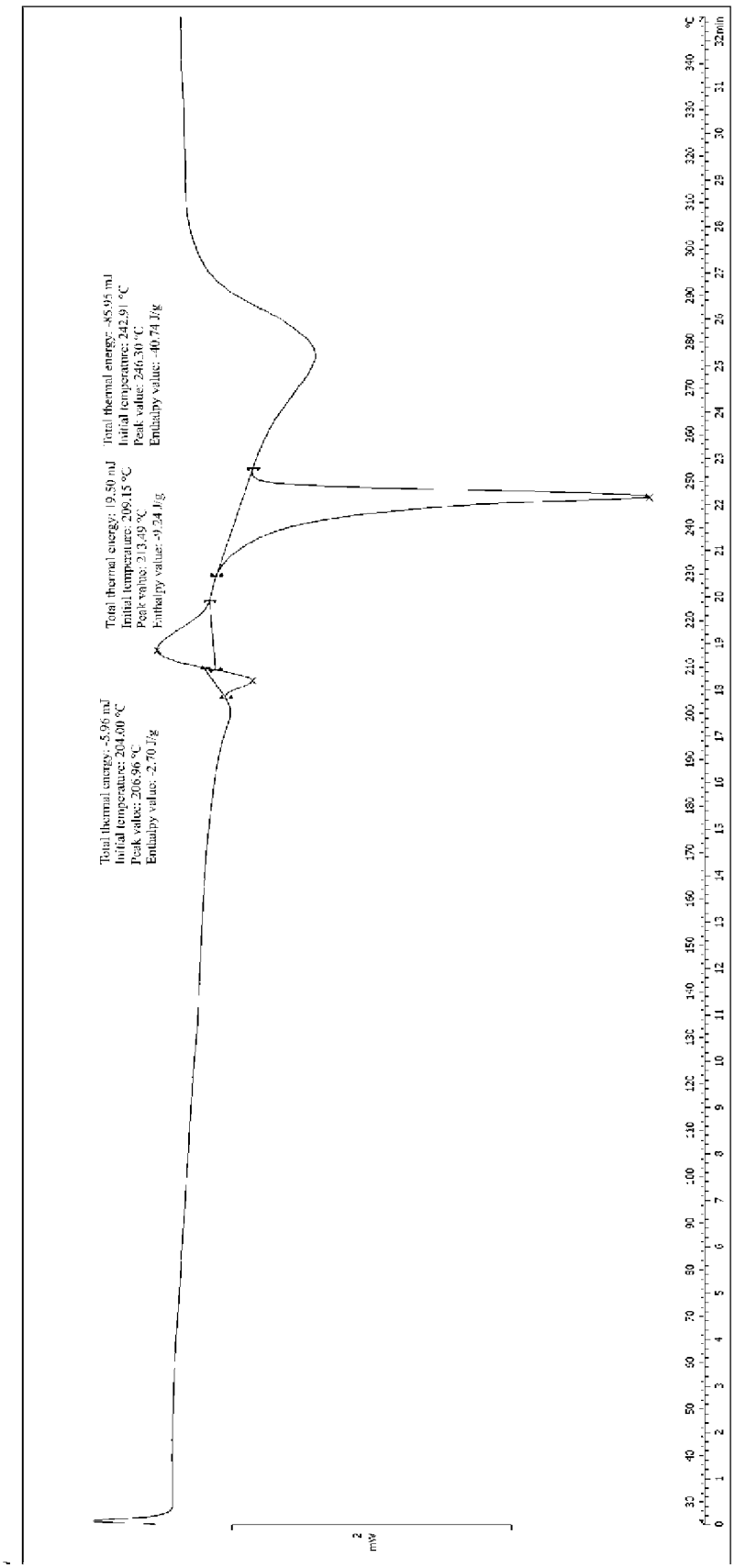
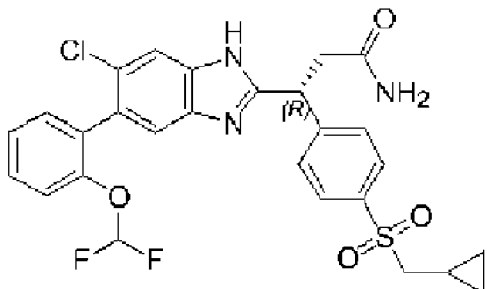


FIG. 36



II