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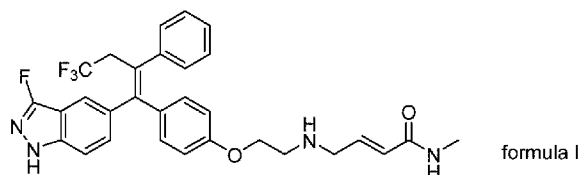
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(54) Title: SALTS OF INDAZOLE DERIVATIVE AND CRYSTALS THEREOF



formula I

(57) Abstract: The present invention provides salts of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I and acids, and crystals thereof, possessing a potential to be used as drug substance in pharmaceuticals. [Chem. 1]



Description

Title of Invention: SALTS OF INDAZOLE DERIVATIVE AND CRYSTALS THEREOF

Technical Field

[0001] The present invention relates to salts of an indazole derivative and crystals thereof.

Background Art

[0002] Breast cancer is the most commonly diagnosed malignancy among women today with nearly 200,000/1.7 million new cases diagnosed in the US/worldwide each year respectively. Since about 70% of breast tumors are positive for the estrogen receptor alpha (ER α)- a key oncogenic driver in this subset of tumors- several classes of therapies have been developed to antagonize ER α function, including 1) selective estrogen receptor downregulators (SERDs) of which fulvestrant is an example, 2) selective estrogen receptor modulators (SERMs) of which tamoxifen is an example and 3) aromatase inhibitors that reduce systemic levels of estrogen. These therapies have been largely effective in the clinic reducing occurrence and progression of ER α + breast tumors. However, there are on-target liabilities associated with these different classes of compounds. For example, tamoxifen has been shown to activate signaling activity in the endometrium leading to an increase in risk of endometrial cancers in the clinic (Fisher et al., (1994) J. Natl. Cancer Inst. Apr 6; 86 (7): 527-37; van Leeuwen et al., (1994) Lancet Feb 19; 343 (8895): 448-52). In contrast, since fulvestrant is a pure antagonist, it can lead to loss of bone density in post-menopausal women as ER α activity is critical for bone building. In addition to on-target side effects, clinical resistance is also beginning to emerge to these classes of ER α antagonists highlighting the need to develop next-generation compounds.

[0003] Several mechanisms of resistance have been identified using in vitro and in vivo models of resistance to various endocrine therapies. These include increased ER α / HER2 “crosstalk” (Shou et al., (2004) J. Natl. Cancer Inst. Jun 16; 96 (12): 926-35), aberrant expression of ER α coactivators/corepressors (Osborne et al., (2003) J. Natl. Cancer Inst. Mar 5; 95(5): 353-61) or loss of ER α altogether to allow ER-independent growth (Osborne CK, Schiff R (2011) Annu .Rev. Med. 62: 233-47).

[0004] In the hopes of identifying clinically relevant mechanisms of resistance, great effort has also recently gone into deeply characterizing the genetics of endocrine-therapy resistant metastases isolated from patients. Several independent labs have recently published the multitude of genetic lesions observed in the resistant vs the primary tumors (Li et al., (2013) Cell Rep. Sep 26; 4(6): 1116-30; Robinson et al., (2013) Nat. Genet. Dec; 45 (12): 1446-51; Toy et al., (2013) Nat. Genet. 2013 Dec;

45(12):1439-45). Among these are the highly recurrent mutations in the ligand-binding domain of ESR1 (gene which encodes ER α protein) found to be significantly enriched in about 20% of resistant tumors relative to endocrine therapy naive tumors (Jeselson et al., (2014) Clin. Cancer Res. Apr 1; 20 (7): 1757-67; Toy et al., (2013) Nat. Genet. 2013 Dec; 45 (12): 1439-45; Robinson et al., (2013) Nat. Genet. Dec; 45 (12): 1446-51; Merenbakh-Lamin et al., (2013) Cancer Res. Dec 1; 73 (23): 6856-64; Yu et al., (2014) Science Jul 11; 345 (6193): 216-20; Segal and Dowsett (2014), Clin. Cancer Res. Apr 1; 20 (7): 1724-6), suggesting the potential for these mutations to functionally drive clinical resistance. In contrast to the enrichment in ESR1 mutations observed in therapy-resistant tumors, mutations in other cancer-related genes failed to show such a robust enrichment strongly implying the importance of ER α mutations in promoting resistance (Jeselson et al., (2014) Clin. Cancer Res. Apr 1; 20 (7): 1757-67).

- [0005] ER+ breast cancer patients on average are treated with seven independent therapies including chemotherapies and various anti-estrogen therapies such as tamoxifen, fulvestrant and aromatase inhibitors. Recent genomic profiling has revealed that the ER α pathway remains a critical driver of tumor growth in the resistant setting as activating mutations in ER α have emerged. Thus, it is critical that more potent ER-directed therapies be developed that can overcome resistance in the clinical setting. Hence, there is a need for novel compounds that can potentially suppress the growth of both wild-type (WT) and ER α -mutant positive tumors.
- [0006] Most inhibitory drug interactions with cytochrome (CYP) P450 enzymes are reversible, but in some cases the inhibitory effect increases over time and is not promptly reversible. This effect is due to irreversible covalent binding or quasi-irreversible non-covalent tight binding of a chemically reactive intermediate to the enzyme that catalyzes its formation. This class of inhibitory drug interactions is called Time-Dependent Inhibition ("TDI"). When TDI is the mode of inhibition, the inhibitory interaction will generally be greater over time following multiple dosing and be longer lasting after discontinuation of the inhibitor than in a situation when the inhibitory interaction is reversible. Therefore, TDI should be studied in standard in vitro screening protocols by pre-incubating the drug (a potential inhibitor) before the addition of a substrate (Food and Drug Administration (FDA) guidance; Cf. [fda.gov/downloads/drugs/guidances/ucm292362.pdf](https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf) (FDA guidance, In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies, Draft Guidance, October 24, 2017.)). Whether an investigational drug inhibits CYP enzymes is usually investigated in vitro using human liver tissues such as human liver microsomes to determine the inhibition mechanisms (e.g., reversible or TDI) and inhibition potency. Id.
- [0007] Citing to Grimm et al., ("The conduct of in vitro studies to address time-dependent

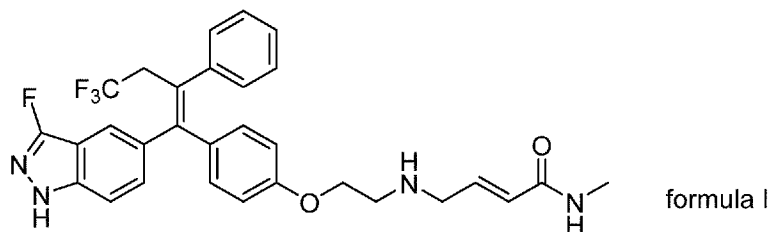
inhibition of drug-metabolizing enzymes: a perspective of the Pharmaceutical Research and Manufacturers of America,” *Drug Metab Dispos.* 37:1355-1370, 2009), the FDA recently described how pharmaceutical companies should evaluate investigational drugs for TDI potential. In particular, the FDA indicated that pharmaceutical companies “should routinely study TDI in standard in vitro screening protocols by pre-incubating the investigational drug (e.g., for at least 30 min) before adding any substrate. Any significant time-dependent and co-factor-dependent (e.g., NADPH for CYPs) loss of initial product formation may indicate TDI. In these circumstances, the sponsor should conduct definitive in vitro studies to obtain TDI parameters (i.e., k_{inact} and K_i).” See FDA guidance, *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry, Draft Guidance*, October 24, 2017, pg. 24, lines 854-858.

[0008] Patients frequently use more than one medication at a time. Unanticipated, unrecognized, or mismanaged drug-drug interactions (DDIs) are an important cause of morbidity and mortality associated with prescription drug use and have occasionally caused the withdrawal of approved drugs from the market. Determination of an investigational drug’s potential to inhibit CYPs in both a reversible manner (i.e., reversible inhibition) and time-dependent manner (i.e., TDI) will allow for better characterization of potentially clinically relevant DDI. Hence, there is a need to identify and develop investigational drugs that further mitigate or remove the TDI potential.

Summary of Invention

Technical Problem

[0009] A compound represented by the formula I, namely,
 (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (hereafter referred to as compound (I)), suppresses the growth of both wild-type (WT) and ER α -mutant positive tumors.
 [Chem.1]



Generally, the physical properties of a compound, salts thereof, and their crystals used as a pharmaceutical product largely influence on the bioavailability of a drug, the purity of an active pharmaceutical ingredient, prescription of a preparation and the like. An object of the present invention is therefore to provide salts of compound (I) or crystals thereof with a potential to be used as drug substance in pharmaceuticals.

Solution to Problem

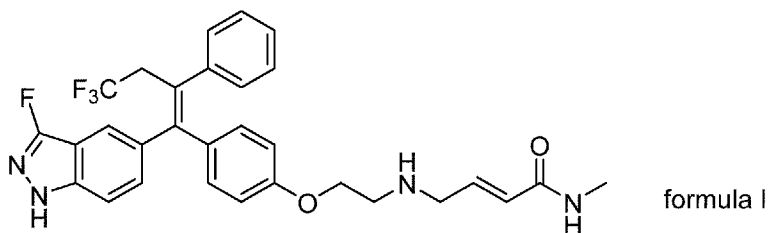
[0010] The present inventor has found salts of compound (I) or crystals thereof with a potential to be used as drug substance in pharmaceuticals, thereby completing the invention.

[0011] Specifically, the present invention provides the following <1> to <69>.

<1> A salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, and an acid selected from the group consisting of hydrobromic acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, p-toluenesulfonic acid, succinic acid, maleic acid, mandelic acid and methanesulfonic acid.

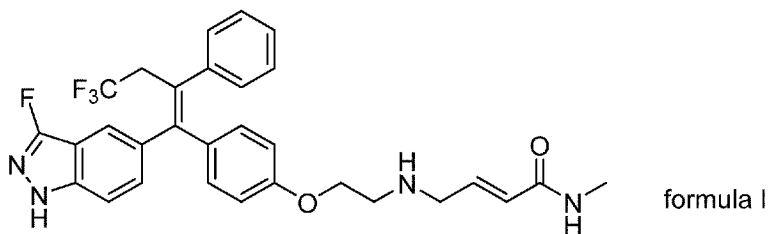
[Chem.2]



<2> A crystal of hydrochloride salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 12.2° , 16.8° , 18.2° , 19.7° and 23.3° in a powder X-ray diffractometry.

[Chem.3]



<3> The crystal according to <2> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.7° in a powder X-ray diffractometry.

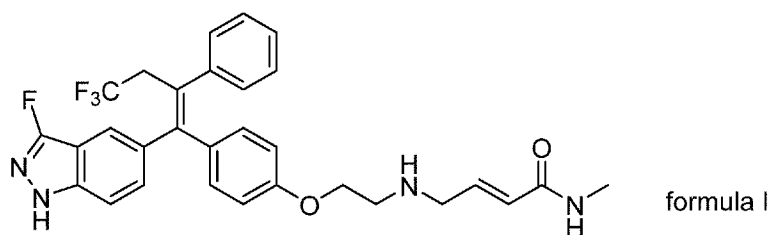
<4> The crystal according to <2> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.2° and 19.7° in a powder X-ray diffractometry.

<5> A crystal of hydrochloride salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, char-

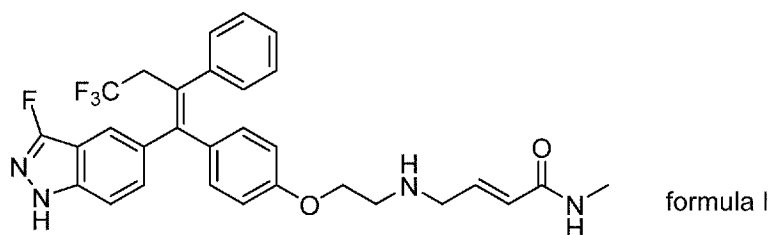
acterized by having peaks at chemical shifts (± 0.5 ppm) of 144.5 ppm, 156.8 ppm and 165.8 ppm in a solid state ^{13}C NMR spectrum.

[Chem.4]



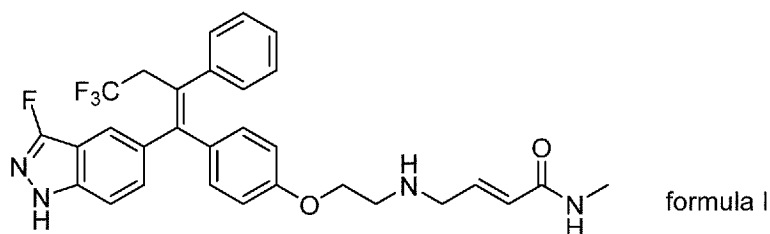
<6> A crystal of hydrochloride salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 1.

[Chem.5]



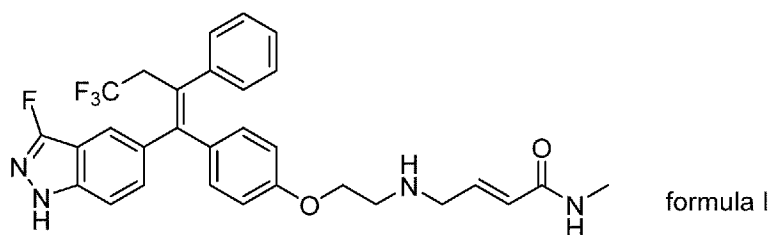
<7> A crystal of hydrochloride salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 12.

[Chem.6]



<8> A crystal of hydrobromide salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 18.4° , 19.7° , 21.6° , 22.9° and 25.6° in a powder X-ray diffractometry.

[Chem.7]



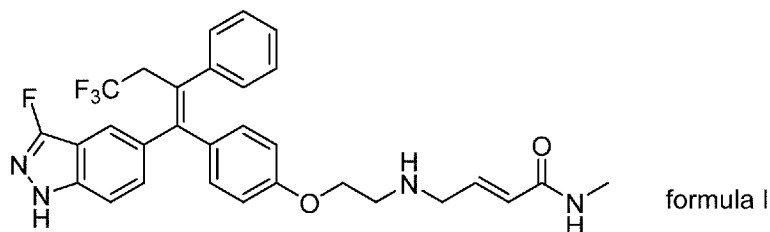
<9> The crystal according to <8> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.4° in a powder X-ray diffractometry.

<10> The crystal according to <8> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 18.4° , 19.7° and 25.6° in a powder X-ray diffractometry.

<11> A crystal of hydrobromide salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 144.2 ppm, 156.7 ppm and 165.2 ppm in a solid state ^{13}C NMR spectrum.

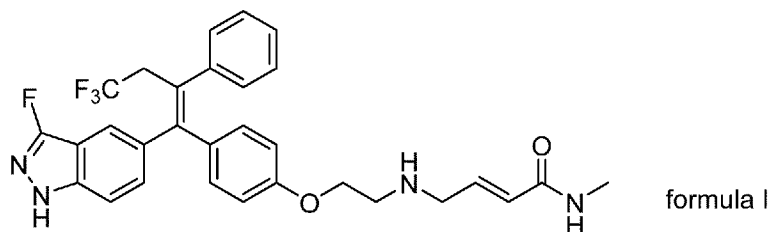
[Chem.8]



<12> A crystal of hydrobromide salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 2.

[Chem.9]

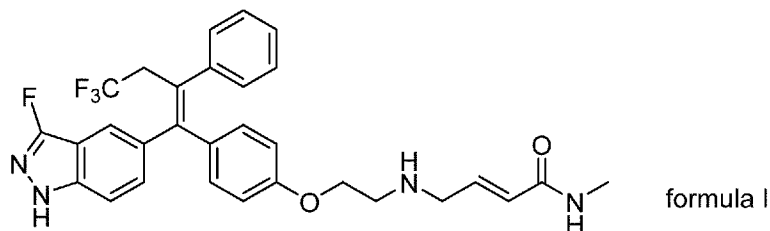


<13> A crystal of hydrobromide salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid

state ^{13}C NMR spectrum shown in Figure 13.

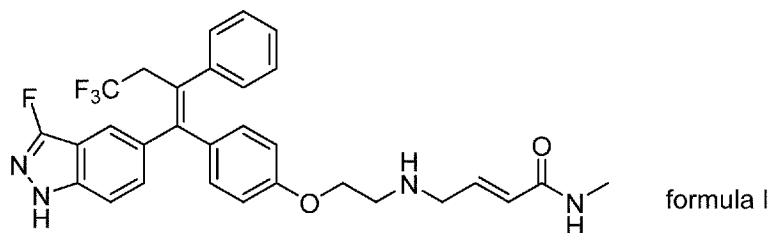
[Chem.10]



<14> A crystal of phosphate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 6.5° , 13.5° , 16.7° , 19.9° and 20.4° in a powder X-ray diffractometry.

[Chem.11]



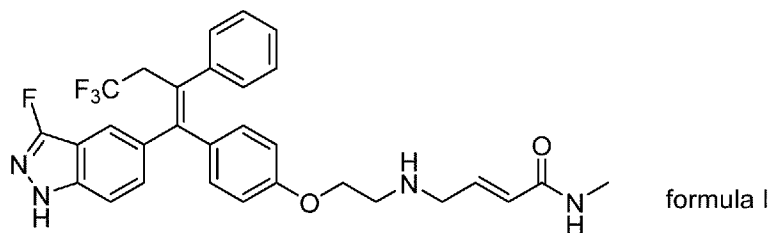
<15> The crystal according to <14> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 6.5° in a powder X-ray diffractometry.

<16> The crystal according to <14> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5° , 16.7° and 19.9° in a powder X-ray diffractometry.

<17> A crystal of phosphate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 135.3 ppm, 140.9 ppm and 169.8 ppm in a solid state ^{13}C NMR spectrum.

[Chem.12]

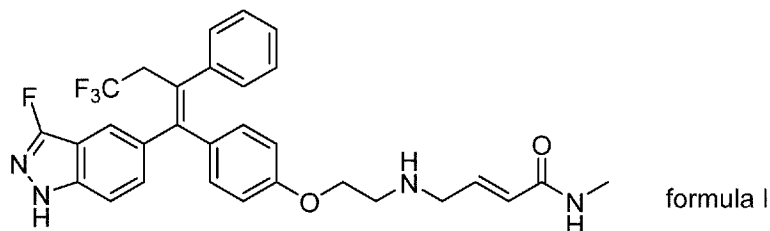


<18> A crystal of phosphate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1

-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 3.

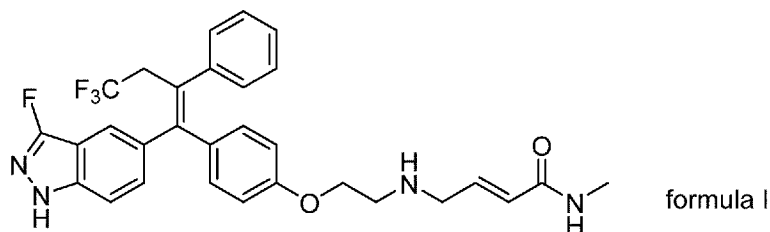
[Chem.13]



<19> A crystal of phosphate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 14.

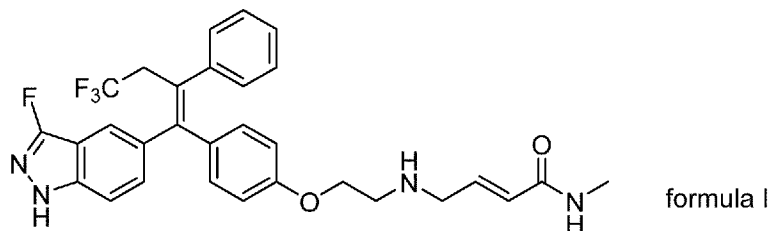
[Chem.14]



<20> A crystal of sulfate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.6° , 11.3° , 13.0° , 19.0° and 19.8° in a powder X-ray diffractometry.

[Chem.15]



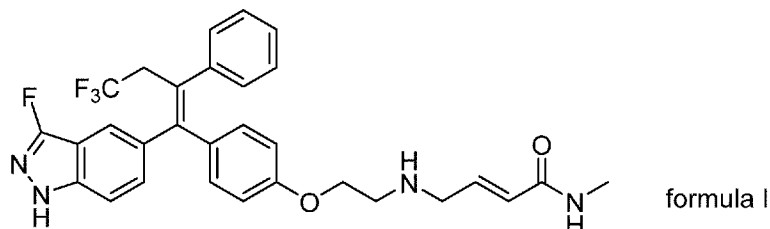
<21> The crystal according to <20> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.0° in a powder X-ray diffractometry.

<22> The crystal according to <20> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.6° , 19.0° and 19.8° in a powder X-ray diffractometry.

<23> A crystal of sulfate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 117.8 ppm, 157.4 ppm and 165.0 ppm in a solid state ^{13}C NMR spectrum.

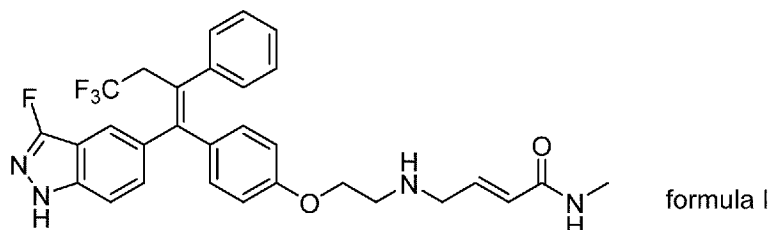
[Chem.16]



<24> A crystal of sulfate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 4.

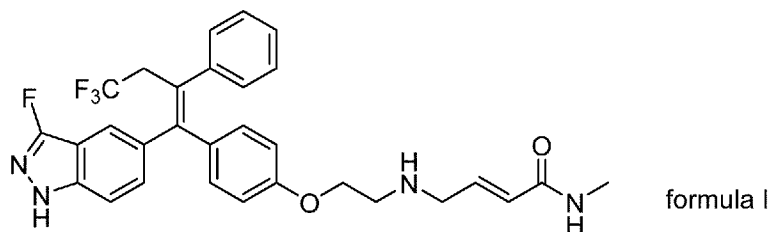
[Chem.17]



<25> A crystal of sulfate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 15.

[Chem.18]

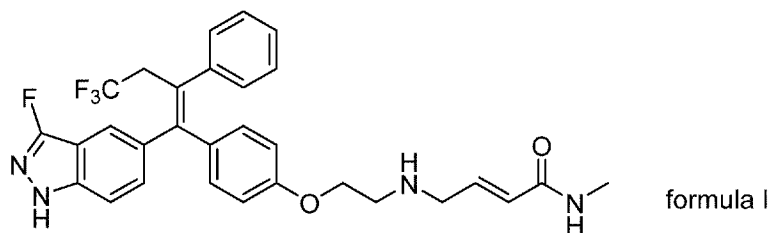


<26> A crystal of benzenesulfonate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$)

selected from the group consisting of 10.9°, 17.6°, 19.9°, 21.9° and 24.1° in a powder X-ray diffractometry.

[Chem.19]



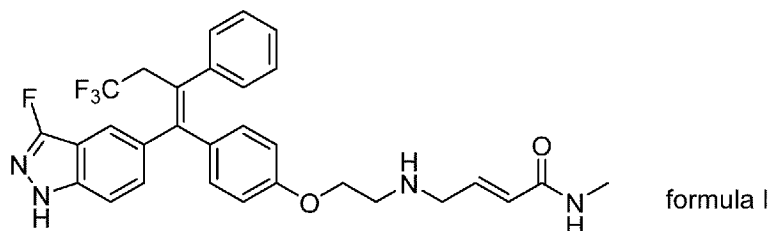
<27> The crystal according to <26> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 10.9° in a powder X-ray diffractometry.

<28> The crystal according to <26> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.9°, 17.6° and 24.1° in a powder X-ray diffractometry.

<29> A crystal of benzenesulfonate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 136.1 ppm, 156.7 ppm and 164.4 ppm in a solid state ^{13}C NMR spectrum.

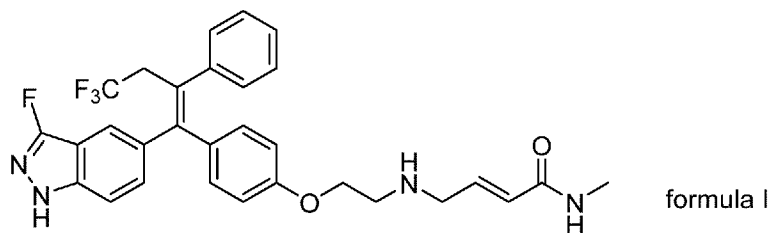
[Chem.20]



<30> A crystal of benzenesulfonate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 5.

[Chem.21]

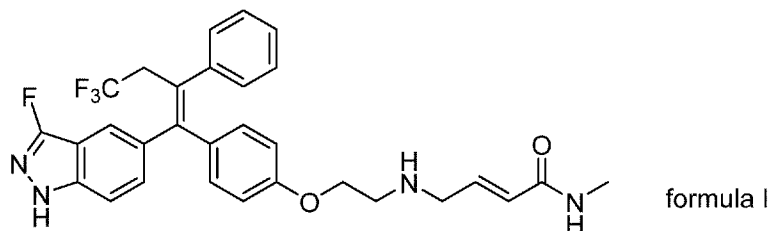


<31> A crystal of benzenesulfonate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1

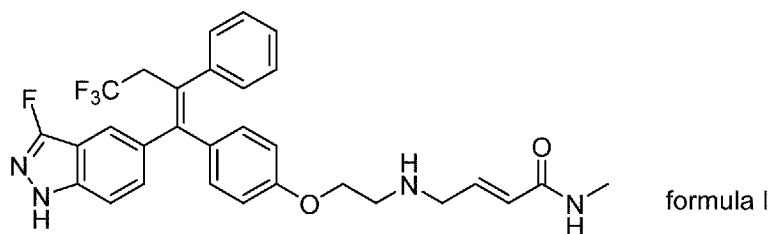
-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 16.

[Chem.22]



<32> A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 8.9° , 12.5° , 21.4° , 22.1° and 23.4° in a powder X-ray diffractometry.

[Chem.23]

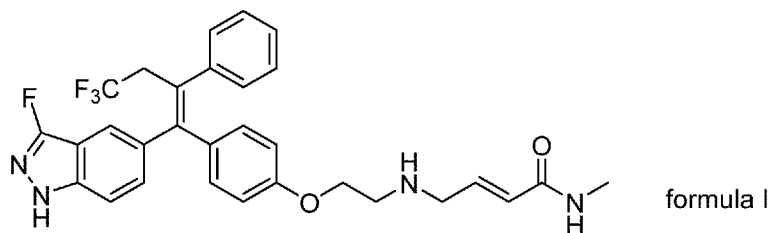


<33> The crystal according to <32> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 8.9° in a powder X-ray diffractometry.

<34> The crystal according to <32> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.9° , 21.4° and 22.1° in a powder X-ray diffractometry.

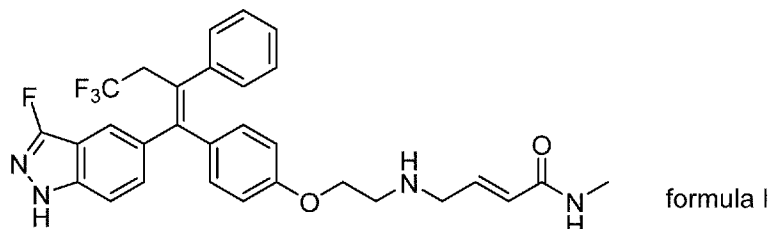
<35> A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 140.7 ppm, 156.4 ppm and 166.9 ppm in a solid state ^{13}C NMR spectrum.

[Chem.24]



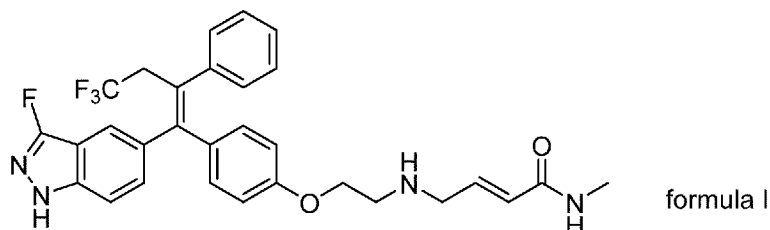
<36> A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 6.

[Chem.25]



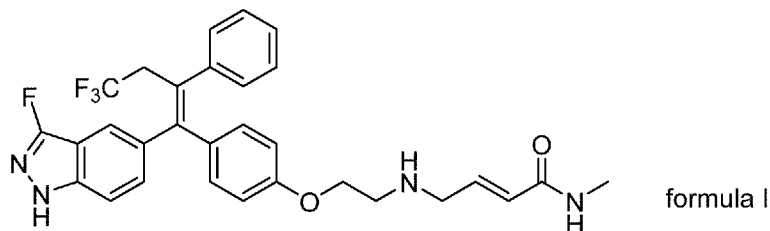
<37> A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 17.

[Chem.26]



<38> A crystal of succinate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 14.8° , 17.0° , 17.5° , 18.2° and 19.1° in a powder X-ray diffractometry.

[Chem.27]



<39> The crystal according to <38> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry.

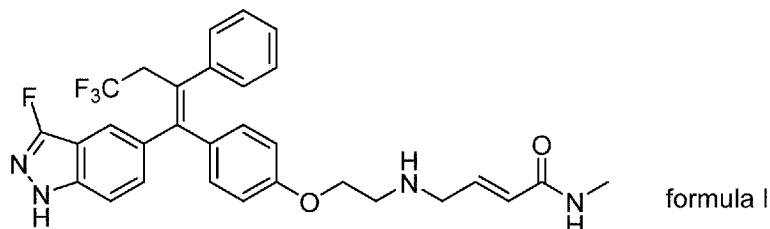
<40> The crystal according to <38> above, characterized by having diffraction peaks

at diffraction angles ($2\theta \pm 0.2^\circ$) of 17.0° , 18.2° and 19.1° in a powder X-ray diffractometry.

<41> A crystal of succinate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 156.1 ppm, 175.0 ppm and 181.3 ppm in a solid state ^{13}C NMR spectrum.

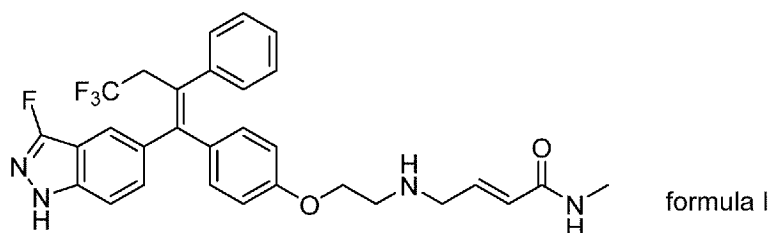
[Chem.28]



<42> A crystal of succinate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 7.

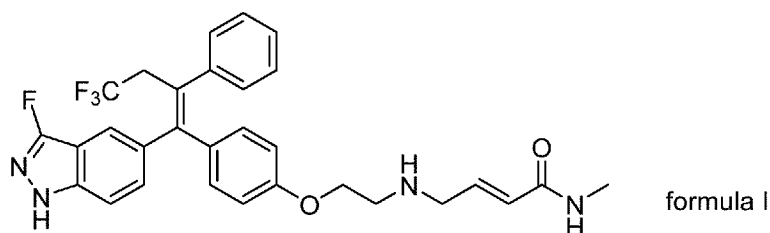
[Chem.29]



<43> A crystal of succinate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 18.

[Chem.30]

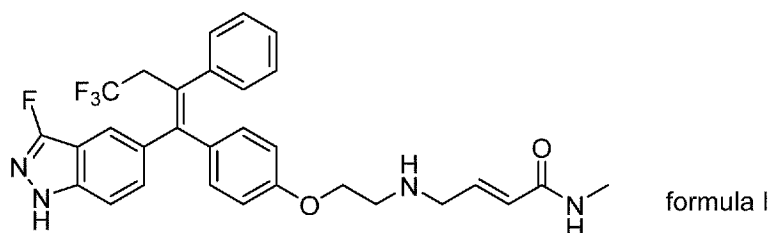


<44> A crystal form A of maleate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1

-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 5.4° , 11.6° , 16.8° , 18.9° and 20.2° in a powder X-ray diffractometry.

[Chem.31]



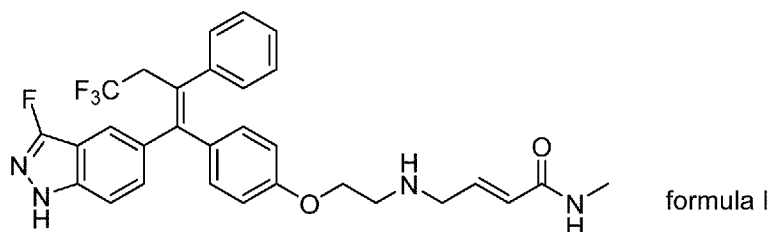
<45> The crystal according to <44> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.9° in a powder X-ray diffractometry.

<46> The crystal according to <44> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.9° and 20.2° in a powder X-ray diffractometry.

<47> A crystal form A of maleate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 43.4 ppm, 44.8 ppm and 145.0 ppm in a solid state ^{13}C NMR spectrum.

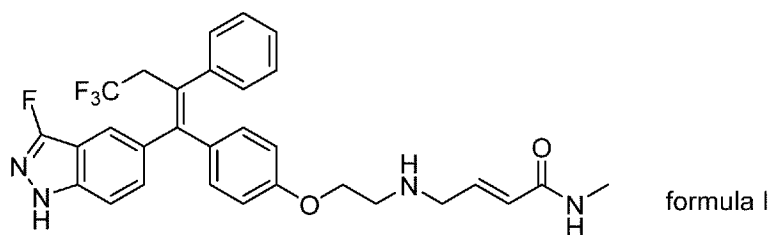
[Chem.32]



<48> A crystal form A of maleate salt of

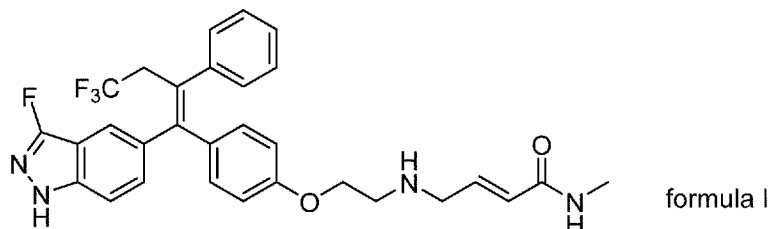
(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 8.

[Chem.33]



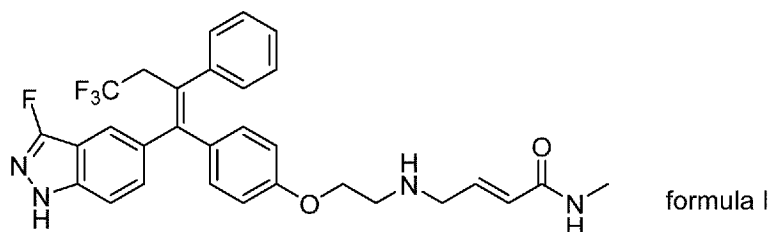
<49> A crystal form A of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 19.

[Chem.34]



<50> A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 10.4° , 15.2° , 19.4° , 20.8° and 22.2° in a powder X-ray diffractometry.

[Chem.35]

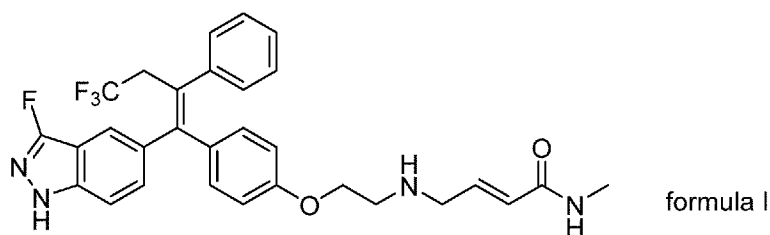


<51> The crystal according to <50> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.4° in a powder X-ray diffractometry.

<52> The crystal according to <50> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 15.2° , 19.4° and 20.8° in a powder X-ray diffractometry.

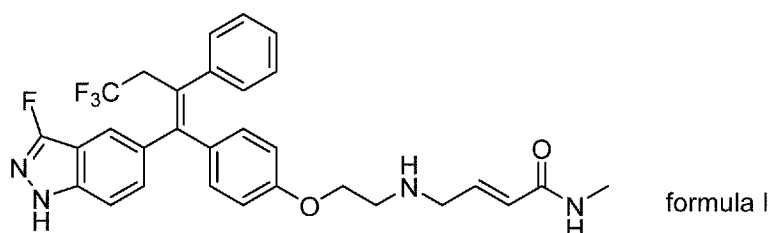
<53> A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 143.6 ppm and 166.8 ppm in a solid state ^{13}C NMR spectrum.

[Chem.36]



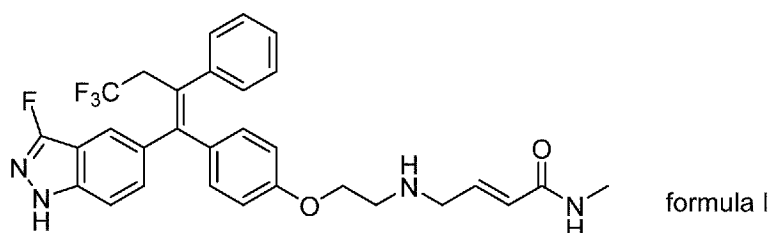
<54> A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 9.

[Chem.37]



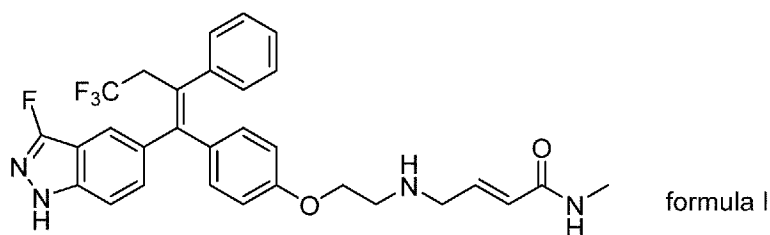
<55> A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 20.

[Chem.38]



<56> A crystal of L-mandelate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 5.1° , 8.7° , 10.3° , 18.2° and 20.3° in a powder X-ray diffractometry.

[Chem.39]



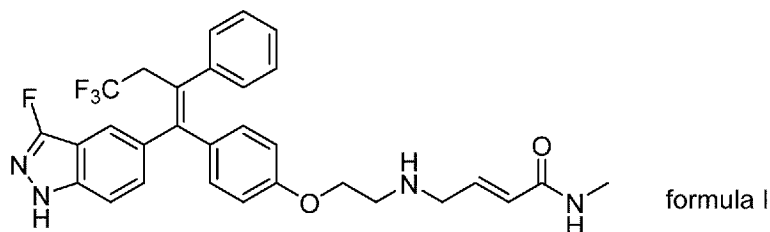
<57> The crystal according to <56> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry.

<58> The crystal according to <56> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.1° , 10.3° and 18.2° in a powder X-ray diffractometry.

<59> A crystal of L-mandelate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 128.1 ppm, 156.7 ppm and 177.8 ppm in a solid state ^{13}C NMR spectrum.

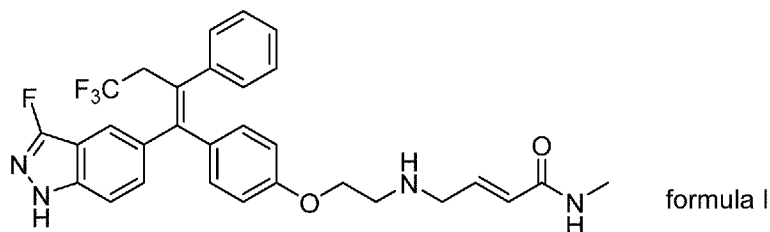
[Chem.40]



<60> A crystal of L-mandelate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 10.

[Chem.41]

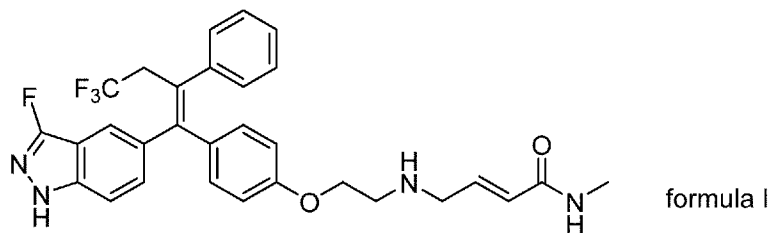


<61> A crystal of L-mandelate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid

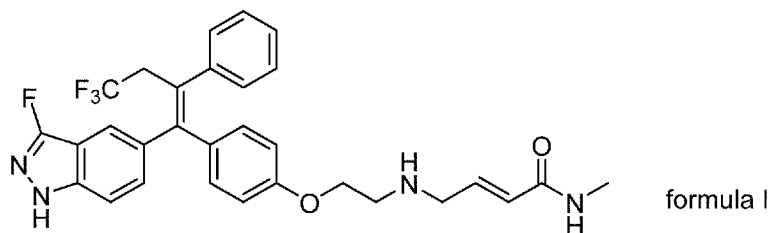
state ^{13}C NMR spectrum shown in Figure 21.

[Chem.42]



<62> A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 12.7° , 18.9° , 19.7° , 21.8° and 25.6° in a powder X-ray diffractometry.

[Chem.43]

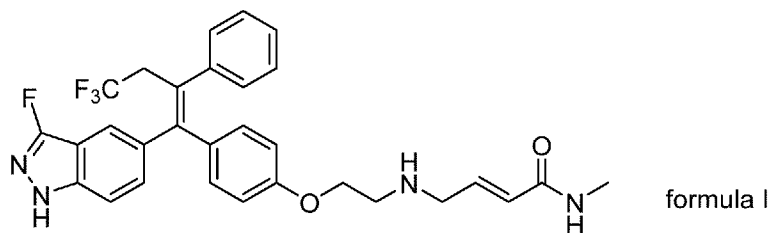


<63> The crystal according to <62> above, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 12.7° in a powder X-ray diffractometry.

<64> The crystal according to <62> above, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.7° , 18.9° and 25.6° in a powder X-ray diffractometry.

<65> A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 40.4 ppm, 158.3 ppm and 166.0 ppm in a solid state ^{13}C NMR spectrum.

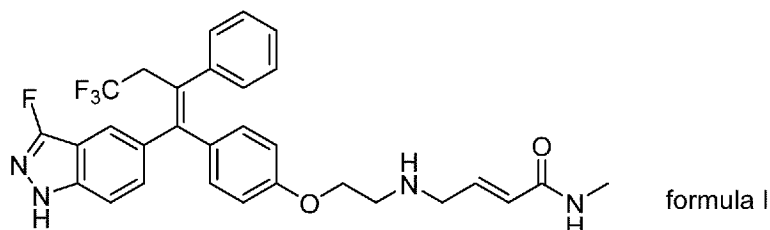
[Chem.44]



<66> A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1

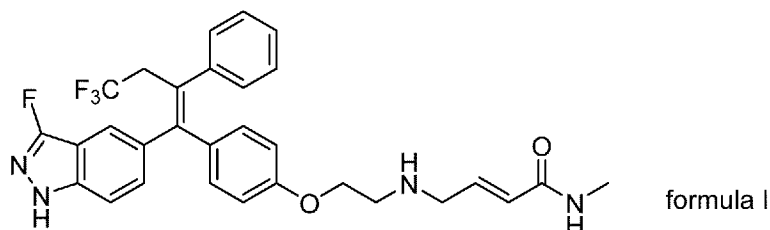
-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 11.

[Chem.45]



<67> A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 22.

[Chem.46]



<68> A pharmaceutical composition comprising the salt or the crystal thereof according to any one of <1> to <67> above.

<69> The pharmaceutical composition according to <68> above, for use in treating cancer.

Advantageous Effects of Invention

[0012] The salts of compound (I) and the crystals thereof provided by the present invention possess properties such as hygroscopicity as shown in the examples described in later and a potential to be used as drug substance in pharmaceuticals.

Brief Description of Drawings

[0013] [fig.1]Figure 1 shows a powder X-ray diffraction pattern of the crystal of the compound (I) hydrochloride salt obtained in Example 1. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.2]Figure 2 shows a powder X-ray diffraction pattern of the crystal of the compound (I) hydrobromide salt obtained in Example 2. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.3]Figure 3 shows a powder X-ray diffraction pattern of the crystal of the compound (I) phosphate salt obtained in Example 3. The abscissa shows the diffraction

angle (2θ) and the ordinate shows the peak intensity.

[fig.4]Figure 4 shows a powder X-ray diffraction pattern of the crystal of the compound (I) sulfate salt obtained in Example 4. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.5]Figure 5 shows a powder X-ray diffraction pattern of the crystal of the compound (I) benzenesulfonate salt obtained in Example 5. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.6]Figure 6 shows a powder X-ray diffraction pattern of the crystal of the compound (I) p-toluenesulfonate salt obtained in Example 6. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.7]Figure 7 shows a powder X-ray diffraction pattern of the crystal of the compound (I) succinate salt obtained in Example 7. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.8]Figure 8 shows a powder X-ray diffraction pattern of the crystal form A of the compound (I) maleate salt obtained in Example 8. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.9]Figure 9 shows a powder X-ray diffraction pattern of the crystal form B of the compound (I) maleate salt obtained in Example 9. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.10]Figure 10 shows a powder X-ray diffraction pattern of the crystal of the compound (I) L-mandelate salt obtained in Example 10. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.11]Figure 11 shows a powder X-ray diffraction pattern of the crystal of the compound (I) methanesulfonate salt obtained in Example 11. The abscissa shows the diffraction angle (2θ) and the ordinate shows the peak intensity.

[fig.12]Figure 12 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) hydrochloride salt obtained in Example 1. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.13]Figure 13 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) hydrobromide salt obtained in Example 2. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.14]Figure 14 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) phosphate salt obtained in Example 3. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.15]Figure 15 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) sulfate salt obtained in Example 4. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.16]Figure 16 shows a solid state ^{13}C NMR spectrum of the crystal of the

compound (I) benzenesulfonate salt obtained in Example 5. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.17]Figure 17 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) p-toluenesulfonate salt obtained in Example 6. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.18]Figure 18 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) succinate salt obtained in Example 7. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.19]Figure 19 shows a solid state ^{13}C NMR spectrum of the crystal form A of the compound (I) maleate salt obtained in Example 8. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.20]Figure 20 shows a solid state ^{13}C NMR spectrum of the crystal form B of the compound (I) maleate salt obtained in Example 9. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.21]Figure 21 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) L-mandelate salt obtained in Example 10. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.22]Figure 22 shows a solid state ^{13}C NMR spectrum of the crystal of the compound (I) methanesulfonate salt obtained in Example 11. The abscissa shows the chemical shift (ppm) and the ordinate shows the peak intensity.

[fig.23]Figure 23 is a graph showing hygroscopicity of the crystal of the compound (I) hydrochloride salt obtained in Example 1. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.24]Figure 24 is a graph showing hygroscopicity of the crystal of the compound (I) hydrobromide salt obtained in Example 2. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.25]Figure 25 is a graph showing hygroscopicity of the crystal of the compound (I) phosphate salt obtained in Example 3. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.26]Figure 26 is a graph showing hygroscopicity of the crystal of the compound (I) sulfate salt obtained in Example 4. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.27]Figure 27 is a graph showing hygroscopicity of the crystal of the compound (I) benzenesulfonate salt obtained in Example 5. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.28]Figure 28 is a graph showing hygroscopicity of the crystal of the compound (I) p-toluenesulfonate salt obtained in Example 6. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.29]Figure 29 is a graph showing hygroscopicity of the crystal of the compound (I) succinate salt obtained in Example 7. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.30]Figure 30 is a graph showing hygroscopicity of the crystal form A of the compound (I) maleate salt obtained in Example 8. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.31]Figure 31 is a graph showing hygroscopicity of the crystal form B of the compound (I) maleate salt obtained in Example 9. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.32]Figure 32 is a graph showing hygroscopicity of the crystal of the compound (I) L-mandelate salt obtained in Example 10. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.33]Figure 33 is a graph showing hygroscopicity of the crystal of the compound (I) methanesulfonate salt obtained in Example 11. The abscissa shows the relative humidity and the ordinate shows the weight change.

[fig.34]Figure 34 is a graph showing in vitro proliferation effects of wild-type and mutant ER-bearing MCF7 lines to clinical therapies 4-hydroxytamoxifen (4-OHT), raloxifene and fulvestrant, where phenotypic resistance observed in mutant-bearing lines relative to control lines to existing clinical compounds, whereby MCF7 cells engineered to overexpress various $ER\alpha^{MUT}$ showed partial resistance to various endocrine therapies.

[fig.35]Figure 35 is a graph showing antitumor and body weight effects of oral compound (I) as a hydrochloride salt in PDX-Y537S xenograft bearing athymic nude female mice.

[fig.36]Figure 36 is a graph showing the anti-tumor and body weight effects of compound (I), prepared as an HCl salt, in the MCF7 tumor model bearing $ER\alpha^{WT/WT}$ xenograft.

[fig.37]Figure 37 is a graph showing the anti-tumor and body weight effects of compound (I), prepared as an HCl salt, in a PDX model bearing $ER\alpha^{WT/WT}$ xenograft.

Description of Embodiments

[0014] A salt of the compound (I) of the present invention, a crystal thereof, and production methods thereof will be described in detail.

[0015] As used herein, a "salt" refers to a chemical entity made up of the compound (I) as the basic component and a specific number of equivalents of an acid to the compound (I). Here, the term "a salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, and an acid

selected from the group consisting of hydrobromic acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, p-toluenesulfonic acid, succinic acid, maleic acid, mandelic acid and methanesulfonic acid" is used for the same meaning as "a salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I formed with an acid selected from the group consisting of hydrobromic acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, p-toluenesulfonic acid, succinic acid, maleic acid, mandelic acid and methanesulfonic acid".

- [0016] Examples of a "salt" used herein include salts with organic carboxylic acids, with organic sulfonic acids and with inorganic acids, and in particular, pharmaceutically acceptable salts are preferred.
- [0017] Examples of organic carboxylic acids include acetic acid, oxalic acid, maleic acid, mandelic acid, tartaric acid, fumaric acid, citric acid, malonic acid, succinic acid, benzoic acid, hippuric acid and malic acid. Preferred examples of organic carboxylic acids include maleic acid, mandelic acid (preferably L-mandelic acid), tartaric acid, malonic acid and succinic acid.
- [0018] Examples of organic sulfonic acids include methanesulfonic acid, trifluoromethanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and camphorsulfonic acid. Preferred examples of organic sulfonic acids include methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid.
- [0019] Examples of inorganic acids include hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, perchloric acid, phosphoric acid, carbonic acid and bicarbonic acid. Preferred examples of inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid.
- [0020] A salt of the compound (I) may also be a solvate. As used herein, a solvate of the salt of compound (I) means a solid formed from the salt of the compound (I) together with solvent molecules. Examples of the solvent in the solvate include: a ketone solvent such as acetone, methyl ethyl ketone or cyclohexanone; an ester solvent such as ethyl acetate or methyl acetate; an ether solvent such as 1, 2-dimethoxyethane or methyl-tert-butyl ether; an alcohol solvent such as methanol, ethanol, 1-propanol or isopropanol; a polar solvent such as N-methyl-2-pyrrolidone, N,N-dimethylformamide or dimethyl sulfoxide; and water.
- [0021] As used herein, a "crystal" refers to a crystal of the salt of compound (I). Accordingly, a crystal of hydrochloride salt of compound (I), for example, means a crystal of the salt formed between compound (I) and hydrochloric acid.
- [0022] Examples of crystals preferred herein include:
- (a1) a crystal of hydrochloride salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.7° in a powder X-ray diffractometry;

- (a2) a crystal of hydrochloride salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.2° and 19.7° in a powder X-ray diffractometry;
- (a3) a crystal of hydrochloride salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.2° , 16.8° , 18.2° , 19.7° and 23.3° in a powder X-ray diffractometry;
- (a4) a crystal of hydrochloride salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.2° , 16.8° , 18.2° , 19.7° , 21.3° , 21.8° , 23.3° , 24.5° , 25.5° and 29.4° in a powder X-ray diffractometry;
- (b1) a crystal of hydrobromide salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.4° in a powder X-ray diffractometry;
- (b2) a crystal of hydrobromide salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 18.4° , 19.7° and 25.6° in a powder X-ray diffractometry;
- (b3) a crystal of hydrobromide salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 18.4° , 19.7° , 21.6° , 22.9° and 25.6° in a powder X-ray diffractometry;
- (b4) a crystal of hydrobromide salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.1° , 12.0° , 16.6° , 18.4° , 19.7° , 21.6° , 22.9° , 24.1° , 25.6° and 29.8° in a powder X-ray diffractometry;
- (c1) a crystal of phosphate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 6.5° in a powder X-ray diffractometry;
- (c2) a crystal of phosphate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5° , 16.7° and 19.9° in a powder X-ray diffractometry;
- (c3) a crystal of phosphate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5° , 13.5° , 16.7° , 19.9° and 20.4° in a powder X-ray diffractometry;
- (c4) a crystal of phosphate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5° , 13.5° , 14.0° , 16.7° , 19.9° , 20.4° , 21.6° and 23.2° in a powder X-ray diffractometry;
- (d1) a crystal of sulfate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.0° in a powder X-ray diffractometry;
- (d2) a crystal of sulfate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.6° , 19.0° and 19.8° in a powder X-ray diffractometry;
- (d3) a crystal of sulfate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.6° , 11.3° , 13.0° , 19.0° and 19.8° in a powder X-ray diffractometry;
- (d4) a crystal of sulfate salt of compound (I), having one or more diffraction peaks at

diffraction angles ($2\theta \pm 0.2^\circ$) of 3.7° , 7.6° , 11.3° , 13.0° , 16.9° , 19.0° and 19.8° in a powder X-ray diffractometry;

(e1) a crystal of benzenesulfonate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 10.9° in a powder X-ray diffractometry;

(e2) a crystal of benzenesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.9° , 17.6° and 24.1° in a powder X-ray diffractometry;

(e3) a crystal of benzenesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.9° , 17.6° , 19.9° , 21.9° and 24.1° in a powder X-ray diffractometry;

(e4) a crystal of benzenesulfonate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.5° , 9.8° , 10.9° , 17.6° , 19.2° , 19.9° , 21.9° , 24.1° and 26.5° in a powder X-ray diffractometry;

(f1) a crystal of p-toluenesulfonate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 8.9° in a powder X-ray diffractometry;

(f2) a crystal of p-toluenesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.9° , 21.4° and 22.1° in a powder X-ray diffractometry;

(f3) a crystal of p-toluenesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.9° , 12.5° , 21.4° , 22.1° and 23.4° in a powder X-ray diffractometry;

(f4) a crystal of p-toluenesulfonate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.9° , 11.5° , 12.5° , 16.2° , 17.5° , 20.0° , 20.9° , 21.4° , 22.1° and 23.4° in a powder X-ray diffractometry;

(g1) a crystal of succinate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry;

(g2) a crystal of succinate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 17.0° , 18.2° and 19.1° in a powder X-ray diffractometry;

(g3) a crystal of succinate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 14.8° , 17.0° , 17.5° , 18.2° and 19.1° in a powder X-ray diffractometry;

(g4) a crystal of succinate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.2° , 10.4° , 12.9° , 14.8° , 17.0° , 17.5° , 18.2° , 19.1° , 21.8° and 23.6° in a powder X-ray diffractometry;

(h1) a crystal form A of maleate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.9° in a powder X-ray diffractometry;

(h2) a crystal form A of maleate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.9° and 20.2° in a powder X-ray

diffractometry;

(h3) a crystal form A of maleate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.4° , 11.6° , 16.8° , 18.9° and 20.2° in a powder X-ray diffractometry;

(h4) a crystal form A of maleate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.4° , 11.6° , 13.3° , 14.3° , 16.8° , 18.9° , 20.2° , and 21.6° in a powder X-ray diffractometry;

(i1) a crystal form B of maleate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.4° in a powder X-ray diffractometry;

(i2) a crystal form B of maleate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 15.2° , 19.4° and 20.8° in a powder X-ray diffractometry;

(i3) a crystal form B of maleate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.4° , 15.2° , 19.4° , 20.8° and 22.2° in a powder X-ray diffractometry;

(i4) a crystal form B of maleate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.4° , 15.2° , 19.4° , 20.8° , 22.2° , 23.7° , 25.7° and 28.6° in a powder X-ray diffractometry;

(j1) a crystal of L-mandelate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry;

(j2) a crystal of L-mandelate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.1° , 10.3° and 18.2° in a powder X-ray diffractometry;

(j3) a crystal of L-mandelate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.1° , 8.7° , 10.3° , 18.2° and 20.3° in a powder X-ray diffractometry;

(j4) a crystal of L-mandelate salt of compound (I), having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.1° , 8.7° , 10.3° , 13.9° , 18.2° and 20.3° in a powder X-ray diffractometry;

(k1) a crystal of methanesulfonate salt of compound (I), having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 12.7° in a powder X-ray diffractometry;

(k2) a crystal of methanesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.7° , 18.9° and 25.6° in a powder X-ray diffractometry;

(k3) a crystal of methanesulfonate salt of compound (I), having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.7° , 18.9° , 19.7° , 21.8° and 25.6° in a powder X-ray diffractometry;

(k4) a crystal of methanesulfonate salt of compound (I), having one or more diffraction

peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.5° , 12.1° , 12.7° , 17.1° , 18.9° , 19.7° , 20.9° , 21.8° and 25.6° in a powder X-ray diffractometry;

(11) a crystal of hydrochloride salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 144.5 ppm, 156.8 ppm and 165.8 ppm in a solid state ^{13}C NMR spectrum;

(12) a crystal of hydrochloride salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 139.0 ppm, 141.4 ppm, 144.5 ppm, 156.8 ppm and 165.8 ppm in a solid state ^{13}C NMR spectrum;

(13) a crystal of hydrochloride salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 45.9 ppm, 117.3 ppm, 128.5 ppm, 133.9 ppm, 139.0 ppm, 141.4 ppm, 144.5 ppm, 156.8 ppm and 165.8 ppm in a solid state ^{13}C NMR spectrum;

(m1) a crystal of hydrobromide salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 144.2 ppm, 156.7 ppm and 165.2 ppm in a solid state ^{13}C NMR spectrum;

(m2) a crystal of hydrobromide salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 139.4 ppm, 141.6 ppm, 144.2 ppm, 156.7 ppm and 165.2 ppm in a solid state ^{13}C NMR spectrum;

(m3) a crystal of hydrobromide salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 26.4 ppm, 45.2 ppm, 47.3 ppm, 116.9 ppm, 129.3 ppm, 139.4 ppm, 141.6 ppm, 144.2 ppm, 156.7 ppm and 165.2 ppm in a solid state ^{13}C NMR spectrum;

(n1) a crystal of phosphate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 135.3 ppm, 140.9 ppm and 169.8 ppm in a solid state ^{13}C NMR spectrum;

(n2) a crystal of phosphate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 126.6 ppm, 135.3 ppm, 140.9 ppm, 146.6 ppm and 169.8 ppm in a solid state ^{13}C NMR spectrum;

(n3) a crystal of phosphate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 26.9 ppm, 45.5 ppm, 49.2 ppm, 126.6 ppm, 135.3 ppm, 138.3 ppm, 140.9 ppm, 145.5 ppm, 146.6 ppm and 169.8 ppm in a solid state ^{13}C NMR spectrum;

(o1) a crystal of sulfate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 117.8 ppm, 157.4 ppm and 165.0 ppm in a solid state ^{13}C NMR spectrum;

(o2) a crystal of sulfate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 47.8 ppm, 49.9 ppm, 117.8 ppm, 157.4 ppm and 165.0 ppm in a solid state ^{13}C NMR spectrum;

(o3) a crystal of sulfate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 25.0 ppm, 47.8 ppm, 49.9 ppm, 113.6 ppm, 117.8 ppm, 124.7 ppm, 141.3 ppm, 146.5 ppm, 157.4 ppm and 165.0 ppm in a solid state ^{13}C NMR spectrum;

(p1) a crystal of benzenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 136.1 ppm, 156.7 ppm and 164.4 ppm in a solid state ^{13}C NMR spectrum;

(p2) a crystal of benzenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 116.8 ppm, 132.3 ppm, 136.1 ppm, 156.7 ppm and 164.4 ppm in a solid state ^{13}C NMR spectrum;

(p3) a crystal of benzenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 27.6 ppm, 44.9 ppm, 47.1 ppm, 116.8 ppm, 132.3 ppm, 136.1 ppm, 156.7 ppm and 164.4 ppm in a solid state ^{13}C NMR spectrum;

(q1) a crystal of p-toluenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 140.7 ppm, 156.4 ppm and 166.9 ppm in a solid state ^{13}C NMR spectrum;

(q2) a crystal of p-toluenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 125.9 ppm, 140.7 ppm, 144.2 ppm, 156.4 ppm and 166.9 ppm in a solid state ^{13}C NMR spectrum;

(q3) a crystal of p-toluenesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 19.2 ppm, 27.5 ppm, 46.4 ppm, 112.3 ppm, 117.0 ppm, 125.9 ppm, 140.7 ppm, 144.2 ppm, 156.4 ppm and 166.9 ppm in a solid state ^{13}C NMR spectrum;

(r1) a crystal of succinate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 156.1 ppm, 175.0 ppm and 181.3 ppm in a solid state ^{13}C NMR spectrum;

(r2) a crystal of succinate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 145.8 ppm, 156.1 ppm, 165.5 ppm, 175.0 ppm and 181.3 ppm in a solid state ^{13}C NMR spectrum;

(r3) a crystal of succinate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 26.0 ppm, 35.1 ppm, 116.0 ppm, 125.3 ppm, 139.2 ppm, 145.8 ppm, 156.1 ppm, 165.5 ppm, 175.0 ppm and 181.3 ppm in a solid state ^{13}C NMR spectrum;

(s1) a crystal form A of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 43.4 ppm, 44.8 ppm and 145.0 ppm in a solid state ^{13}C NMR spectrum;

(s2) a crystal form A of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 43.4 ppm, 44.8 ppm, 63.0 ppm, 133.8 ppm and 145.0 ppm in a solid state ^{13}C NMR spectrum;

(s3) a crystal form A of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 43.4 ppm, 44.8 ppm, 47.8 ppm, 63.0 ppm, 66.0 ppm, 125.2 ppm, 133.8 ppm, 140.6 ppm, 145.0 ppm and 165.5 ppm in a solid state ^{13}C NMR spectrum;

(t1) a crystal form B of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 143.6 ppm and 166.8 ppm in a solid state ^{13}C NMR spectrum;

(t2) a crystal form B of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 48.8 ppm, 135.1 ppm, 143.6 ppm and 166.8 ppm in a solid state ^{13}C NMR spectrum;

(t3) a crystal form B of maleate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 48.8 ppm, 110.7 ppm, 115.7 ppm, 135.1 ppm, 136.6 ppm, 143.6 ppm, 156.3 ppm, 166.8 ppm and 172.6 ppm in a solid state ^{13}C NMR spectrum;

(u1) a crystal of L-mandelate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 128.1 ppm, 156.7 ppm and 177.8 ppm in a solid state ^{13}C NMR spectrum;

(u2) a crystal of L-mandelate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 128.1 ppm, 141.9 ppm, 156.7 ppm, 164.6 ppm and 177.8 ppm in a solid state ^{13}C NMR spectrum;

(u3) a crystal of L-mandelate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 62.9 ppm, 76.5 ppm, 116.2 ppm, 123.6 ppm, 128.1 ppm, 141.9 ppm, 146.3 ppm, 156.7 ppm, 164.6 ppm and 177.8 ppm in a solid state ^{13}C NMR spectrum;

(v1) a crystal of methanesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 40.4 ppm, 158.3 ppm and 166.0 ppm in a solid state ^{13}C NMR spectrum;

(v2) a crystal of methanesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 40.4 ppm, 136.0 ppm, 146.7 ppm, 158.3 ppm and 166.0 ppm in a solid state ^{13}C NMR spectrum; and

(v3) a crystal of methanesulfonate salt of compound (I), having peaks at chemical shifts (± 0.5 ppm) of 24.8 ppm, 40.4 ppm, 47.2 ppm, 117.8 ppm, 133.9 ppm, 136.0 ppm, 140.4 ppm, 146.7 ppm, 158.3 ppm and 166.0 ppm in a solid state ^{13}C NMR spectrum.

[0023] The peaks in a powder X-ray diffractometry, described above, are characteristic for each of the crystal of hydrochloride salt of compound (I), the crystal of hydrobromide salt of compound (I), the crystal of phosphate salt of compound (I), the crystal of sulfate salt of compound (I), the crystal of benzenesulfonate salt of compound (I), the crystal of p-toluenesulfonate salt of compound (I), the crystal of succinate salt of compound (I), the crystal form A of maleate salt of compound (I), the crystal form B of maleate salt of compound (I), the crystal of L-mandelate salt of compound (I), and the crystal of methanesulfonate salt of compound (I).

[0024] Generally, errors in diffraction angles (2θ) within the range of $\pm 0.2^\circ$ may arise in powder X-ray diffractometry, and thus the above-described values of diffraction angles need to be considered to include values within the range of approximately $\pm 0.2^\circ$. Included in the present invention are, therefore, not only crystals with peaks at exactly the same diffraction angles in powder X-ray diffractometry, but also crystals with peaks within an error range of approximately $\pm 0.2^\circ$ of the diffraction angles. Hence, "having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.7° " as used herein, for example, means "having a diffraction peak at a diffraction angle (2θ) of 19.5° to 19.9° ". The same is also applied to other diffraction angles.

- [0025] Generally, peak intensities and half-value widths of diffraction angles (2θ) in powder X-ray diffraction are different for each measurement because of differences in measurement conditions and dispersions of size and shape of each particle of powder crystal and not always stable even though forms of crystals are same. Therefore, in case of comparing a powder X-ray diffraction pattern, when diffraction angles (2θ) are the same but peak intensities, relative peak intensities and half-value widths are different, those differences does not imply that the measured forms of crystals differ from each other. Thus, a crystal of salt having a powder X-ray diffraction pattern, which has aforementioned differences with respect to characteristic diffraction peaks of a certain crystal of salt according to the present invention, means that the crystal has the same crystal form of the crystal of salt according to the present invention.
- [0026] As used herein, "having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 1" means it includes not only the case of having exactly the same powder X-ray diffraction pattern as shown in Figure 1, but also the case that at least one selected from the group consisting of peak intensities, relative peak intensities and half-value widths are different, or the case of having the characteristic peaks within an error range of approximately $\pm 0.2^\circ$ of the diffraction angles. Thus every crystal having such the powder X-ray diffraction pattern means that the crystal is identical to the crystal according to the present invention.
- [0027] The peaks in solid state ^{13}C NMR spectrum, described above, are characteristic for each of the crystal of hydrochloride salt of compound (I), the crystal of hydrobromide salt of compound (I), the crystal of phosphate salt of compound (I), the crystal of sulfate salt of compound (I), the crystal of benzenesulfonate salt of compound (I), the crystal of p-toluenesulfonate salt of compound (I), the crystal of succinate salt of compound (I), the crystal form A of maleate salt of compound (I), the crystal form B of maleate salt of compound (I), the crystal of L-mandelate salt of compound (I), and the crystal of methanesulfonate salt of compound (I).
- [0028] As used herein, "having peaks at chemical shifts of 144.5 ppm, 156.8 ppm and 165.8 ppm" means "having peaks each substantially equivalent to the peaks at chemical shifts of 144.5 ppm, 156.8 ppm and 165.8 ppm, when solid state ^{13}C NMR spectrometry is performed under a conventional measurement condition or substantially the same condition as in the present specification".
- [0029] When determining whether "having peaks substantially equivalent to" or not, the above-described values of the chemical shifts need to be considered to include values within the range of approximately ± 0.5 ppm since generally errors in chemical shifts (ppm) within the range of ± 0.5 ppm may arise in a solid state ^{13}C NMR spectrum. Included in the present invention are, therefore, not only crystals with exactly the same chemical shifts in a solid state ^{13}C NMR spectrum, but also crystals with chemical

shifts within an error range of approximately ± 0.5 ppm. Hence, "having a peak at chemical shift of 144.5 ppm" as used herein, for examples, means "having a peak at a chemical shift of 144.0 ppm to 145.0 ppm". The same is also applied to other chemical shifts in solid state ^{13}C NMR spectra.

[0030] As used herein, "having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 12" means it includes not only the case of having exactly the same solid state ^{13}C NMR spectrum as shown in Figure 12, but also the case that peak intensities are different, or the case of having the characteristic peaks within an error range of approximately ± 0.5 ppm. Thus every crystal having such the solid state ^{13}C NMR spectrum means that the crystal is identical to the crystal according to the present invention.

[0031] Methods for producing a salt of the compound (I) and a crystal thereof will be described in detail.

[0032] (Production of compound (I))

Compound (I) can be synthesized as described specifically in Production Example 1 below.

[0033] (Method for producing a salt of the compound (I))

A salt of the compound (I) can be obtained by a conventional method for producing a salt. Specifically, it can be produced, for example, by suspending or dissolving compound (I) in a solvent, with heating if necessary, then by adding an acid to the obtained suspension or solution and by stirring or leaving the resultant suspension or solution for several minutes to several days at room temperature or with ice-bath cooling. A salt of the compound (I) may be obtained as crystals or amorphous substances according to the production methods. Examples of the solvents to be used in these methods include alcohol solvents such as ethanol, 1-propanol and isopropanol; acetonitrile; ketone solvents such as acetone and 2-butanone; ester solvents such as ethyl acetate; saturated hydrocarbon solvents such as hexane and heptane; ether solvents such as t-butyl methyl ether or water. Each of these solvents may be used alone, or two or more may be mixed and used.

[0034] (Method for producing a crystal of the salt of compound (I))

A crystal of the salt of compound (I) may be produced by the above-mentioned methods for producing a salt of the compound (I), or by heat-dissolving a salt of the compound (I) in a solvent and crystallizing it through cooling with stirring.

[0035] A salt of the compound (I) to be used in the crystallization may be in any form: it may be a solvate, a hydrate, an anhydrate, an amorphous substance, a crystalline substance (including those consisting of a plurality of crystalline polymorphs) or a combination thereof.

[0036] Examples of the solvents to be used in the crystallization include alcohol solvents

such as methanol, ethanol, isopropanol and 1-propanol; acetonitrile; amide solvents such as N,N-dimethylformamide; ester solvents such as ethyl acetate; saturated hydrocarbon solvents such as hexane and heptane; ketone solvents such as acetone and 2-butanone; ether solvents such as t-butyl methyl ether or water. Furthermore, each of these solvents may be used alone, or two or more may be mixed and used.

[0037] The amount of the solvent to be used may be suitably selected, provided that the lower limit is the amount with which the free form of compound (I) or the salt thereof is dissolved by heating or the suspension can be stirred, and that the upper limit is the amount with which the yield of the crystal is not significantly reduced.

[0038] A seed crystal (e.g., the crystal of the desired salt of compound (I)) may be added or may not be added during the crystallization. The temperature at which the seed crystal is added is not particularly limited, but is preferably 0 to 80°C.

[0039] As the temperature to be employed when the salt of compound (I) is dissolved by heating, that at which compound (I) dissolves may be suitably selected depending on the solvent, but it is preferably within the range between the temperature at which the recrystallization solvent starts to reflux and 50°C, and more preferably 65 to 55°C.

[0040] Cooling during the crystallization could give substances containing different forms of crystals (polymorphism) in the case of rapid cooling. It is therefore desirable to perform the cooling while controlling the cooling rate as appropriate based on the consideration of its effect on the quality, grain size and the like of the crystal. Preferred is, for example, cooling at a cooling rate of 40 to 5°C/hour. More preferred is cooling at a cooling rate of, for example, 25 to 5°C/hour.

[0041] Furthermore, the final crystallization temperature may be selected suitably for the yield, quality and the like of the crystal, but is preferably 30 to -25°C.

[0042] The target crystal can be obtained by isolating the formed crystal through a conventional filtration procedure, washing the filtered-off crystal with a solvent if necessary, and further drying it. As the solvent to be used for washing the crystal, the same solvent as in the crystallization can be used. Furthermore, each of these solvents may be used alone, or two or more may be mixed and used. Preferably, it is, for example, acetone, 2-butanone, ethyl acetate, t-butyl methyl ether, hexane or a mixed solvent of hexane/2-butanone.

[0043] The crystal isolated through the filtration procedure may be dried appropriately by leaving it in air or under nitrogen flow, or by heating.

[0044] As the drying time, the time until the amount of residual solvent becomes less than the predefined amount may be selected as appropriate depending on the amount of production, the drying apparatus, the drying temperature and the like. Furthermore, drying may be performed under airflow or under reduced pressure. The degree of pressure reduction may be selected as appropriate depending on the amount of

production, the drying apparatus, the drying temperature and the like. The obtained crystal may be left in air as required after drying.

[0045] A pharmaceutical composition of the present invention could be prepared by mixing pharmaceutically acceptable additives with the salt of compound (I) or the crystal thereof. A pharmaceutical composition of the present invention could be prepared according to the known method such as a method described in the general rules for preparations of the Japanese Pharmacopoeia 17th edition.

[0046] A pharmaceutical composition of the present invention could be administered to patients appropriately depending on the dosage form.

[0047] A pharmaceutical composition of the present invention has usability as a therapeutic agent for treating cancers since the salt of compound (I) or the crystal thereof can potently suppress the growth of both wild-type (WT) and ER α -mutant positive tumors. Examples of cancers include breast cancer, uterine endometrial, ovarian carcinoma, sarcoma, thyroid carcinoma, prostate, lung adenocarcinoma, and hepatocellular carcinoma. Preferred example of cancers includes breast cancer. More preferred example of cancers includes ER-positive breast cancer.

[0048] The dosage of the salt of compound (I) or the crystal thereof varies depending on the extent of the symptom, age, gender, body weight, dosage form, the type of the salt, the specific type of the disease and the like. In the case of adults, typically, about 30 μ g to 10 g, preferably 100 μ g to 5 g, and more preferably 100 μ g to 1 g per day is orally administered, or about 30 μ g to 1 g, preferably 100 μ g to 500 mg, and more preferably 100 μ g to 300 mg per day is administered by injection, in each case, in a single dose or in divided doses.

Example

[0049] Hereinafter, the present invention will be described in detail with the production examples and examples. However, the present invention is not intended to be limited by these examples.

[0050] The following abbreviations may be used herein:

ACN: Acetonitrile

Boc: tert-Butyloxycarbonyl

CAN: Ceric ammonium nitrate

Conc.: concentrated

Cs₂CO₃: Cesium carbonate

DABCO: 1, 4-Diazabicyclo[2.2.2]octane

DCM: Dichloromethane

DHP: Dihydropyran

DIPEA: N, N-diisopropylethylamine, Hunig's base

DMA: Dimethylacetamide

DMF: Dimethylformamide
DMSO: Dimethylsulfoxide
DPEphos: (Oxydi-2, 1-phenylene)bis(diphenylphosphine)
EDCI.HCl: N-(3-Dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride
EtOH: Ethanol
EtOAc: Ethyl acetate
Et₃N: Triethylamine
Ex.: Example
h: Hours
HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HCl: Hydrochloric acid
HMPA: Hexamethylphosphoramide
HPLC: High-performance liquid chromatography
H₂SO₄: Sulfuric acid
IPA: Isopropyl alcohol
K₂CO₃: Potassium carbonate
KOH: Potassium hydroxide
LCMS: Liquid chromatography - mass spectrometry
MeOH: Methanol
Na₂CO₃: Sodium carbonate
NBS: n-Bromosuccinimide
nBuLi: n-Butyllithium
NH₄Cl: Ammonium chloride
NH₄OH: Ammonium hydroxide
NMR: nuclear magnetic resonance
on or o.n.: overnight
Pd/C: Palladium (0) on carbon
Pd₂(dba)₃: Tris(dibenzylideneacetone)dipalladium(0)
PPTS: Pyridinium p-toluenesulfonate
PTSA: p-Toluenesulfonic acid
RT or r.t.: room temperature
TBAF: Tetrabutylammonium fluoride
TEA: Triethylamine
TFA: Trifluoroacetic acid
THF: Tetrahydrofuran
TLC: Thin-layer chromatography
Pt/C: Platinum (0) on carbon

¹H NMR: proton nuclear magnetic resonance

The coupling constant is recorded in hertz (Hz). The abbreviations of splitting patterns are as follows:

s: singlet, d: doublet, t: triplet, q: quartet, m: multiplex, bs: broad singlet, br s: broad singlet, dd: doublet of doublets, dt: doublet of triplets, br d: broad doublet, br t: broad triplet

Unless indicated otherwise, ¹H NMR spectra were taken on a Bruker 300 MHz or 400 MHz NMR.

[0051] Powder X-ray diffractometry

The powder X-ray diffractometry of the crystal obtained by the method described in the following Examples was analyzed under the following measurement conditions.

[0052] Measurement conditions

Apparatus: RINT TTR-III (Rigaku)

Sample pan: aluminum

X-ray: Cu K alpha

Detection: scintillation counter

Tube voltage: 50 kV

Tube current: 300 mA

Slit: divergence slit 0.5 mm (Height limiting slit 2 mm), scattering slit open, receiving slit open

Scan speed: 5°/minute

Step size: $2\theta = 0.02^\circ$

Scan range: $2\theta = 3^\circ$ to 35°

[0053] Solid state ¹³C NMR spectroscopy

The solid state ¹³C NMR spectrum of the crystal obtained by the method described in the following Examples was measured under the following measurement conditions

[0054] Measurement conditions

Apparatus: AVANCE400MHz (Bruker)

Measurement temperature: room temperature (23°C)

Reference material: glycine (external standard: 176.03 ppm)

Measured nucleus: ¹³C (100.6248425 MHz)

Number of transients: 5000

Pulse repetition time: 4 seconds

Contact time: 1 m second

Rotational speed: 5000 Hz

Pulse mode: TOSS measurement

[0055] Hygroscopicity

The crystal obtained by the method described in the following Examples was

weighed into a sampling cup and then the sampling cup was placed inside an isothermal chamber at 25°C. The relative humidity (RH) was controlled from 0% to 95% using a gravimetric vapor sorption system and the weight change of the sample at each stage was measured under the condition described below.

[0056] Measurement conditions

Sample temperature: 25°C

First stage RH: 0%

Maximum stage RH: 95%

Step number: 39 (0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 5, 0)

Equilibrium criterion: 0.002 wt% in 1 minute

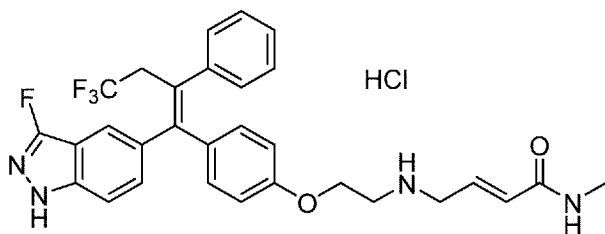
Max equilibrium time: 360 minutes

[0057] Production Example 1

Preparation of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (compound (I))

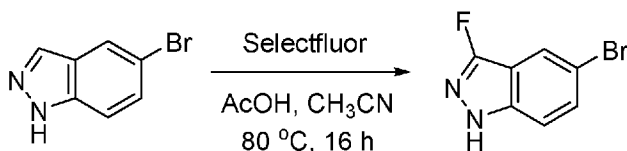
[Chem.47]



[0058] Production Example 1a

Synthesis of 5-bromo-3-fluoro-1H-indazole

[Chem.48]



Into a 5-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-bromo-1H-indazole (200 g, 1.0204mol, 1.00 equiv), CH₃CN (3.5L), acetic acid (120 mL), and selectfluor (544 g, 1.5367mol, 1.51 equiv). The resulting solution was stirred at 80 °C until completion. The reaction progress was monitored by LCMS. The resulting solution was diluted with 8 L of ethyl acetate and washed with 3x4000 mL of H₂O. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0:100-15:85). The collected fractions were combined and concentrated under vacuum to deliver the title

compound in 72 g (33%) as a yellow solid.

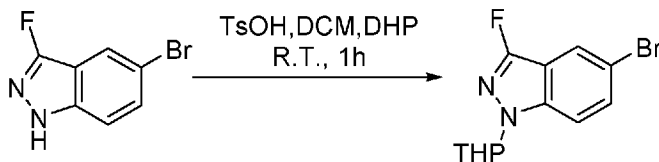
¹H NMR (400 MHz, DMSO-d₆) δ 12.77 (s, 1H), 8.03-7.90 (m, 1H), 7.59-7.48 (m, 2H).

LCMS: 215 [M+H]⁺.

[0059] Production Example 1b

Synthesis of 5-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[Chem.49]



Into a 2-L 3-necked round-bottom flask was placed 5-bromo-3-fluoro-1H-indazole (70 g, 325.55 mmol, 1.00 equiv), DCM (700 mL), and TsOH (5.6 g, 32.52 mmol, 0.10 equiv). This was followed by the drop-wise addition of DHP (82.4 g, 979.55 mmol, 3.01 equiv) while stirring at 0 °C. The resulting solution was stirred at 0 °C until completion. The reaction was monitored by LCMS. The resulting mixture was washed with 2x500 mL of H₂O, and the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0:100-10:90). The collected fractions were combined and concentrated under vacuum to deliver the title compound in 96.3 g (99%) as yellow oil.

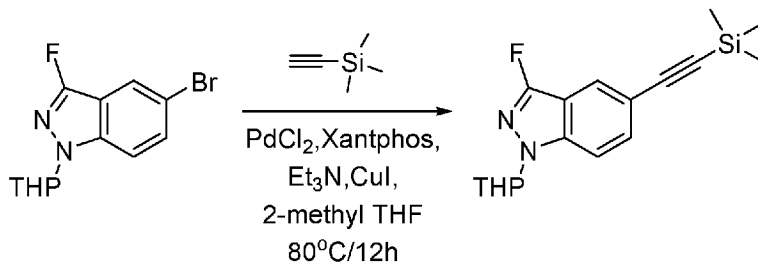
¹H NMR (300 MHz, DMSO-d₆) δ 8.02 (d, J = 1.8 Hz, 1H), 7.78-7.74 (m, 1H), 7.67-7.63 (m, 1H), 5.88-5.71 (m, 1H), 3.95-3.79 (m, 1H), 3.75-3.71 (m, 1H), 2.31-2.13 (m, 1H), 2.11-1.86 (m, 2H), 1.74-1.70 (m, 1H), 1.58-1.50 (m, 2H). LCMS: 299 [M+H]⁺.

[0060] Production Example 1c

Synthesis of

3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-((trimethylsilyl)ethynyl)-1H-indazole

[Chem.50]



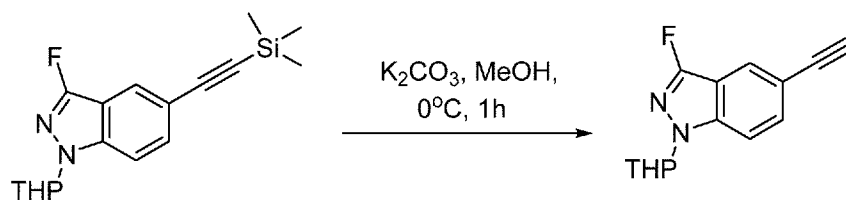
Into a 2-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-bromo-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (94.3 g, 315.24 mmol, 1.00 equiv), 2-Methyl THF (950 mL), TEA (95.6 g, 944.76 mmol, 3.00 equiv), ethynyltrimethylsilane (154.5 g, 1.57 mol, 4.99 equiv), PdCl₂ (5.6 g, 31.64

mmol, 0.10 equiv), Xantphos (36.5 g, 63.08 mmol, 0.20 equiv), and CuI (12 g, 63.01mmol, 0.20 equiv). The resulting solution was stirred at 80 °C until completion. The reaction progress was monitored by LCMS. The resulting solution was diluted with 1 L of 2-Methyl THF and was washed with 1x1 L of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum to deliver the title compound in 134 g (crude) as a black oil. The crude product was used directly to the next step.

[0061] Production Example 1d

Synthesis of 5-ethynyl-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[Chem.51]



Into a 2-L round-bottom flask was placed 3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-((trimethylsilyl)ethynyl)-1H-indazole (131.3 g, 414.92mmol, 1.00 equiv), methanol (950 mL), and potassium carbonate (114.7 g, 829.90mmol, 2.00 equiv). The resulting solution was stirred at 0 °C until completion. The reaction progress was monitored by LCMS. The resulting mixture was concentrated under vacuum and then diluted with 1 L of H₂O. The solution was extracted with 3x1 L of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate, and concentrated under vacuum to deliver the title compound in 77 g (76%) as black oil.

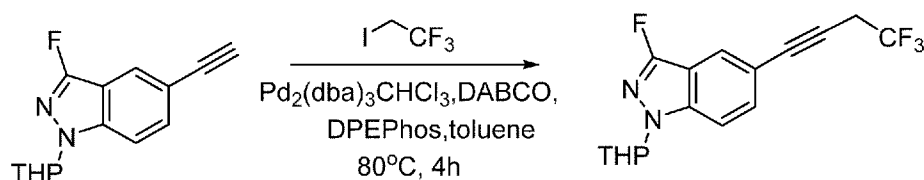
LCMS: 245 [M+H]⁺.

[0062] Production Example 1e

Synthesis of

3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,4-trifluorobut-1-yn-1-yl)-1H-indazole

[Chem.52]



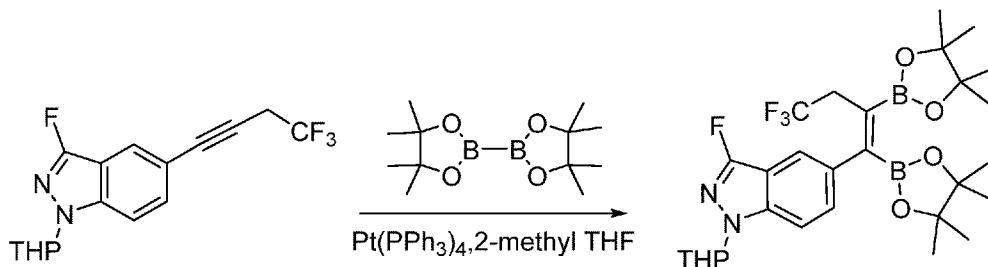
Into a 2-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 5-ethynyl-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (72 g, 294.76mmol, 1.00 equiv), toluene (900 mL), 1,1,1-trifluoro-2-iodoethane (186 g, 885.98mmol, 3.01 equiv), DABCO (99 g, 883.93mmol, 3.00equiv), DPEPhos (31.8 g, 59.00mmol, 0.20 equiv), and Pd₂(dba)₃CHCl₃ (15.3 g, 14.78mmol, 0.05 equiv). The

resulting solution was stirred at 80 °C until completion. The reaction progress was monitored by LCMS. The resulting solution was diluted with 1 L of H₂O and extracted with 2x1 L of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0:100-15:85). The collected fractions were combined and concentrated under vacuum to deliver the title compound in 45 g (47%) as a yellow solid.

¹H NMR (300 MHz, DMSO-d₆) δ 7.89 (d, J = 1.4 Hz, 1H), 7.81-7.77 (m, 1H), 7.58-7.54 (m, 1H), 5.84-5.80 (m, 1H), 3.94-3.60 (m, 4H), 2.35-2.12 (m, 1H), 2.06-1.89 (m, 2H), 1.86-1.64 (m, 1H), 1.58-1.54 (m, 2H). LCMS: 327 [M+H]⁺

[0063] Production Example 1f

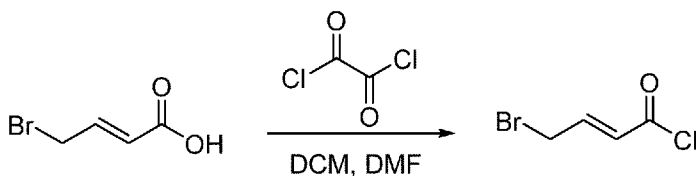
Synthesis of
(Z)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,4-trifluoro-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)-1H-indazole
 [Chem.53]



Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (57 g, 219.74 mmol, 2.00 equiv), 3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,4-trifluorobut-1-en-1-yl)-1H-indazole (36 g, 110.34 mmol, 1.00 equiv), Pt(PPh₃)₄ (6.84 g, 0.05 equiv), and 2-Methyl THF (450 mL). The solution was stirred at 90 °C until completion to deliver the title compound (crude) that was used directly to the next step.

[0064] Production Example 1g

Synthesis of (E)-4-bromobut-2-enoyl chloride
 [Chem.54]



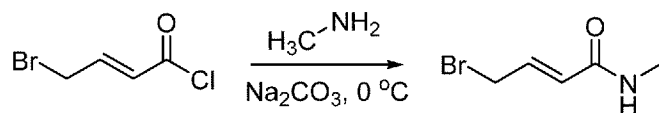
Into a 500-mL round-bottom flask, was placed (E)-4-bromobut-2-enoic acid (10 g, 60.61mmol, 1.00 equiv), DCM (200 mL), and N, N-dimethylformamide (0.5 mL).

Oxalyl dichloride (7.7 g, 1.00 equiv) was added at 0 °C in dropwise. The resulting solution was stirred until completion at 0 °C. The mixture was used directly to the next step without isolation of the product.

[0065] Production Example 1h

Synthesis of (E)-4-bromo-N-methylbut-2-enamide

[Chem.55]



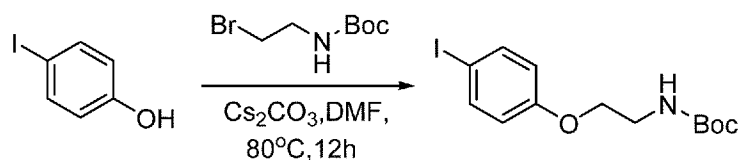
Into a 250-mL round-bottom flask was placed $\text{CH}_3\text{NH}_2\cdot\text{HCl}$ (1.005g, 1.00 equiv), sodium carbonate (3.18 g, 30.00 mmol, 2.00 equiv), and DCM (100 mL). Then, (E)-4-bromobut-2-enoyl chloride (15.00 mmol, 1.00 equiv) was added dropwise at 0 °C. The resulting solution was stirred at 0 °C in a water/ice bath until completion. The mixture was then washed with 2x100 mL of water. The organic layer was concentrated under vacuum to deliver the title compound in 3 g (62%) as a yellow solid.

LCMS: 178, 180[M+H]⁺.

[0066] Production Example 1i

Synthesis of tert-butyl (2-(4-iodophenoxy)ethyl)carbamate

[Chem.56]



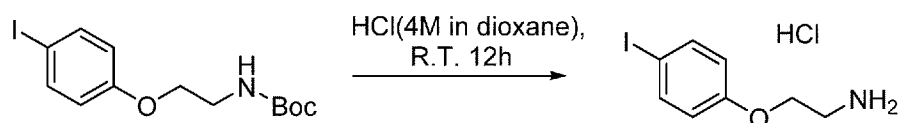
To a stirred solution of 4-iodophenol (50 g, 0.227 mol) in DMF (750 mL) was added Cs_2CO_3 (493 g, 1.363 mol). The mixture was stirred for 30 min at room temperature and then tert-butyl (2-bromoethyl)carbamate (71.27 g, 0.318 mol) was added. The solution was stirred at 80 °C until completion. The reaction mixture was then poured onto ice water, solid separated was filtered and dried under reduced pressure to deliver the title compound in 80 g (97%) as an off-white solid.

LCMS: 264 [M-Boc+H]⁺.

[0067] Production Example 1j

Synthesis of 2-(4-iodophenoxy)ethan-1-amine hydrochloride

[Chem.57]



To a stirred solution of tert-butyl (2-(4-iodophenoxy)ethyl)carbamate (25 g, 68.6 mmol) in dioxane (50 mL) at 0 °C was added 4M HCl in dioxane (250 mL). The

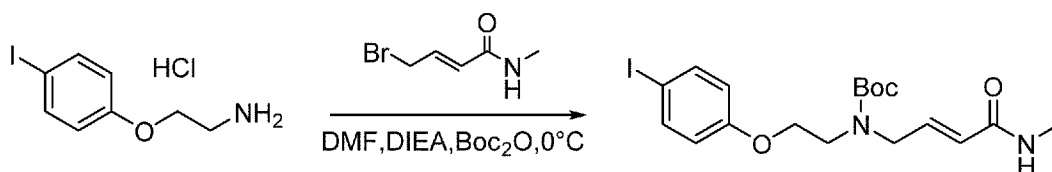
reaction mixture was stirred at room temperature until completion. The reaction mixture was then concentrated under reduced pressure to deliver the title compound in 16 g (88%) as crude material, used in next step without further purification.

[0068] Production Example 1k

Synthesis of tert-butyl

(E)-2-(4-iodophenoxy)ethyl(4-(methylamino)-4-oxobut-2-enyl)carbamate

[Chem.58]



Into a 40-mL vial was placed 2-(4-iodophenoxy)ethan-1-amine hydrochloride (2.26 g, 7.57 mmol, 1.00 equiv), DIEA (1.9 g, 14.70 mmol, 2.00 equiv), and N,N-dimethylformamide (20 mL). (E)-4-bromo-N-methylbut-2-enamide (1.08 g, 6.07 mmol, 0.80 equiv) was then added to the solution at 0 °C, which was then stirred at R.T. until completion. Boc₂O (2.62 g, 12 mmol) was then added and the resulting mixture was stirred at room temperature until completion. Upon completion by TLC, the reaction mixture was cooled to 0 °C, quenched with ice cold water (100 mL) and extracted with 3x250 mL of DCM. The combined organic extracts were washed with brine (250 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography over 100-200 mesh silica using 50-80% ethyl acetate in n-hexane as an eluent, then further purified with C18 column (MeOH/H₂O=7:3) to deliver the title compound in 690 mg (20%).

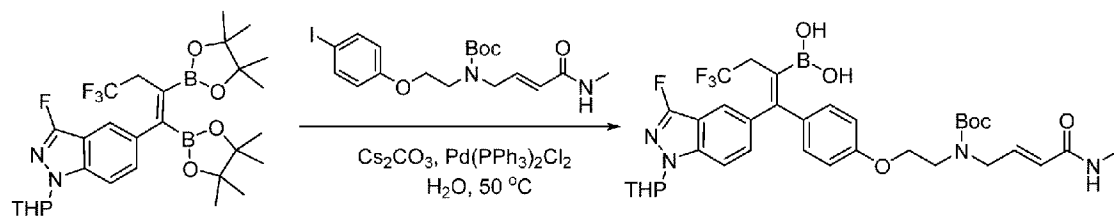
¹H NMR (400 MHz, DMSO-d₆) δ 7.97-7.91 (m, 1H), 7.63-7.55 (m, 2H), 6.84-6.76 (m, 2H), 6.52 (d, J = 12.9 Hz, 1H), 5.89 (d, J = 15.5 Hz, 1H), 4.08-4.02 (m, 2H), 4.01-3.94 (m, 2H), 3.49 (d, J = 4.8 Hz, 2H), 2.63 (d, J = 4.6 Hz, 3H), 1.37 (s, 9H).
LCMS: 461 [M+H]⁺.

[0069] Production Example 1l

Synthesis of

((Z)-1-(4-(2-(((tert-butoxycarbonyl)((E)-4-(methylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)but-1-en-2-yl)boronic acid

[Chem.59]



Into a 1000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed

(Z)-3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-5-(4,4,4-trifluoro-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-1-en-1-yl)-1H-indazole (53 g, 91.94 mmol, 1.00 equiv), 2-Methyl THF (500 mL), tert-butyl

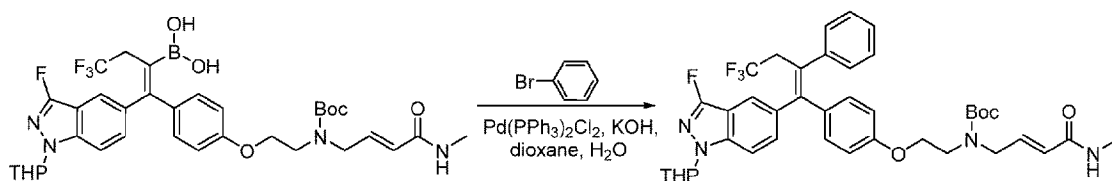
(E)-(2-(4-iodophenoxy)ethyl)(4-(methylamino)-4-oxobut-2-en-1-yl)carbamate (42.3 g, 91.90 mmol, 1.00 equiv), Cs₂CO₃ (90 g, 276.23 mmol, 3.00 equiv), Pd(PPh₃)₂Cl₂ (6.46 g, 9.20 mmol, 0.10 equiv), and water (100 mL) were added. The resulting solution was stirred at 50 °C until completion. The reaction progress was monitored by LCMS. The solution was diluted with 500 mL of H₂O, extracted with 2x600 mL of ethyl acetate, then the organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). The collected fractions were combined and concentrated under vacuum to deliver the title compound in 36 g (54%) as yellow oil.

[0070] Production Example 1m

Synthesis of tert-butyl

((E)-4-(methylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate

[Chem.60]

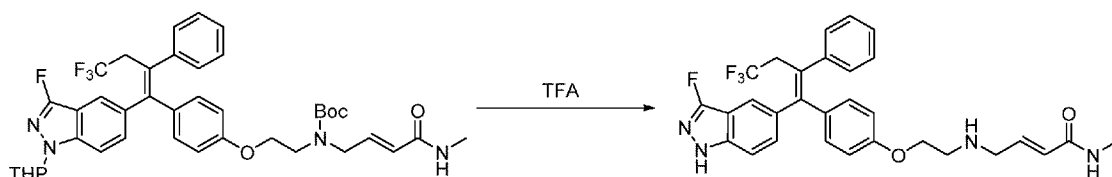


Into a 1-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed

((Z)-1-(4-(2-((tert-butoxycarbonyl)((E)-4-(methylamino)-4-oxobut-2-en-1-yl)amino)ethoxy)phenyl)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)but-1-en-2-yl)boronic acid (36 g, 51.10 mmol, 1.00 equiv), Pd(PPh₃)₂Cl₂ (3.5 g, 4.99 mmol, 0.10 equiv), potassium hydroxide (8.4 g, 149.71 mmol, 3.00 equiv), dioxane (200 mL), water (40 mL), and bromobenzene (8.4 g, 53.50 mmol, 1.00 equiv). The resulting solution was stirred at 80 °C until completion. The reaction progress was monitored by LCMS. The resulting solution was diluted with 200 ml of H₂O, extracted with 3x500 ml of ethyl acetate, then the organic layers combined, washed with brine (200 ml) and dried over anhydrous sodium sulfate. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3). The collected fractions were combined and concentrated under vacuum to deliver the title compound in 16 g (42%) as a yellow solid.

[0071] Production Example 1n

Synthesis of
(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (compound (I))
 [Chem.61]



Into a 250-mL round-bottom flask was placed tert-butyl ((E)-4-(methylamino)-4-oxobut-2-en-1-yl)(2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)carbamate (16 g, 21.72 mmol, 1.00 equiv) and TFA (100 mL). The resulting solution was stirred at 25 °C until completion. The reaction progress was monitored by LCMS. The resulting solution was concentrated under vacuum and the crude product was purified by Prep-HPLC with the following conditions: Column: X-Bridge Prep OBD C18 Column 30×150mm 5um; Mobile Phase A: Water(10mmol/L NH₄HCO₃), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 55% B in 60 min; 254,220 nm, to deliver the title compound as a free base in 4.05 g as a yellow solid.

¹H NMR (400 MHz, Methanol-d₄) δ 7.60 (s, 1H), 7.52-7.42 (m, 1H), 7.25-7.11 (m, 6H), 6.83-6.81 (m, 2H), 6.78-6.71 (m, 1H), 6.63-6.61 (m, 2H), 6.05-6.01 (m, 1H), 3.97-3.94 (t, J = 5.3 Hz, 2H), 3.41-3.33 (m, 4H), 2.98-2.88 (t, J = 5.2 Hz, 2H), 2.76 (s, 3H).

The solid was then dissolved in 100 mL CH₃CN and acidified with 8.07 mL HCl (1N) (1 mL 12N HCl(aq) dissolved in 11 mL CH₃CN) at 0 °C, and stirred for 30 min at R.T., then evaporated at 30 °C to remove the excess HCl. Then the product was dissolved in 150 mL H₂O and lyophilized for 48h to deliver the title compound in 4.4 g, 0.96% overall yield, as a yellow solid.

¹H NMR (400 MHz, Methanol-d₄) δ 7.59 (s, 1H), 7.46-7.44 (m, 1H), 7.27 (m, 1H) 7.25-7.12 (m, 5H), 6.91-6.87 (m, 2H), 6.72-6.65 (m, 3H), 6.30-6.26 (m, 1H), 4.16-4.14 (t, J = 4.9 Hz, 2H), 3.86-3.84 (m, 2H), 3.42-3.34 (m, 4H), 2.79 (s, 3H). LCMS: 553 [M+H]⁺.

[0072] Example 1

Preparation of crystal of
(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide hydrochloride

To a solution of
 (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1

-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.01 mg) in acetonitrile (3 mL) was added a solution of hydrochloric acid (62.1 μ L, 1eq) in acetonitrile (2 mL). Then, 3 mL of acetonitrile was added to the mixture and it was stirred at 50 °C for an hour, at room temperature overnight, at 50 °C for an hour, at room temperature for 6 hours, at 50 °C for an hour. Then, 2 mL of acetonitrile was added to the mixture again and it was stirred at room temperature for 4 days. The obtained solid was filtered off, washed with acetonitrile and dried for 10 days to give the titled crystal (358 mg, 84%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 1 are shown in Figures 1, 12 and 23, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.64 (d, J=4.6 Hz, 3H), 3.22 (t, J=4.6 Hz, 2H), 3.44 (q, J=10.7 Hz, 2H), 3.74 (d, J=6.5 Hz, 2H), 4.10 (t, J=4.7 Hz, 2H), 6.16 (d, J=15.4 Hz, 1H), 6.57 (dt, J=15.4, 6.8 Hz, 1H), 6.68 (d, J=8.9 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 7.15 (dddd, J=6.9, 6.9, 1.3, 1.3 Hz, 1H), 7.17-7.26 (m, 5H), 7.52 (dd, J=8.7, 1.5 Hz, 1H), 7.57 (br s, 1H), 8.15 (q, J=4.6 Hz, 1H), 9.09 (br s, 2H), 12.69 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 1 are shown below.

^{13}C NMR (100MHz, solid state): δ 25.8, 45.9, 117.3, 128.5, 133.9, 139.0, 141.4, 144.5, 156.8, 165.8.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 12.2° , 16.8° , 18.2° , 19.7° , 21.3° , 21.8° , 23.3° , 24.5° , 25.5° , 29.4° .

[0073] Example 2

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide hydrobromide

To a solution of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.44 mg) in acetonitrile (2 mL) was added a solution of hydrobromic acid (119.6 μ L, 1eq) in acetonitrile (2 mL). Then, 5 mL of tert-butyl methyl ether was added to the solution and the mixture was stirred at room temperature for 4 days. The obtained solid was filtered off, washed with tert-butyl methyl ether and dried for 10 days to give the titled crystal (322 mg, 70%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 2 are shown in Figures 2, 13 and 24, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.64 (d, J=4.7 Hz, 3H), 3.25 (t, J=4.6 Hz, 2H), 3.44 (q, J=10.8 Hz, 2H), 3.77 (d, J=6.7 Hz, 2H), 4.08 (t, J=4.7 Hz, 2H),

6.16 (d, J=15.5 Hz, 1H), 6.55 (dt, J=15.4, 6.8 Hz, 1H), 6.69 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 7.15 (dddd, J=6.9, 6.9, 1.5, 1.5 Hz, 1H), 7.18-7.25 (m, 5H), 7.52 (dd, J=8.8, 1.5 Hz, 1H), 7.56 (br s, 1H), 8.13 (q, J=4.6 Hz, 1H), 8.83 (br s, 2H), 12.66 (s, 1H),

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 2 are shown below.

^{13}C NMR (100MHz, solid state): δ 26.4, 45.2, 47.3, 116.9, 129.3, 139.4, 141.6, 144.2, 156.7, 165.2.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 6.1° , 12.0° , 16.6° , 18.4° , 19.7° , 21.6° , 22.9° , 24.1° , 25.6° , 29.8° .

[0074] Example 3

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide phosphate

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.25 mg) in acetonitrile (4 mL) was added a solution of phosphoric acid (49.4 μL , 1eq) in acetonitrile (1 mL). The mixture was stirred at 50°C for 3 hours and at room temperature overnight. Again, it was stirred at 50°C for an hour, 3 mL of acetonitrile was added to the mixture and it was stirred at room temperature for 3 days. The obtained solid was filtered off, washed with acetonitrile and dried for 10 days to give the titled crystal (416 mg, 88%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 3 are shown in Figures 3, 14 and 25, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.61 (d, J=4.7 Hz, 3H), 2.87 (m, 2H), 3.39 (m, 2H), 3.43 (q, J=10.8 Hz, 2H), 3.92 (t, J=5.1 Hz, 2H), 6.01 (d, J=15.4 Hz, 1H), 6.56 (dt, J=15.4, 5.7 Hz, 1H), 6.64 (d, J=8.7 Hz, 2H), 6.81 (d, J=8.7 Hz, 2H), 7.14 (m, 1H), 7.17-7.25 (m, 5H), 7.52 (dd, J=8.7, 1.2 Hz, 1H), 7.56 (br s, 1H), 7.92 (m, 1H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 3 are shown below.

^{13}C NMR (100MHz, solid state): δ 26.9, 45.5, 49.2, 126.6, 135.3, 138.3, 140.9, 145.5, 146.6, 169.8.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 6.5° , 13.5° , 14.0° , 16.7° , 19.9° , 20.4° , 21.6° , 23.2° .

[0075] Example 4

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide sulfate

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.08 mg) in acetonitrile (2 mL) was added a solution of sulfuric acid (40.6 μ L, 1eq) in acetonitrile (2 mL). Then, 1 mL of acetonitrile was added to the solution, the mixture was stirred at 50 °C for an hour and at room temperature overnight. Again, it was stirred at 50 °C for 2 hours, 3 mL of acetonitrile was added to the mixture and it was stirred at room temperature for 3 days. The obtained solid was filtered off, and dried for 10 days to give the titled crystal (428 mg, 91%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 4 are shown in Figures 4, 15 and 26, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.65 (d, $J=4.7$ Hz, 3H), 3.24 (t, $J=4.7$ Hz, 2H), 3.44 (q, $J=10.8$ Hz, 2H), 3.76 (d, $J=6.6$ Hz, 2H), 4.07 (t, $J=4.7$ Hz, 2H), 6.15 (d, $J=15.5$ Hz, 1H), 6.55 (dt, $J=15.5$, 6.8 Hz, 1H), 6.69 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.8$ Hz, 2H), 7.15 (dddd, $J=7.1$, 7.1, 1.5, 1.5 Hz, 1H), 7.18-7.26 (m, 5H), 7.52 (dd, $J=8.8$, 1.3 Hz, 1H), 7.56 (br s, 1H), 8.11 (q, $J=4.6$ Hz, 1H), 8.83 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 4 are shown below.

^{13}C NMR (100MHz, solid state): δ 25.0, 47.8, 49.9, 113.6, 117.8, 124.7, 141.3, 146.5, 157.4, 165.0.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 3.7° , 7.6° , 11.3° , 13.0° , 16.9° , 19.0° , 19.8° .

[0076] Example 5

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide benzenesulfonate

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.35 mg) in acetonitrile (2 mL) was added a solution of benzenesulfonic acid monohydrate (100 mg/mL) in acetonitrile (1.3 mL). Then, the mixture was stirred at 50 °C for 30 minutes, 1.5 mL of tert-butyl methyl ether was added, and stirred at room temperature overnight. Again, 1.5 mL of tert-butyl methyl ether was added to the mixture, it was stirred at 50 °C for an hour and at room temperature overnight. The obtained solid was filtered off, washed with tert-butyl methyl ether, and dried for 9 days to give the titled crystal (461 mg, 90%). A

powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 5 are shown in Figures 5, 16 and 27, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.64 (d, $J=4.7$ Hz, 3H), 3.24 (t, $J=4.4$ Hz, 2H), 3.44 (q, $J=10.8$ Hz, 2H), 3.76 (d, $J=6.6$ Hz, 2H), 4.07 (t, $J=4.7$ Hz, 2H), 6.15 (d, $J=15.5$ Hz, 1H), 6.55 (dt, $J=15.5$, 6.8 Hz, 1H), 6.68 (d, $J=8.7$ Hz, 2H), 6.85 (d, $J=8.7$ Hz, 2H), 7.15 (m, 1H), 7.17-7.25 (m, 5H), 7.26-7.33 (m, 3H), 7.52 (dd, $J=8.7$, 1.4 Hz, 1H), 7.56 (br s, 1H), 7.59 (dd, $J=7.9$, 1.8 Hz, 2H), 8.11 (q, $J=4.6$ Hz, 1H), 8.74 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 5 are shown below.

^{13}C NMR (100MHz, solid state): δ 27.6, 44.9, 47.1, 116.8, 132.3, 136.1, 156.7, 164.4.
Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 5.5° , 9.8° , 10.9° , 17.6° , 19.2° , 19.9° , 21.9° , 24.1° , 26.5° .

[0077] Example 6

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide p-toluenesulfonate

To a solution of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.05 mg) in acetonitrile (2 mL) was added a solution of p-toluenesulfonic acid monohydrate (100 mg/mL) in acetonitrile (1.4 mL). Then, 5 mL of acetonitrile and 2 mL of tert-butyl methyl ether were added the mixture, it was stirred at 50°C for an hour. Then, 2 mL of tert-butyl methyl ether was added to the mixture again, it was stirred at room temperature 3 days, at 50°C for an hour and at room temperature overnight. The obtained solid was filtered off, washed with tert-butyl methyl ether, and dried for 9 days to give the titled crystal (448 mg, 85%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 6 are shown in Figures 6, 17 and 28, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.27 (s, 3H), 2.65 (d, $J=4.7$ Hz, 3H), 3.26 (br s, 2H), 3.44 (q, $J=10.8$ Hz, 2H), 3.77 (br s, 2H), 4.07 (t, $J=4.8$ Hz, 2H), 6.16 (d, $J=15.4$ Hz, 1H), 6.55 (dt, $J=15.5$, 6.8 Hz, 1H), 6.68 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.9$ Hz, 2H), 7.10 (d, $J=7.8$ Hz, 2H), 7.15 (dddd, $J=7.0$, 7.0, 1.6, 1.6 Hz, 1H), 7.18-7.25 (m, 5H), 7.46 (d, $J=8.1$ Hz, 2H), 7.52 (dd, $J=8.8$, 1.5 Hz, 1H), 7.56 (br s, 1H), 8.12 (q, $J=4.5$ Hz, 1H), 8.83 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 6 are shown below.

^{13}C NMR (100MHz, solid state): δ 19.2, 27.5, 46.4, 112.3, 117.0, 125.9, 140.7, 144.2, 156.4, 166.9.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 8.9° , 11.5° , 12.5° , 16.2° , 17.5° , 20.0° , 20.9° , 21.4° , 22.1° , 23.4° .

[0078] Example 7

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide succinate

To a solution of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.23 mg) in tert-butyl methyl ether (2 mL) was added a solution of succinic acid (86 mg, 1eq) in acetonitrile (2 mL). Then, 4 mL of tert-butyl methyl ether was added to the mixture, it was stirred at 50°C for 30 minutes, at room temperature overnight, and at 50°C for 30 minutes. After cooling down to room temperature, the obtained solid was filtered off, and dried for 9 days to give the titled crystal (388 mg, 80%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 7 are shown in Figures 7, 18 and 29, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.38 (s, 4H), 2.61 (d, $J=4.7$ Hz, 3H), 2.82 (t, $J=5.5$ Hz, 2H), 3.33 (d, $J=4.6$ Hz, 2H), 3.43 (q, $J=10.8$ Hz, 2H), 3.89 (t, $J=5.6$ Hz, 2H), 5.99 (d, $J=15.5$ Hz, 1H), 6.56 (dt, $J=15.4$, 5.6 Hz, 1H), 6.63 (d, $J=8.9$ Hz, 2H), 6.80 (d, $J=8.8$ Hz, 2H), 7.14 (dddd, $J=6.9$, 6.9, 1.6, 1.6 Hz, 1H), 7.17-7.25 (m, 5H), 7.51 (dd, $J=8.7$, 1.5 Hz, 1H), 7.56 (br s, 1H), 7.87 (q, $J=4.5$ Hz, 1H), 12.65 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 7 are shown below.

^{13}C NMR (100MHz, solid state): δ 26.0, 35.1, 116.0, 125.3, 139.2, 145.8, 156.1, 165.5, 175.0, 181.3.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 5.2° , 10.4° , 12.9° , 14.8° , 17.0° , 17.5° , 18.2° , 19.1° , 21.8° , 23.6° .

[0079] Example 8

Preparation of crystal form A of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide maleate

To (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.08 mg) was added a solution of maleic acid (84 mg, 1eq) in acetonitrile (3 mL). Then, 6 mL of acetonitrile was added

the mixture, it was stirred at 50 °C for 30 minutes, at room temperature for 2 hours, at 50 °C for 30 minutes and at room temperature overnight. Again, 1 mL of acetonitrile was added to the mixture, it was stirred at 55 °C for 2 hours and room temperature overnight, at 55 °C for 3 hours and room temperature overnight, at 55 °C for 5 hours and room temperature overnight, at 55 °C for 2.5 hours and room temperature overnight, and at room temperature for 4 days. The obtained solid was filtered off, and dried overnight to give the titled crystal (353 mg, 73%). A powder X-ray diffraction pattern, a solid state ¹³C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 8 are shown in Figures 8, 19 and 30, respectively.

¹H NMR (600MHz, Bruker AVANCE, DMSO-d₆): δ 2.65 (d, J=4.7 Hz, 3H), 3.24 (t, J=4.7 Hz, 2H), 3.44 (q, J=10.9 Hz, 2H), 3.76 (d, J=6.6 Hz, 2H), 4.07 (t, J=4.7 Hz, 2H), 6.01 (s, 2H), 6.15 (d, J=15.5 Hz, 1H), 6.55 (dt, J=15.5, 6.7 Hz, 1H), 6.68 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.9 Hz, 2H), 7.15 (dddd, J=7.0, 7.0, 1.4, 1.4 Hz, 1H), 7.18-7.25 (m, 5H), 7.52 (dd, J=8.7, 1.6 Hz, 1H), 7.56 (br s, 1H), 8.11 (q, J=4.6 Hz, 1H), 8.74 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ¹³C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 8 are shown below.

¹³C NMR (100MHz, solid state): δ 43.4, 44.8, 47.8, 63.0, 66.0, 125.2, 133.8, 140.6, 145.0, 165.5.

Powder X-ray diffraction angle (2θ ± 0.2°): 5.4°, 11.6°, 13.3°, 14.3°, 16.8°, 18.9°, 20.2°, 21.6°.

[0080] Example 9

Preparation of crystal form B of
(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide maleate

To

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.31 mg) was added a solution of maleic acid (84 mg, 1eq) in acetone (2 mL). Then, 4 mL of acetone and 1 mL of heptane were added the mixture, it was stirred at room temperature overnight. The obtained solid was filtered off, and dried for 9 days to give the titled crystal (223 mg, 46%). A powder X-ray diffraction pattern, a solid state ¹³C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 9 are shown in Figures 9, 20 and 31, respectively.

¹H NMR (600MHz, Bruker AVANCE, DMSO-d₆): δ 2.65 (d, J=4.7 Hz, 3H), 3.24 (t, J=4.8 Hz, 2H), 3.44 (q, J=10.9 Hz, 2H), 3.76 (d, J=6.6 Hz, 2H), 4.07 (t, J=4.7 Hz, 2H), 6.01 (s, 2H), 6.15 (d, J=15.5 Hz, 1H), 6.55 (dt, J=15.5, 6.7 Hz, 1H), 6.68 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 7.15 (dddd, J=7.0, 7.0, 1.4, 1.4 Hz, 1H), 7.18-7.25 (m,

5H), 7.52 (dd, J=8.7, 1.5 Hz, 1H), 7.56 (br s, 1H), 8.11 (q, J=4.6 Hz, 1H), 8.75 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 9 are shown below.

^{13}C NMR (100MHz, solid state): δ 25.8, 48.8, 110.7, 115.7, 135.1, 136.6, 143.6, 156.3, 166.8, 172.6.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 10.4° , 15.2° , 19.4° , 20.8° , 22.2° , 23.7° , 25.7° , 28.6° .

[0081] Example 10

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide L-mandelate

To

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (400.17 mg) was added a solution of L-mandelic acid (110 mg, 1eq) in acetone (2 mL). Then, 6 mL of acetone and 4 mL of tert-butyl methyl ether were added to the mixture, it was stirred at 50°C for 30 minutes, at room temperature for 2 hours, at 50°C for 30 minutes and at room temperature overnight. Again, 2 mL of acetone was added to the mixture, it was stirred at room temperature overnight, at 50°C for 30 minutes and room temperature overnight, and at 50°C for 30 minutes and room temperature overnight. After adding 2 mL of acetone to the mixture, it was stirred at 40°C for 6 days, 0.12 mL of purified water was added, stirred at 40°C overnight, 0.36 mL of purified water was added again, stirred at 50°C for 6 hours and 40°C for 3 days. After cooling down to room temperature and reducing the solvent by nitrogen purging, the obtained solid was filtered off, and dried for a week to give the titled crystal (399 mg, 78%). A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph showing hygroscopicity for the crystal obtained in Example 10 are shown in Figures 10, 21 and 32, respectively.

^1H NMR (600MHz, Bruker AVANCE, DMSO- d_6): δ 2.61 (d, J=4.6 Hz, 3H), 2.85 (t, J=5.4 Hz, 2H), 3.36 (dd, J=5.6, 0.9 Hz, 2H), 3.43 (q, J=10.8 Hz, 2H), 3.90 (t, J=5.5 Hz, 2H), 4.88 (s, 1H), 6.00 (d, J=15.5 Hz, 1H), 6.56 (dt, J=15.5, 5.6 Hz, 1H), 6.63 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 7.14 (dddd, J=6.8, 6.8, 1.5, 1.5 Hz, 1H), 7.17-7.26 (m, 6H), 7.30 (dd, J=7.4, 7.4 Hz, 2H), 7.39 (d, J=7.2 Hz, 2H), 7.52 (dd, J=8.7, 1.5 Hz, 1H), 7.56 (br s, 1H), 7.89 (q, J=4.6 Hz, 1H), 12.66 (s, 1H).

Typical peaks in a solid state ^{13}C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 10 are shown below.

^{13}C NMR (100MHz, solid state): δ 62.9, 76.5, 116.2, 123.6, 128.1, 141.9, 146.3,

156.7, 164.6, 177.8.

Powder X-ray diffraction angle ($2\theta \pm 0.2^\circ$): 5.1° , 8.7° , 10.3° , 13.9° , 18.2° , 20.3° .

[0082] Example 11

Preparation of crystal of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide methanesulfonate

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (50.22 mg) in 2-butanone (1 mL) was added a solution of methanesulfonic acid (6.2 μ L, 1eq) in 2-butanone (1 mL). Then, the mixture was stirred at room temperature for 2 days.

One mL of the mixture in 2-butanone was transferred to another test tube, the solvent was removed by nitrogen purging. Then, 0.75 mL of acetone was added and the mixture in acetone was stirred at room temperature overnight (hereafter the above obtained mixture is referred to as Mixture 1).

The rest (1 mL) of the mixture in 2-butanone was stirred additionally overnight. The solvent was removed by nitrogen purging. Then, 0.75 mL of acetone was added and the mixture in acetone was stirred at room temperature for 4 days (hereafter the above obtained mixture is referred to as Mixture 2).

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (150.49 mg) in 2-butanone (2 mL) was added a solution of methanesulfonic acid (18.6 μ L, 1eq) in 2-butanone (2 mL). Then, the mixture was stirred at room temperature overnight. Then, the solvent was removed by nitrogen purging, 4 mL of acetone and the Mixture 1 were added, and the mixture was stirred at room temperature for 3 days. Again, the solvent was replaced by 4 mL of acetone and the mixture was stirred at room temperature overnight (hereafter the above obtained mixture is referred to as Mixture 3).

To a solution of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide (200.26 mg) in 2-butanone (2 mL) was added a solution of methanesulfonic acid (24.8 μ L, 1eq) in 2-butanone (2 mL). The mixture was stirred at room temperature for 3 days. Then, the solvent was removed by nitrogen purging, 5 mL of acetone was added, and the mixture was stirred at room temperature overnight. Two mL of acetone, the Mixture 2 and the Mixture 3 were added to the mixture and it was stirred at room temperature overnight. The obtained solid was filtered off, and dried for 2 days to give the titled crystal (260 mg, 55%).

A powder X-ray diffraction pattern, a solid state ^{13}C NMR spectrum and a graph

showing hygroscopicity for the crystal obtained in Example 11 are shown in Figures 11, 22 and 33, respectively.

¹H NMR (600MHz, Bruker AVANCE, DMSO-d₆): δ 2.29 (s, 3H), 2.65 (d, J=4.6 Hz, 3H), 3.26 (br s, 2H), 3.44 (q, J=10.8 Hz, 2H), 3.77 (br s, 2H), 4.08 (t, J=4.8 Hz, 2H), 6.16 (d, J=15.5 Hz, 1H), 6.55 (dt, J=15.4, 6.8 Hz, 1H), 6.69 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 7.15 (m, 1H), 7.18-7.25 (m, 5H), 7.53 (dd, J=8.7, 1.3 Hz, 1H), 7.56 (br s, 1H), 8.12 (q, J=4.6 Hz, 1H), 8.84 (br s, 2H), 12.66 (s, 1H).

Typical peaks in a solid state ¹³C NMR spectrum and typical diffraction peaks in a powder X-ray diffractometry for the crystal obtained in Example 11 are shown below.

¹³C NMR (100MHz, solid state): δ 24.8, 40.4, 47.2, 117.8, 133.9, 136.0, 140.4, 146.7, 158.3, 166.0.

Powder X-ray diffraction angle (2θ ± 0.2°): 7.5°, 12.1°, 12.7°, 17.1°, 18.9°, 19.7°, 20.9°, 21.8°, 25.6°.

[0083] The following test examples were carried out to examine the pharmacological effects of the compound (I).

[0084] (Test Example 1) Compounds that inhibit ERα^{WT/MUT} activity in vitro

[0085] Cell culture

MCF7 BUS cells (Coser, et al., (2003) PNAS 100 (24): 13994-13999) were maintained in Dulbecco's Modified Eagle Medium supplemented with 10% FBS, 4 mM L-glutamine and 1x non-essential amino acids. Lenti-X 293T cells (Clontech, Cat # 632180) were routinely cultured in Dulbecco's Modified Eagle Medium supplemented with 10% FBS.

[0086] Site-direct mutagenesis and cell line engineering

The QuikChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies, Cat #200523) was used to generate Y537S, Y537C, Y537N and D538G mutations within the ERα exon 8. Wild-type ESR1 cDNA (GeneCopoeia Inc., Cat# GC-A0322, accession no. NM 000125) was used as a template with the following mutagenesis primers (where the underlined nucleotides represent site mutations); Y537S: F-AAG AAC GTG GTG CCC CTC TCT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 1), R-CAT CTC CAG CAG CAG GTC AGA GAG GGG CAC CAC GTT CTT (SEQ ID NO: 2); Y537N: F-AAG AAC GTG GTG CCC CTC AAT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 3), R-CAT CTC CAG CAG CAG GTC ATT GAG GGG CAC CAC GTT CTT (SEQ ID NO: 4); Y537C: F-AAG AAC GTG GTG CCC CTC T GT GAC CTG CTG CTG GAG ATG (SEQ ID NO: 5), R-CAT CTC CAG CAG CAG GTC ACA GAG GGG CAC CAC GTT CTT (SEQ ID NO: 6); D538G: F-AAC GTG GTG CCC CTC TAT GGC CTG CTG CTG GAG ATG CTG (SEQ ID NO: 7), R-CAG CAT CTC CAG CAG CAG GCC ATA GAG GGG CAC CAC GTT (SEQ ID NO: 8). WT and mutant ESR1 cDNAs were cloned into the designation lentiviral

vector pLenti6.3/V5-Dest (Invitrogen, Cat #V533-06). To make lentivirus, DNAs (WT and mutant ESR1) were co-transfected with packaging plasmids into Lenti-X 293T cells using TransIT (Mirus, Cat #MIR 2700). 48h post-transfection, virus containing media was filtered and added to MCF7 cells in the presence of 8 µg/ml polybrene overnight. Two days following infection, cells were placed under selection with 10 µg/ml blasticidin for 2 weeks for stable expression.

[0087] In vitro proliferation assays

MCF7-WT and -Y537S cells were seeded at 1500 cells/well in black-walled 96-well plates (assay plates, Costar, Cat #3904). In parallel, cells were also seeded in a separate 96-well plate (8 wells/cell line, control plate) for which a CTG (CellTiter-Glo (registered trademark) Luminescent Viability Assay, Promega, Cat #G7572) was measured the following day (day 0 reading). The day 0 reading was used for the GI₅₀ calculation at the termination of the experiment. The day following seeding, compounds were added to assay plates. Briefly, a 1:4 serial dilution was prepared in DMSO at 200x final concentration for a total of 10 concentrations (9 dilutions containing compound and one is DMSO only). Serially diluted compounds were pipetted into medium to prepare a compound-medium mix at 10x final concentration. 10 µl of compound-medium mix was added to MCF7-WT and -Y537S cells at 3 wells/concentration (triplicate for each concentration). On day 3, media/compound was removed and replaced with fresh media/compound as described above. On day 6, CTG was measured and compared to day 0 readings from control plate to assess GI₅₀.

[0088] Results

Figure 34 shows that ectopic expression of ERα^{Y537S/N/C, D538G} in MCF7 cells conferred phenotypic resistance to currently marketed therapies tamoxifen (SERM), raloxifene (SERM) and fulvestrant (SERD). Similar observations were also recently published by several independent labs (Jeselsohn et al., (2014) Clin Cancer Res. Apr 1; 20 (7): 1757-67; Toy et al., (2013) Nat. Genet. 2013 Dec; 45(12):1439-45; Robinson et al., (2013) Nat. Genet. Dec; 45 (12): 1446-51; Merenbakh-Lamin et al., (2013) Cancer Res. Dec 1; 73(23): 6856-64; Yu et al., (2014) Science Jul 11; 345(6193): 216-20). Having confirmed that ERα^{MUT} drive resistance to current endocrine therapies, identification of novel compounds that would reduce proliferation of the ERα^{MUT}-bearing MCF7 cells more efficaciously than the corresponding clinical compound 4-hydroxytamoxifen was sought. Using the WT and mutant viability assay as a screening tool, compounds were identified that were more potent towards the Y537S-bearing MCF7 line relative to 4-hydroxytamoxifen. The results of the viability assay screen are shown in Table 1. These assays were conducted with free base and/or salt forms of the compounds identified in the table.

[0089]

[Table 1]

Table 1: Viability Screen Results

	MCF7 WT GI50 (nM)	MCF7 Y537S GI50 (nM)
Compound (I)	0.75 ± 0.38 (16)	10.16 ± 11.24 (16)

[0090] Results as presented in Table 1 are presented as the average of one or more trials with standard deviations where available. The number of trials for each compound is presented in parentheses following the value. Those skilled in the art would appreciate that the examples and embodiments reported herein are for illustrative purposes only. Various modifications or changes in light thereof will be suggested to persons skilled in the art, and those modifications or changes are included within the spirit and purview of this application and scope of the appended claims. For example, those skilled in the art will appreciate that GI50 values may vary depending on the lot of fetal bovine serum (FBS), among other factors, used to supplement the culture media, due to varying concentrations of estrogen between batches.

Compounds were tested as prepared in the Examples below with regard to use of free base or salt; results for compound (I) are presented as averages of both free base and HCl salt trials.

[0091] (Test Example 2) In vivo xenograft methods

Methods and materials

Although not wishing to be bound by theory, applicant appreciates that certain in vivo xenograft studies may be useful in identifying effective compounds. Such studies may be conducted, for example, using compounds reported herein and/or their salts. In studies reported herein, the hydrochloride salt form as described herein was used. The WHIM20 xenograft study reported below has not yet been conducted with compounds reported herein, but the Y537S positive PDx xenograft study and studies in the ER α wild-type MCF7 and PDx models have been conducted with certain of the compounds as set forth below.

[0092] Y537S positive PDX xenograft study

A Patient-Derived Xenograft (PDX) tumor model representing an ESR1-Y537S mutated human ER+ breast cancer, designated as PDX-Y537S, was propagated subcutaneously in immunocompromised mice. The tumors were excised within 60 days of implantation and processed to mixed tumor fragments. Solid tumor tissues were depleted of necrotic components, cut into 70 mg fragments, mixed with matrigel and subcutaneously implanted into the right flank of 6-12 week old female athymic Nude (CrI:NU(NCr)-Foxn1nu) mice. The precise number of fragments and volume of matrigel were determined on a case by case basis. When the average tumor volume reaches approximately 125-250 mm³, animals were randomized prior to treatment. All

of the primary human tumors utilized in this study had undergone approximately 5-7 passages in vivo.

Estrogen was not supplemented in the studies. All tested compounds were dosed orally every day at doses ranging from 3 to 30 mg/kg. The administration volume was calculated from the individual mouse body weights prior to dose administration. The body weights (BW) and tumor volumes (TV) were measured twice a week.

Tumor volumes (TV) were calculated based on the formula:

$$TV = \text{length} \times \text{width}^2 \times 0.5$$

length: largest diameter of tumor (mm)

width: diameter perpendicular to length (mm)

The Tumor Growth Inhibition % (TGI) was calculated according to the following formula:

[Math.1]

$$\text{TumorGrowthInhibition\%(TGI)} = \frac{\text{Average Control TV Day X} - \text{Treatment TV Day X}}{\text{Average Control TV Day X}} \times 100$$

Where Day X is the endpoint measurement.

[0093] Results for Y537S Positive PDx Xenograft Studies

Figure 35 shows the anti-tumor and body weight effects of compound (I), prepared as an HCl salt, in the PDX-Y537S model bearing a heterozygous ER $\alpha^{Y537/WT}$ xenograft. Compound (I) dosed daily inhibited xenograft growth in a dose dependent manner with 3 mg/kg QD, 10 mg/kg QD, and 30 mg/kg QD treatments significantly inhibiting growth on day 44 relative to vehicle control (TGI of 43%, 74%, and 77%, and $p < 0.05$, respectively). All doses and regimens were well tolerated with no significant body weight loss.

Compound (I) was given orally once daily for the duration of the study. Data represent the mean $\pm$ SEM (Tumor Volume) or mean $\pm$ SEM (Body Weight) (N=6 for all groups). * $p < 0.05$ versus vehicle control on Day 44 (repeated measures t-test, Holm-Sidak method with $\alpha = 0.05$ without assuming a consistent SD).

[0094] MCF7 Xenograft Studies

The ESR1 wild-type human ER+ breast cancer cell line MCF7 (ATCC) was cultured in DMEM media supplemented with 10% FBS at 37°C in a 5% CO₂ atmosphere and kept in the exponential growth phase. The cells were collected in trypsin and re-suspended in a 1:1 mixture of matrigel and HBSS at a final concentration of 5 $\times 10^7$ cells/ mL. A 0.2mL aliquot of cells was injected subcutaneously into the 3rd mammary fat pad of 6-8 week old female Balb/c nude mice, giving 1 $\times 10^7$ cells/ mouse. When the average tumor volume reached approximately about 200 mm³, animals were randomized prior to treatment.

Estrogen was supplemented for the duration of the study. Compound (I) was dosed

orally every day at doses ranging from 1 to 10 mg/kg. Each treatment was started on Day 0 and the administration schedule was continued for 28 days. The administration volume was calculated from the individual mouse body weights prior to dose administration. The body weights (BW) were measured daily while the tumor volumes were measured twice a week. Tumor volumes (TV) were calculated based on the above formula.

[0095] Results for MCF7 Xenograft Studies

Figure 36 shows the anti-tumor and body weight effects of compound (I), prepared as an HCl salt, in the MCF7 tumor model bearing ER $\alpha^{WT/WT}$ xenograft. Compound (I) dosed daily inhibited xenograft growth in a dose dependent manner with 1 mg/kg QD, 3 mg/kg QD, and 10 mg/kg QD treatments significantly inhibiting growth on day 28 relative to vehicle control (TGI of 9.2%, 52.4%, and 69.3%, and $p < 0.05$ for 10 and 30 mg/kg groups, respectively). All doses and regimens were well tolerated with no significant body weight loss.

Compound (I) was given orally once daily for the duration of the study. Data represent the mean $\pm$ SEM (Tumor Volume) or mean $\pm$ SEM (Body Weight) (N=8 for all groups). * $p < 0.05$ versus vehicle control on Day 28 (repeated measures t-test, Holm-Sidak method with $\alpha = 0.05$ without assuming a consistent SD).

[0096] WHIM20 Xenograft Studies

The Patient-Derived Xenograft (PDX) tumor model, WHIM20, representing an ESR1-Y537S mutated human ER+ breast cancer is propagated in mice. The tumors are excised and processed to mixed tumor fragments and the fragments are re-implanted subcutaneously into new recipient mice. Solid tumor tissues are depleted of necrotic components, cut into fragments, mixed with matrigel and subcutaneously implanted into the right flank of 6-8 week old female SCID-bg mice. The precise number of fragments and volume of matrigel are determined on a case by case basis. When the average tumor volume reaches approximately 200 mm³, animals are randomized prior to treatment. All of the primary human tumors utilized in this study undergo approximately 4 passages in vivo.

Estrogen is not supplemented in WHIM20 studies. Compounds are dosed orally every day at the indicated doses. Each treatment is started on Day 0 and the administration schedule is continued for the indicated days. The administration volume is calculated from the individual mouse body weights prior to dose administration. The body weights are measured daily while the tumor volumes are measured twice a week. Tumor volumes are calculated based on the previously described formula.

[0097] ER α^{WT} -PDX Xenograft Studies

A PDX tumor model representing an ESR1-WT human ER+ breast cancer, designated as PDX-WT, was propagated subcutaneously in immunocompromised

mice. The tumors were excised within 60 days of implantation and processed to mixed tumor fragments. Solid tumor tissues were depleted of necrotic components, cut into 70 mg fragments, mixed with matrigel and subcutaneously implanted into the right flank of 6-12 week old female athymic Nude (CrI:NU(NCr)-Foxn1nu) mice. The precise number of fragments and volume of matrigel were determined on a case by case basis. When the average tumor volume reached approximately 125-250 mm³, animals were randomized prior to treatment.

Estrogen was supplemented for the duration of the study. Compound (I) was dosed orally every day at doses ranging from 1 to 30 mg/kg. The administration volume was calculated from the individual mouse body weights prior to dose administration. The body weights (BW) and tumor volumes (TV) were measured twice a week.

[0098] Results for ER α ^{WT}-PDX Xenograft Studies

Figure 37 shows the anti-tumor and body weight effects of compound (I), prepared as an HCl salt, in a PDX model bearing ER α ^{WT/WT} xenograft. Compound (I) dosed daily inhibited xenograft growth in a dose dependent manner with 1 mg/kg QD, 3 mg/kg QD, 10 mg/kg QD, and 30 mg/kg QD treatments significantly inhibiting growth on day 39 relative to vehicle control (TGI of 78.5%, 92.3%, 93.1%, and 90.7%, and $p < 0.05$, respectively). All doses and regimens were well tolerated with no significant body weight loss.

Compound (I) was given orally once daily for the duration of the study. Data represent the mean $\pm$ SEM (Tumor Volume) or mean $\pm$ SEM (Body Weight) (N=6 for all groups). * $p < 0.05$ versus vehicle control on Day 39 (repeated measures t-test, Holm-Sidak method with $\alpha = 0.05$ without assuming a consistent SD).

[0099] (Test Example 3) Time-Dependent Inhibition Assays

To demonstrate that a compound is (or is not) a CYP inactivator, abbreviated experimental designs are commonly used for screening in drug development. One of these approaches uses multiple test compound concentrations at a single incubation time, e.g. the "IC₅₀ shift" approach. In an IC₅₀ shift experiment, the IC₅₀ is determined for a CYP marker activity before and after the test compound has been incubated with enzyme and the co-factor nicotinamide adenine dinucleotide phosphate (NADPH) for a set preincubation time (Grimm et al, 2009).

The IC₅₀ shift approach was used to determine whether compounds are time-dependent inhibitors of human CYP3A4 using liver microsomes (0.1 mg/mL). A 30-minute pre-incubation time point was selected, where compounds (9 concentrations, 0 to 30 μ mol/L) are incubated at 37°C in presence and absence of 1 mmol/L NADPH. Following the pre-incubation period, 5 μ mol/L midazolam (the probe substrate) was added and formation of hydroxymidazolam was measured by high-performance liquid chromatography-mass spectrometry (LC-MS/MS) analysis

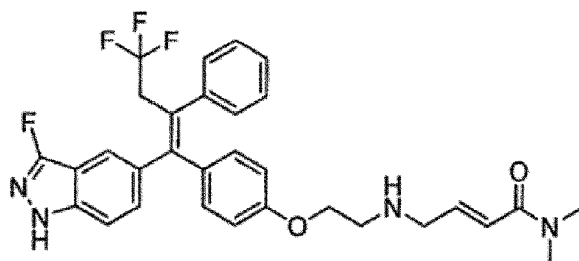
following a 5 minute incubation period. Any decrease in the formation of hydroxymidazolam, in peak area ratios to vehicle control, was used to calculate three IC_{50} values (0 min pre-incubation, 30 min pre-incubation with NADPH, and 30 min pre-incubation without NADPH). Whereas an IC_{50} shift less than 3-fold is accepted as demonstration that a test compound does not possess a TDI risk, an IC_{50} shift 3-fold or more after pre-incubation is indicative of a CYP3A4 TDI risk. Assays were performed in duplicate, and mifepristone was used as positive control. Results are shown in Table 2. In Table 2, “Yes” indicates a TDI shift greater than or equal to 3. “No” indicates a TDI shift greater than or equal to 1 and less than 3.

[0100] [Table 2]

	CYP3A4 TDI
Compound (I)	No

[0101] By way of comparison with the results above, a TDI assay was also conducted for the following compound, which is reported as Compound 69 of PCT International Application Publication No. WO/2016/196346:

[Chem.62]



The IC_{50} shift approach was also used to determine whether Compound 69 of PCT International Application Publication No. WO/2016/196346 is a time-dependent inhibitor of human CYP3A4 using liver microsomes. Similar to the experimental design described above, a 30-minute pre-incubation time point was selected. Minor variations to the method described above were that Compound 69 of PCT International Application Publication No. WO/2016/196346 was tested at 8 concentrations (0 to 10 $\mu\text{mol/L}$). Following the pre-incubation period, 3 $\mu\text{mol/L}$ midazolam was added and formation of hydroxymidazolam was measured following a 2 minute incubation period. Since under these experimental conditions, the formation of hydroxymidazolam followed first order kinetics (considered as a linear process), these changes in assay design are not expected to impact the IC_{50} determinations. In parallel, the IC_{50} shift assay was also performed with 15.6 $\mu\text{mol/L}$ testosterone (0.05 mg/mL liver microsomes, 10 minute incubation) as second probe substrate. Assays for both probe substrates were performed in triplicate, and mifepristone was used as positive

control.

The CYP3A4 TDI shift result for Compound 69 of PCT International Application Publication No. WO/2016/196346 was greater than 3, indicating it to be a TDI risk.

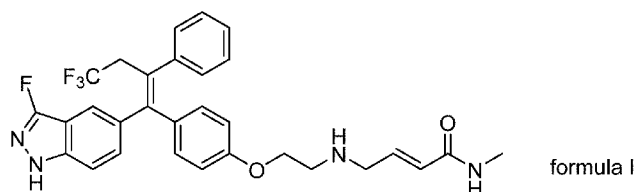
Claims

[Claim 1]

A salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, and an acid selected from the group consisting of hydrobromic acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, p-toluenesulfonic acid, succinic acid, maleic acid, mandelic acid and methanesulfonic acid.

[Chem.1]

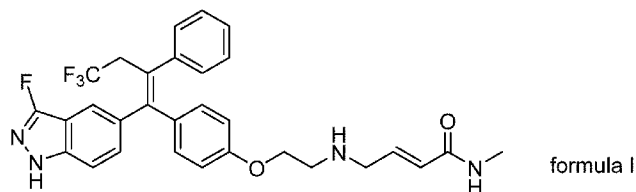


[Claim 2]

A crystal of hydrochloride salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 12.2° , 16.8° , 18.2° , 19.7° and 23.3° in a powder X-ray diffractometry.

[Chem.2]



[Claim 3]

The crystal according to claim 2, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.7° in a powder X-ray diffractometry.

[Claim 4]

The crystal according to claim 2, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.2° and 19.7° in a powder X-ray diffractometry.

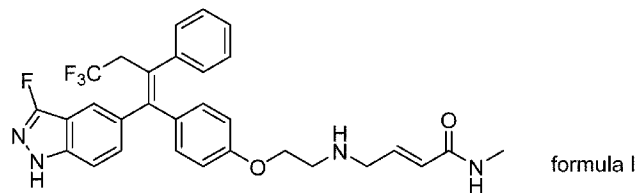
[Claim 5]

A crystal of hydrochloride salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having peaks at chemical shifts (± 0.5 ppm) of 144.5 ppm, 156.8 ppm and 165.8 ppm in a solid

state ^{13}C NMR spectrum.

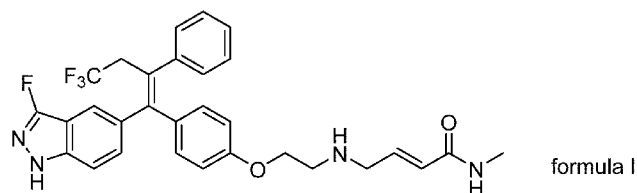
[Chem.3]



[Claim 6]

A crystal of hydrochloride salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 1.

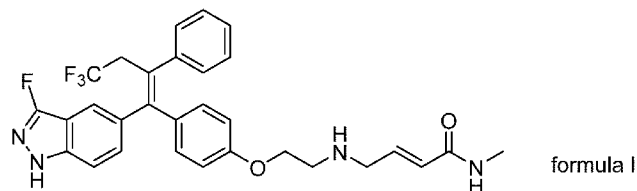
[Chem.4]



[Claim 7]

A crystal of hydrochloride salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 12.

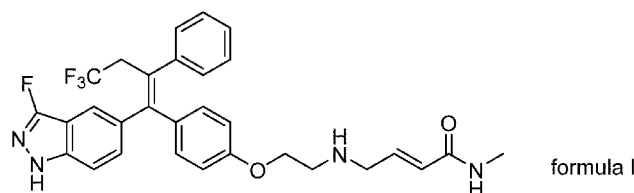
[Chem.5]



[Claim 8]

A crystal of hydrobromide salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 18.4° , 19.7° , 21.6° , 22.9° and 25.6° in a powder X-ray diffractometry.

[Chem.6]

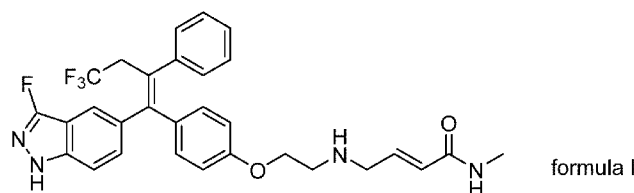


[Claim 9] The crystal according to claim 8, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.4° in a powder X-ray diffractometry.

[Claim 10] The crystal according to claim 8, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 18.4° , 19.7° and 25.6° in a powder X-ray diffractometry.

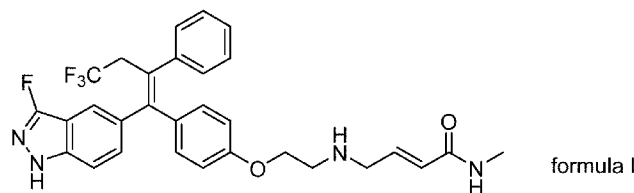
[Claim 11] A crystal of hydrobromide salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 144.2 ppm, 156.7 ppm and 165.2 ppm in a solid state ^{13}C NMR spectrum.

[Chem.7]



[Claim 12] A crystal of hydrobromide salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 2.

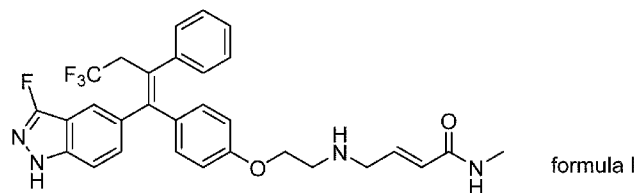
[Chem.8]



[Claim 13] A crystal of hydrobromide salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C

NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 13.

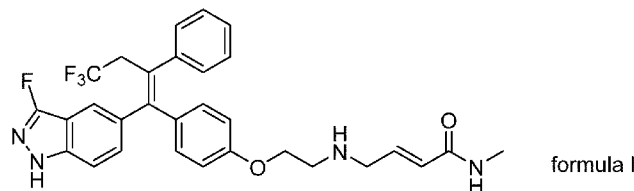
[Chem.9]



[Claim 14]

A crystal of phosphate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 6.5° , 13.5° , 16.7° , 19.9° and 20.4° in a powder X-ray diffractometry.

[Chem.10]



[Claim 15]

The crystal according to claim 14, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 6.5° in a powder X-ray diffractometry.

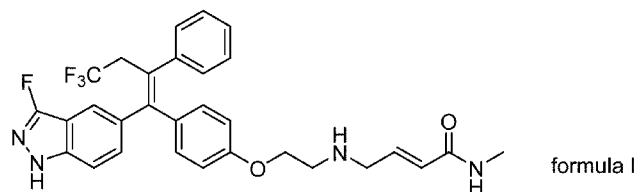
[Claim 16]

The crystal according to claim 14, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 6.5° , 16.7° and 19.9° in a powder X-ray diffractometry.

[Claim 17]

A crystal of phosphate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 135.3 ppm, 140.9 ppm and 169.8 ppm in a solid state ^{13}C NMR spectrum.

[Chem.11]

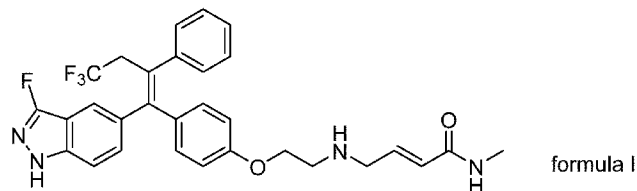


[Claim 18]

A crystal of phosphate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 3.

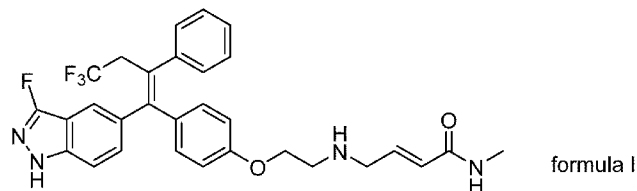
[Chem.12]



[Claim 19]

A crystal of phosphate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 14.

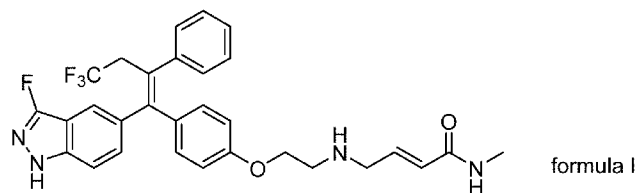
[Chem.13]



[Claim 20]

A crystal of sulfate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 7.6° , 11.3° , 13.0° , 19.0° and 19.8° in a powder X-ray diffractometry.

[Chem.14]



[Claim 21]

The crystal according to claim 20, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.0° in a powder X-ray diffractometry.

[Claim 22]

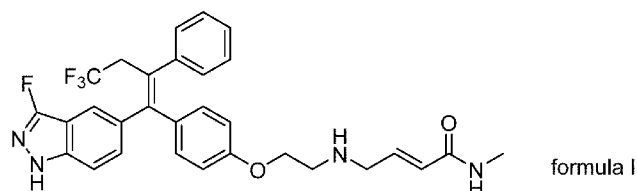
The crystal according to claim 20, characterized by having diffraction

peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.6° , 19.0° and 19.8° in a powder X-ray diffractometry.

[Claim 23]

A crystal of sulfate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 117.8 ppm, 157.4 ppm and 165.0 ppm in a solid state ^{13}C NMR spectrum.

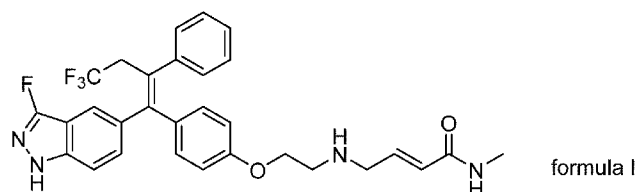
[Chem.15]



[Claim 24]

A crystal of sulfate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 4.

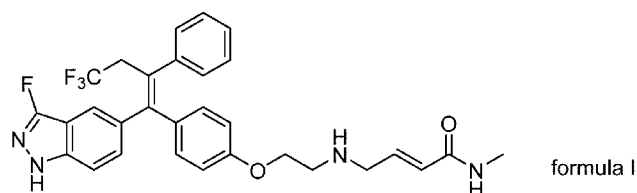
[Chem.16]



[Claim 25]

A crystal of sulfate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 15.

[Chem.17]

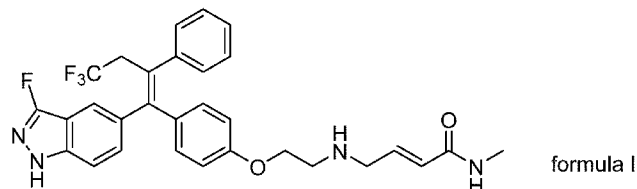


[Claim 26]

A crystal of benzenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 7.6° , 19.0° and 19.8° in a powder X-ray diffractometry.

-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 10.9° , 17.6° , 19.9° , 21.9° and 24.1° in a powder X-ray diffractometry.

[Chem.18]

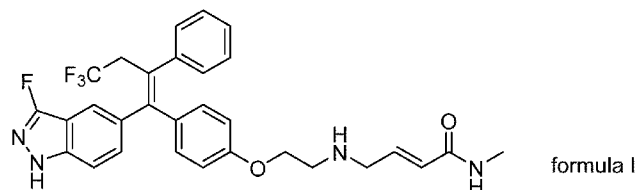


[Claim 27] The crystal according to claim 26, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 10.9° in a powder X-ray diffractometry.

[Claim 28] The crystal according to claim 26, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 10.9° , 17.6° and 24.1° in a powder X-ray diffractometry.

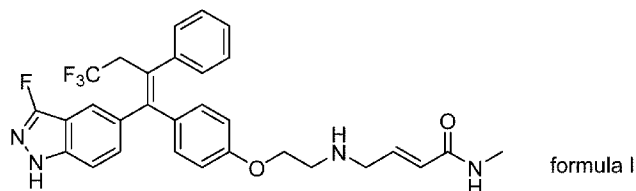
[Claim 29] A crystal of benzenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 136.1 ppm, 156.7 ppm and 164.4 ppm in a solid state ^{13}C NMR spectrum.

[Chem.19]



[Claim 30] A crystal of benzenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 5.

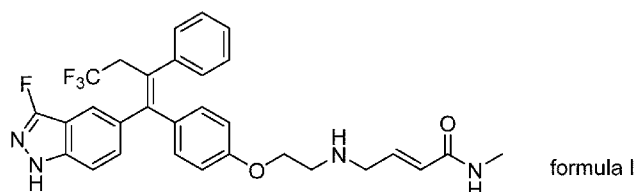
[Chem.20]



[Claim 31]

A crystal of benzenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 16.

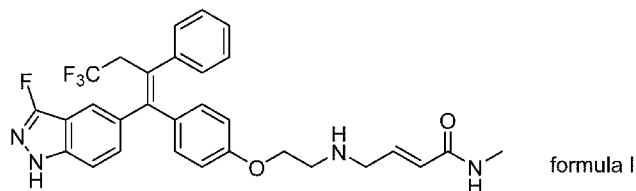
[Chem.21]



[Claim 32]

A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 8.9° , 12.5° , 21.4° , 22.1° and 23.4° in a powder X-ray diffractometry.

[Chem.22]



[Claim 33]

The crystal according to claim 32, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 8.9° in a powder X-ray diffractometry.

[Claim 34]

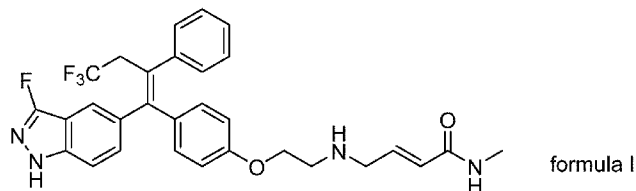
The crystal according to claim 32, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 8.9° , 21.4° and 22.1° in a powder X-ray diffractometry.

[Claim 35]

A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide rep-

resented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 140.7 ppm, 156.4 ppm and 166.9 ppm in a solid state ^{13}C NMR spectrum.

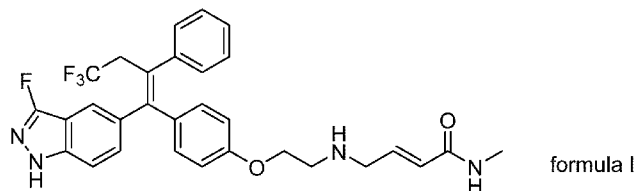
[Chem.23]



[Claim 36]

A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 6.

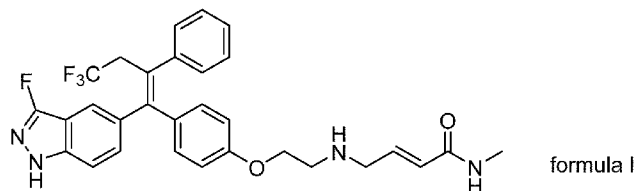
[Chem.24]



[Claim 37]

A crystal of p-toluenesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 17.

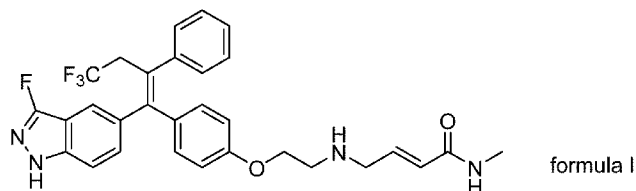
[Chem.25]



[Claim 38]

A crystal of succinate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 14.8° , 17.0° , 17.5° , 18.2° and 19.1° in a powder X-ray diffractometry.

[Chem.26]

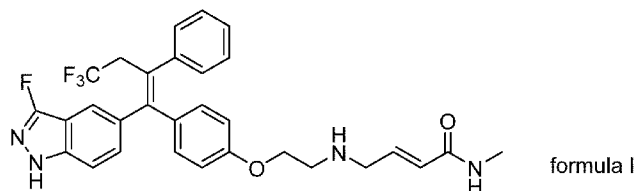


[Claim 39] The crystal according to claim 38, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry.

[Claim 40] The crystal according to claim 38, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 17.0° , 18.2° and 19.1° in a powder X-ray diffractometry.

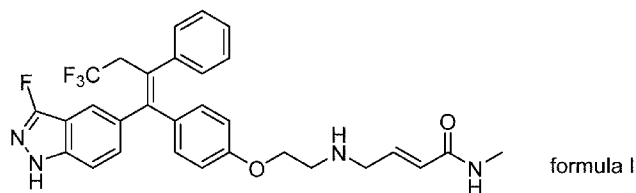
[Claim 41] A crystal of succinate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 156.1 ppm, 175.0 ppm and 181.3 ppm in a solid state ^{13}C NMR spectrum.

[Chem.27]



[Claim 42] A crystal of succinate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 7.

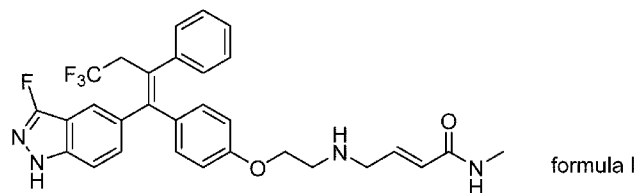
[Chem.28]



[Claim 43] A crystal of succinate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C

NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 18.

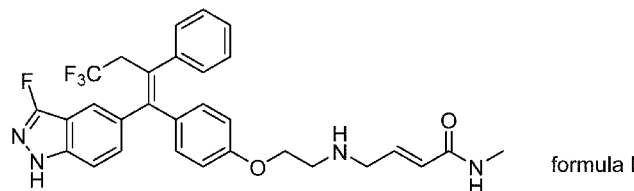
[Chem.29]



[Claim 44]

A crystal form A of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 5.4° , 11.6° , 16.8° , 18.9° and 20.2° in a powder X-ray diffractometry.

[Chem.30]



[Claim 45]

The crystal according to claim 44, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.9° in a powder X-ray diffractometry.

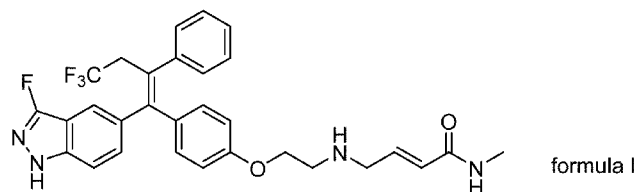
[Claim 46]

The crystal according to claim 44, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 16.8° , 18.9° and 20.2° in a powder X-ray diffractometry.

[Claim 47]

A crystal form A of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 43.4 ppm, 44.8 ppm and 145.0 ppm in a solid state ^{13}C NMR spectrum.

[Chem.31]

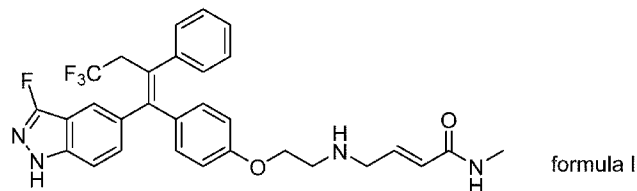


[Claim 48]

A crystal form A of maleate salt of

(E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 8.

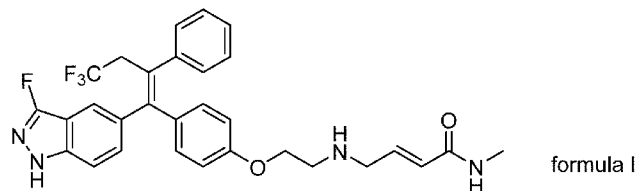
[Chem.32]



[Claim 49]

A crystal form A of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 19.

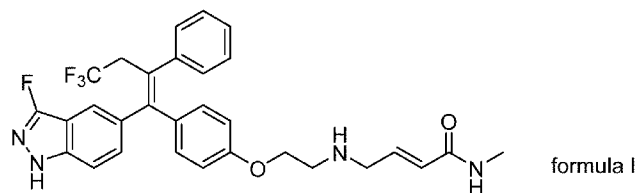
[Chem.33]



[Claim 50]

A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 10.4° , 15.2° , 19.4° , 20.8° and 22.2° in a powder X-ray diffractometry.

[Chem.34]



[Claim 51]

The crystal according to claim 50, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 19.4° in a powder X-ray diffractometry.

[Claim 52]

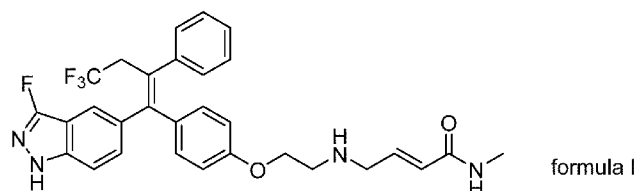
The crystal according to claim 50, characterized by having diffraction

peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 15.2° , 19.4° and 20.8° in a powder X-ray diffractometry.

[Claim 53]

A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 25.8 ppm, 143.6 ppm and 166.8 ppm in a solid state ^{13}C NMR spectrum.

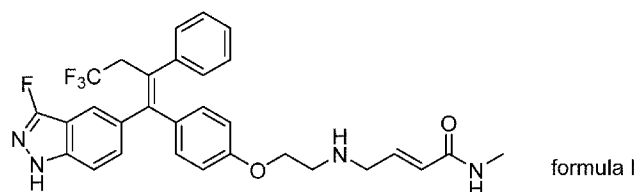
[Chem.35]



[Claim 54]

A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 9.

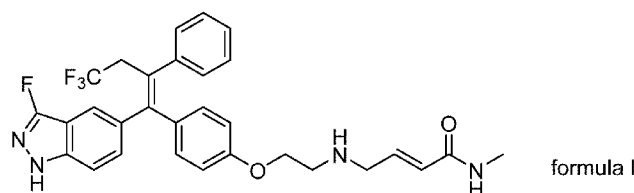
[Chem.36]



[Claim 55]

A crystal form B of maleate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 20.

[Chem.37]

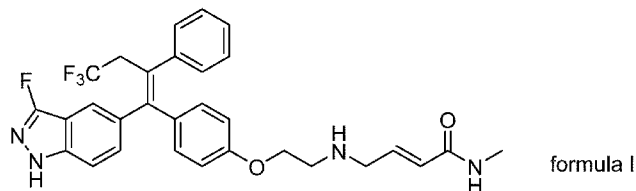


[Claim 56]

A crystal of L-mandelate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide

-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 5.1° , 8.7° , 10.3° , 18.2° and 20.3° in a powder X-ray diffractometry.

[Chem.38]

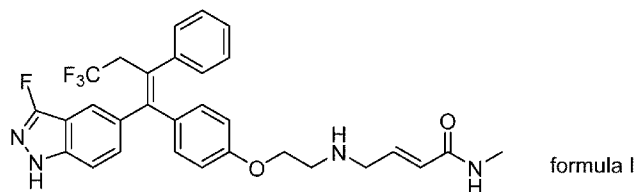


[Claim 57] The crystal according to claim 56, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 18.2° in a powder X-ray diffractometry.

[Claim 58] The crystal according to claim 56, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 5.1° , 10.3° and 18.2° in a powder X-ray diffractometry.

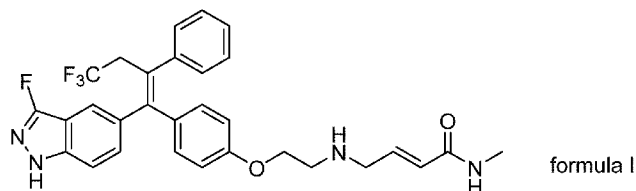
[Claim 59] A crystal of L-mandelate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 128.1 ppm, 156.7 ppm and 177.8 ppm in a solid state ^{13}C NMR spectrum.

[Chem.39]



[Claim 60] A crystal of L-mandelate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 10.

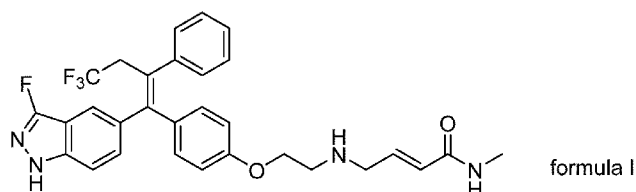
[Chem.40]



[Claim 61]

A crystal of L-mandelate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 21.

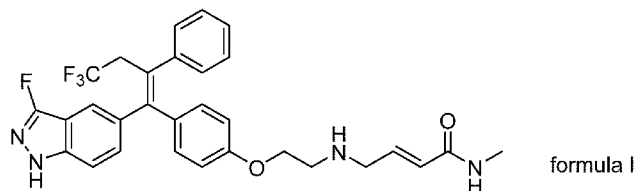
[Chem.41]



[Claim 62]

A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having one or more diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) selected from the group consisting of 12.7° , 18.9° , 19.7° , 21.8° and 25.6° in a powder X-ray diffractometry.

[Chem.42]



[Claim 63]

The crystal according to claim 62, characterized by having a diffraction peak at a diffraction angle ($2\theta \pm 0.2^\circ$) of 12.7° in a powder X-ray diffractometry.

[Claim 64]

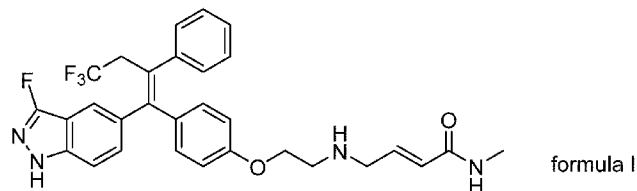
The crystal according to claim 62, characterized by having diffraction peaks at diffraction angles ($2\theta \pm 0.2^\circ$) of 12.7° , 18.9° and 25.6° in a powder X-ray diffractometry.

[Claim 65]

A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide rep-

resented by the formula I, which is characterized by having peaks at chemical shifts (± 0.5 ppm) of 40.4 ppm, 158.3 ppm and 166.0 ppm in a solid state ^{13}C NMR spectrum.

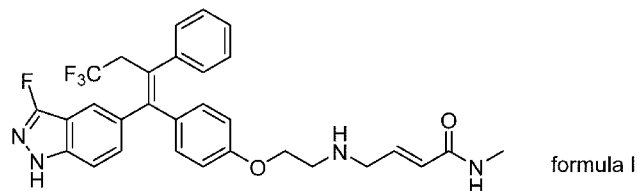
[Chem.43]



[Claim 66]

A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a powder X-ray diffraction pattern substantially the same as the powder X-ray diffraction pattern shown in Figure 11.

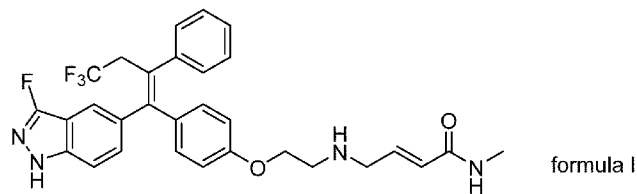
[Chem.44]



[Claim 67]

A crystal of methanesulfonate salt of (E)-N-methyl-4-((2-(4-((E)-4,4,4-trifluoro-1-(3-fluoro-1H-indazol-5-yl)-2-phenylbut-1-en-1-yl)phenoxy)ethyl)amino)but-2-enamide represented by the formula I, characterized by having a solid state ^{13}C NMR spectrum substantially the same as the solid state ^{13}C NMR spectrum shown in Figure 22.

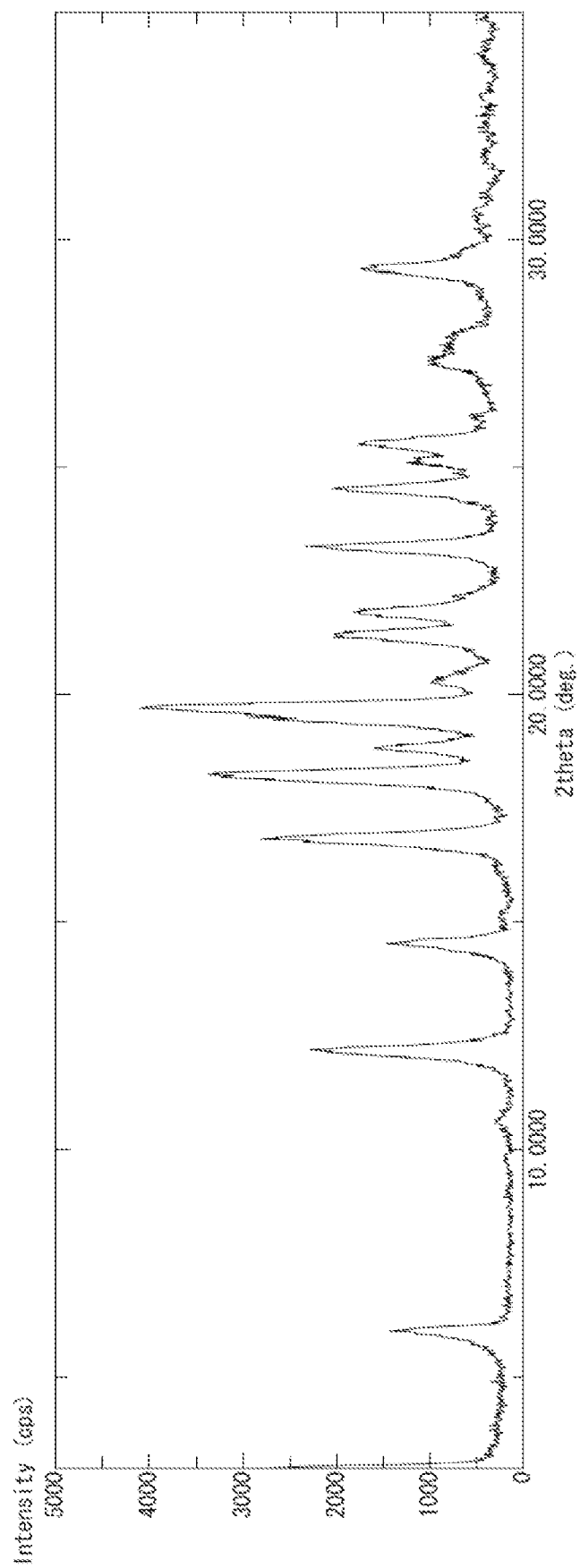
[Chem.45]



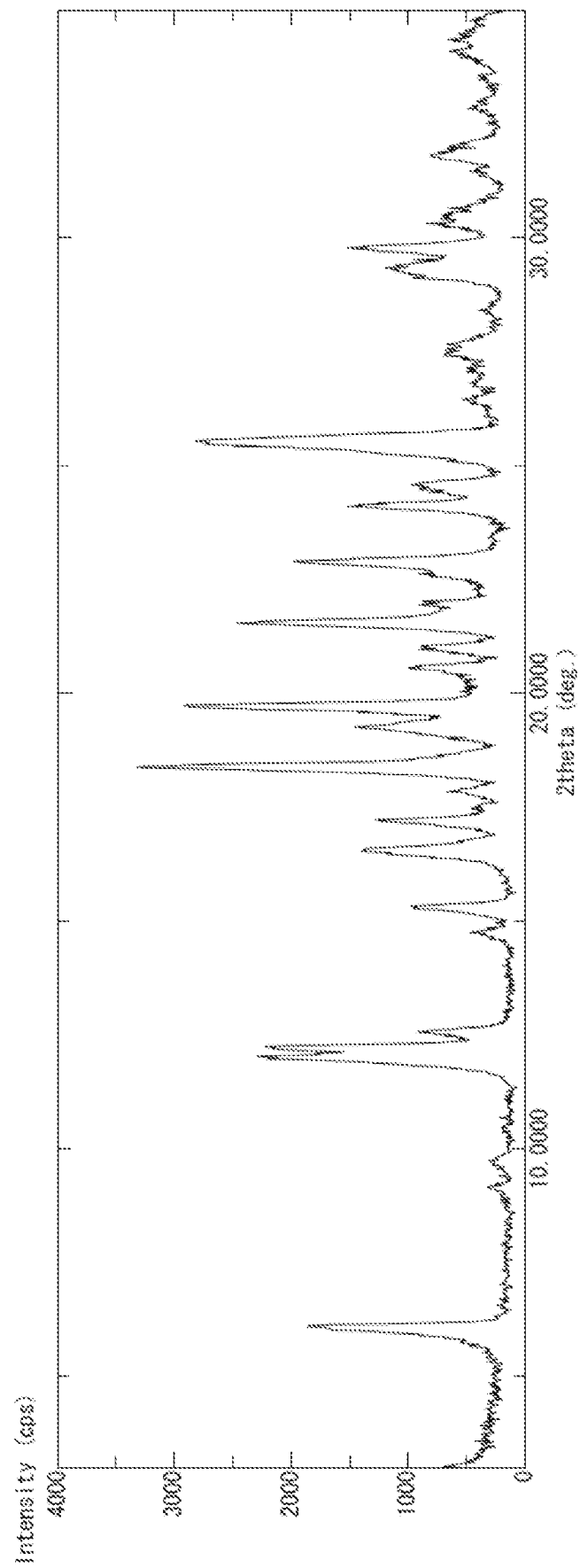
[Claim 68]

A pharmaceutical composition comprising the salt or the crystal thereof according to any one of claims 1 to 67.

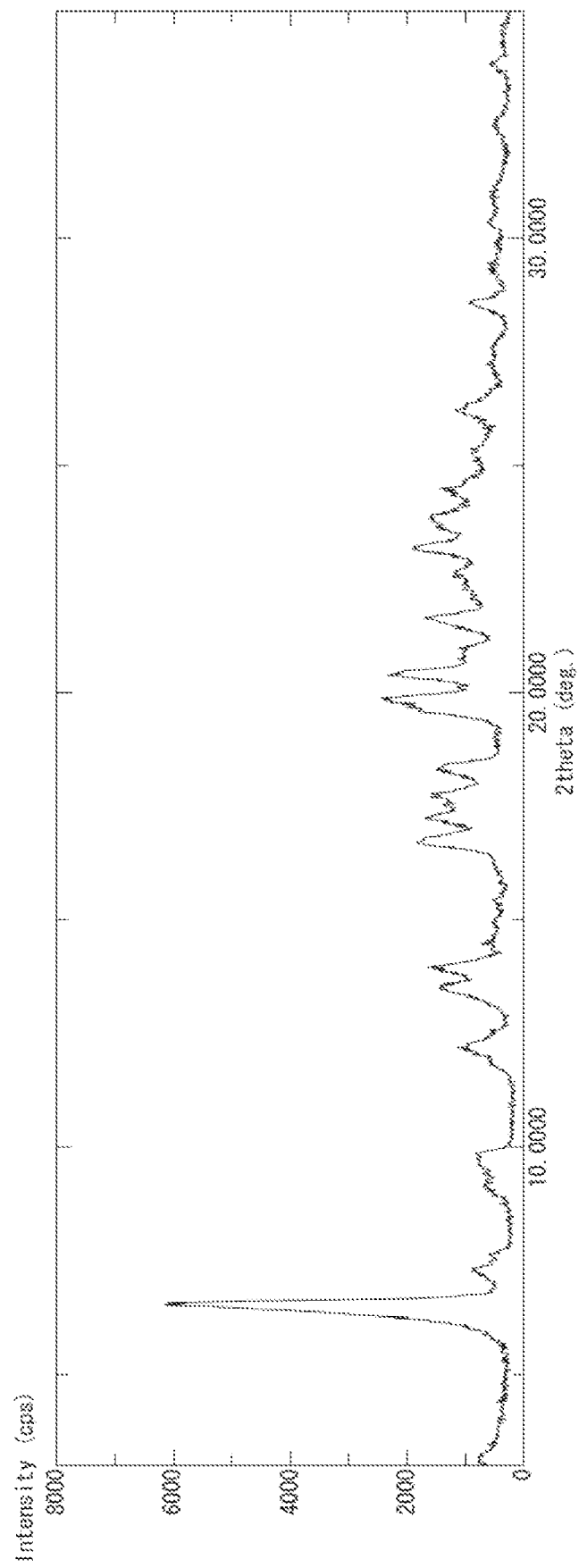
[Fig. 1]



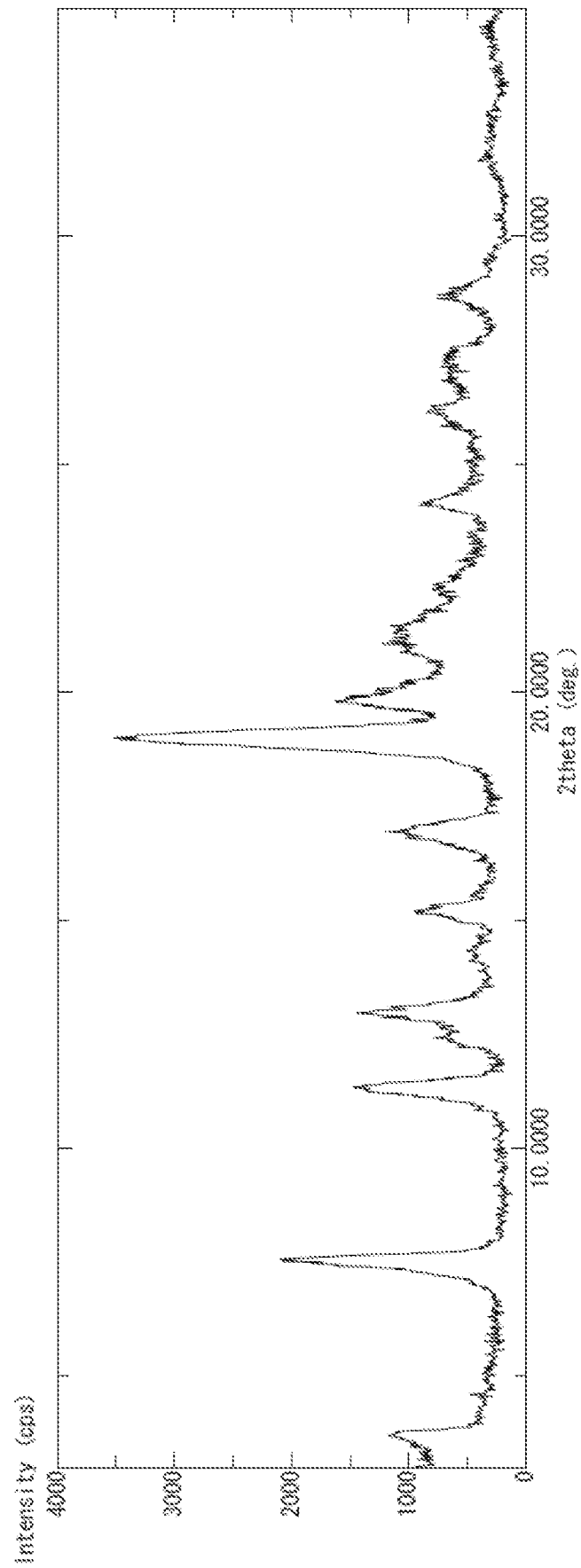
[Fig. 2]



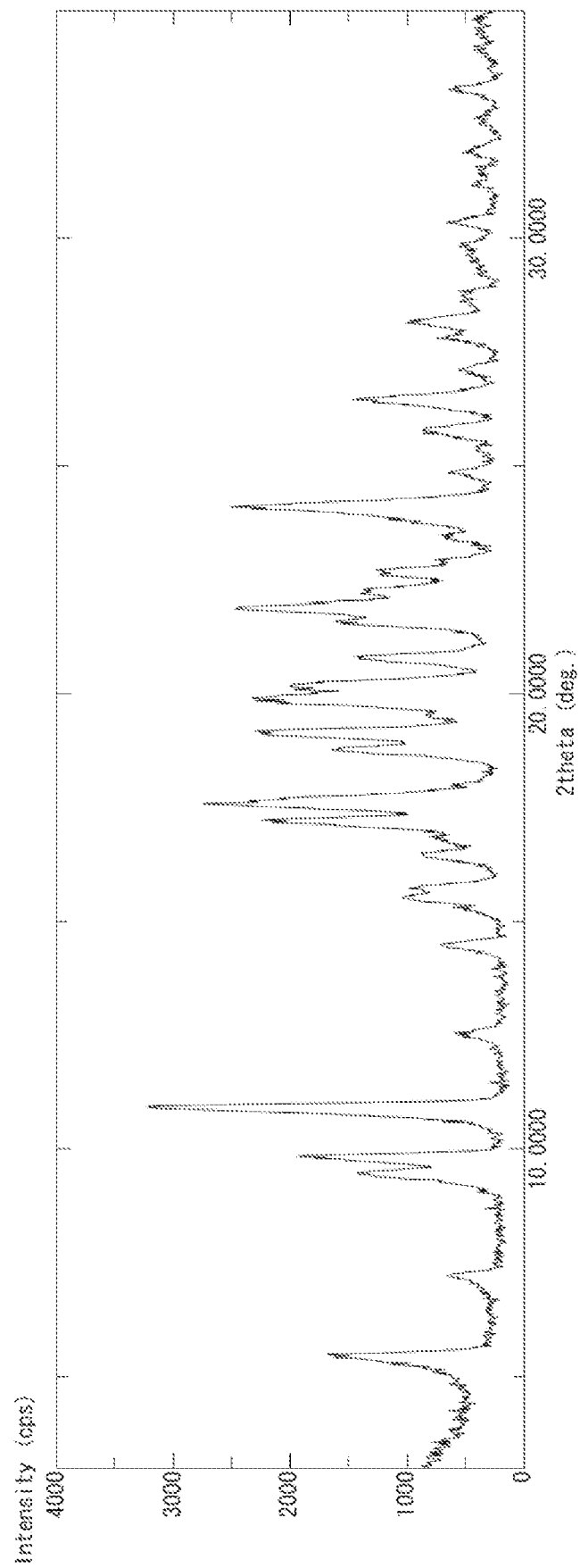
[Fig. 3]



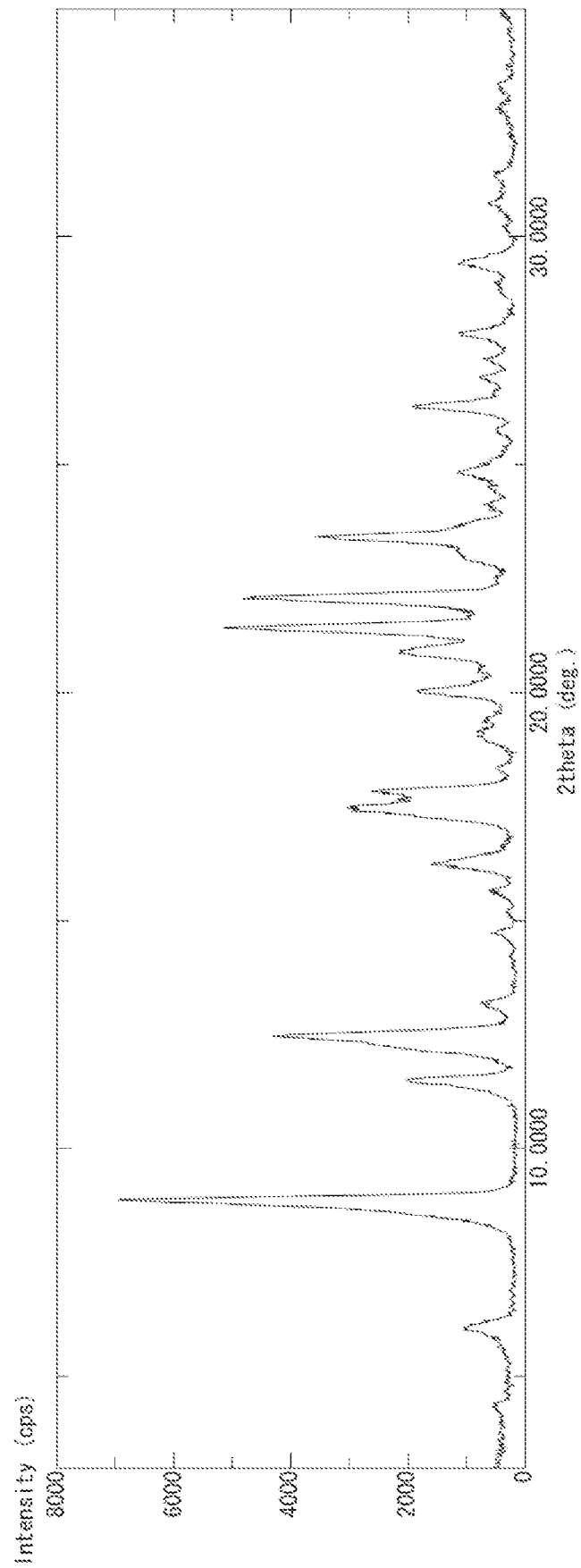
[Fig. 4]



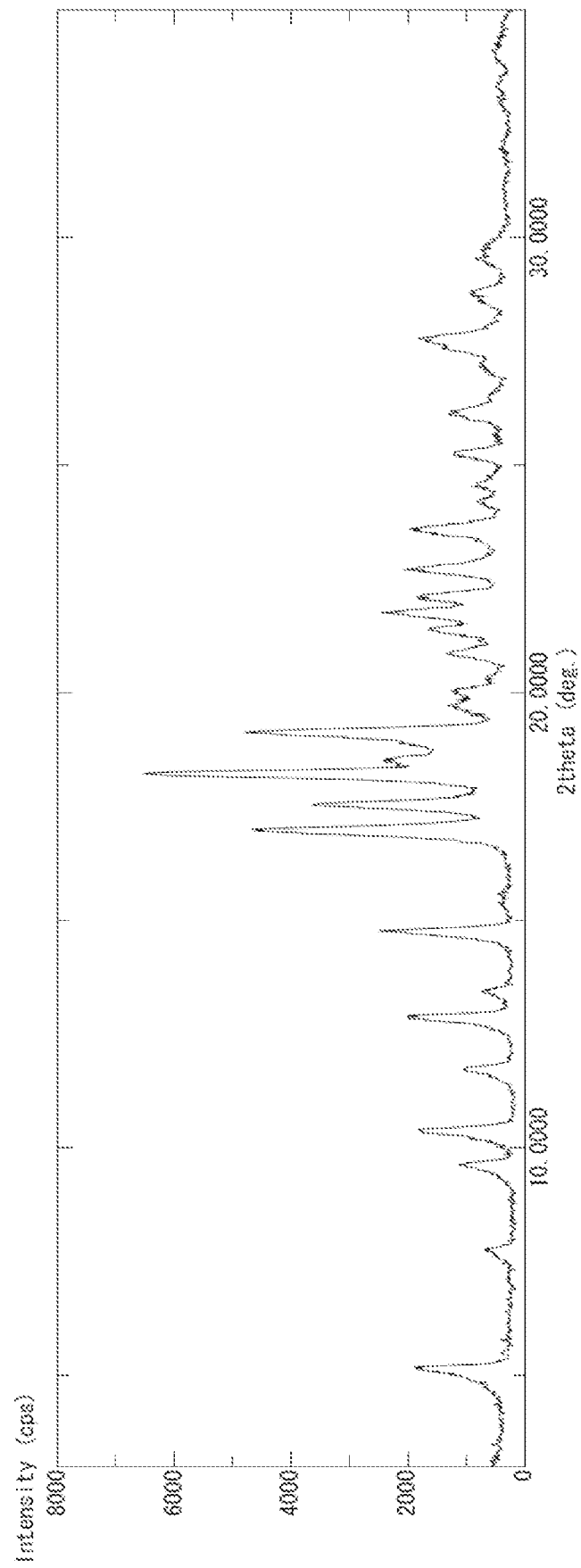
[Fig. 5]



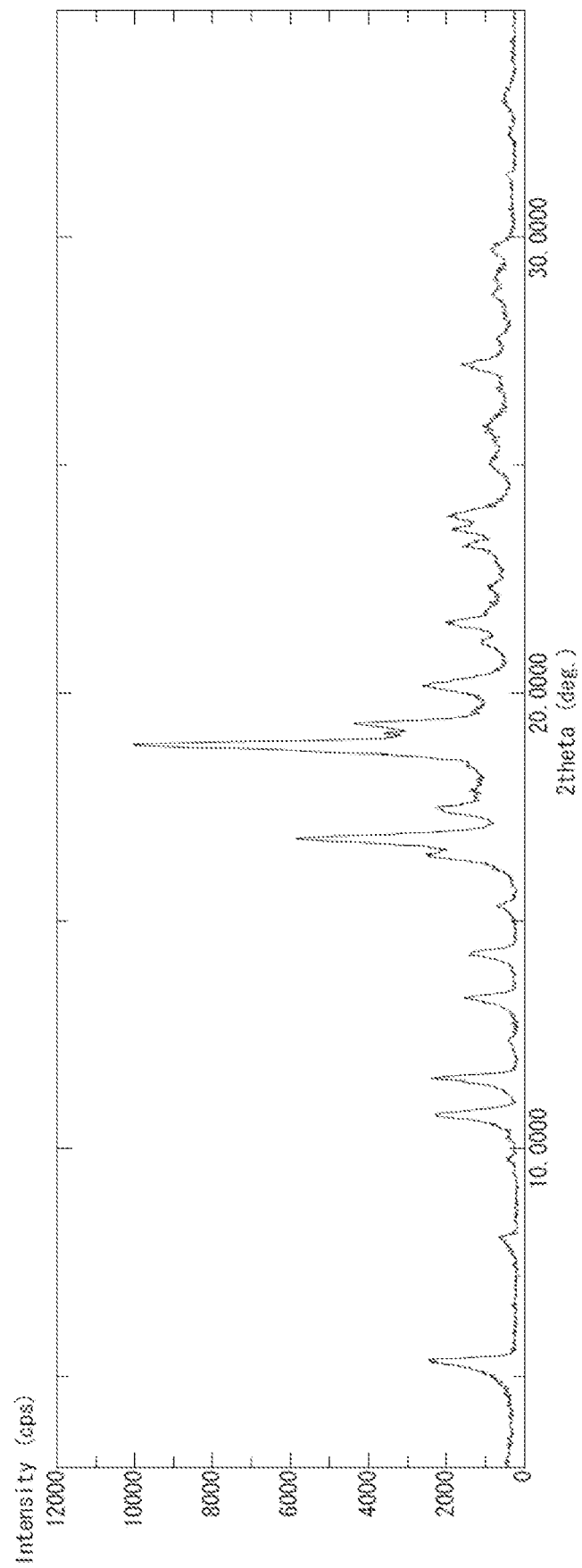
[Fig. 6]



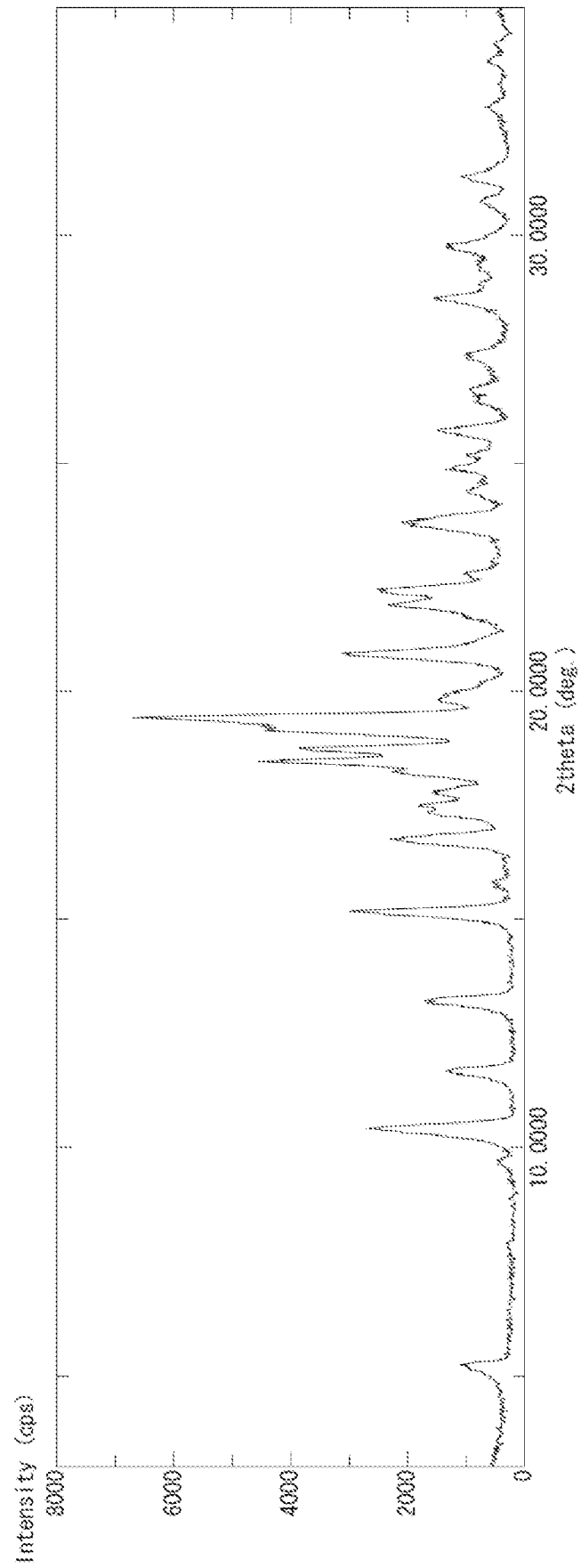
[Fig. 7]



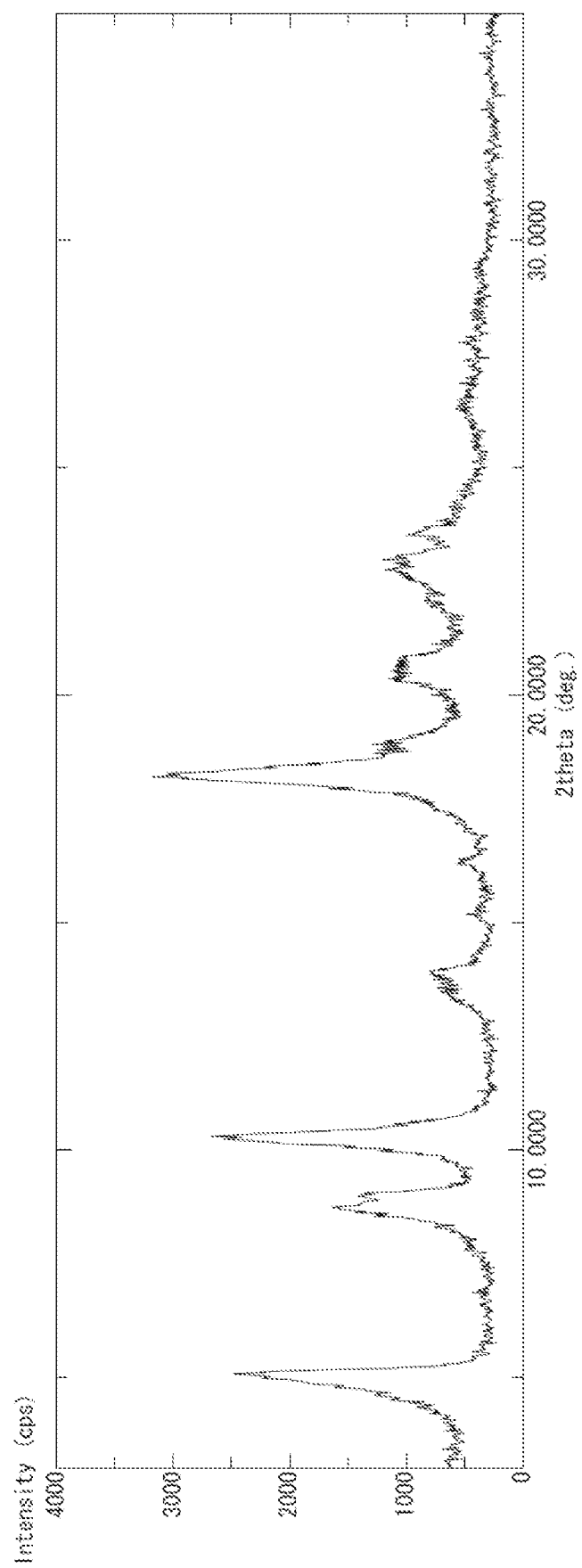
[Fig. 8]



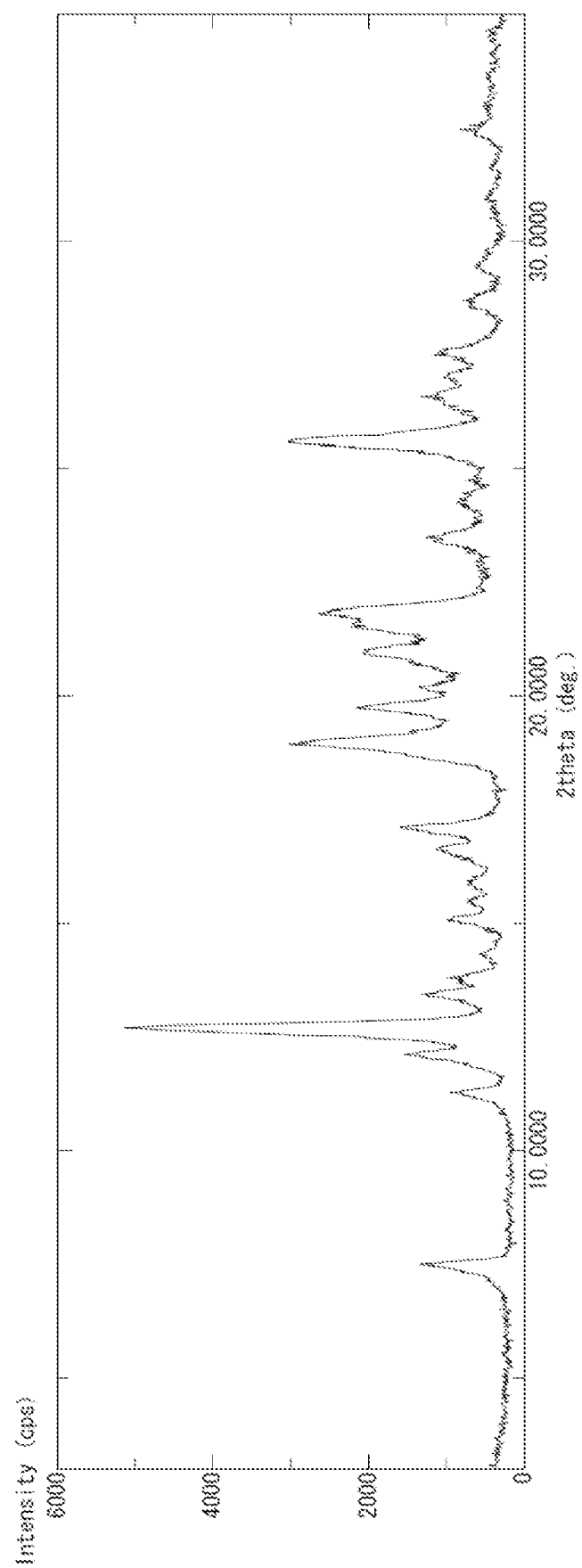
[Fig. 9]



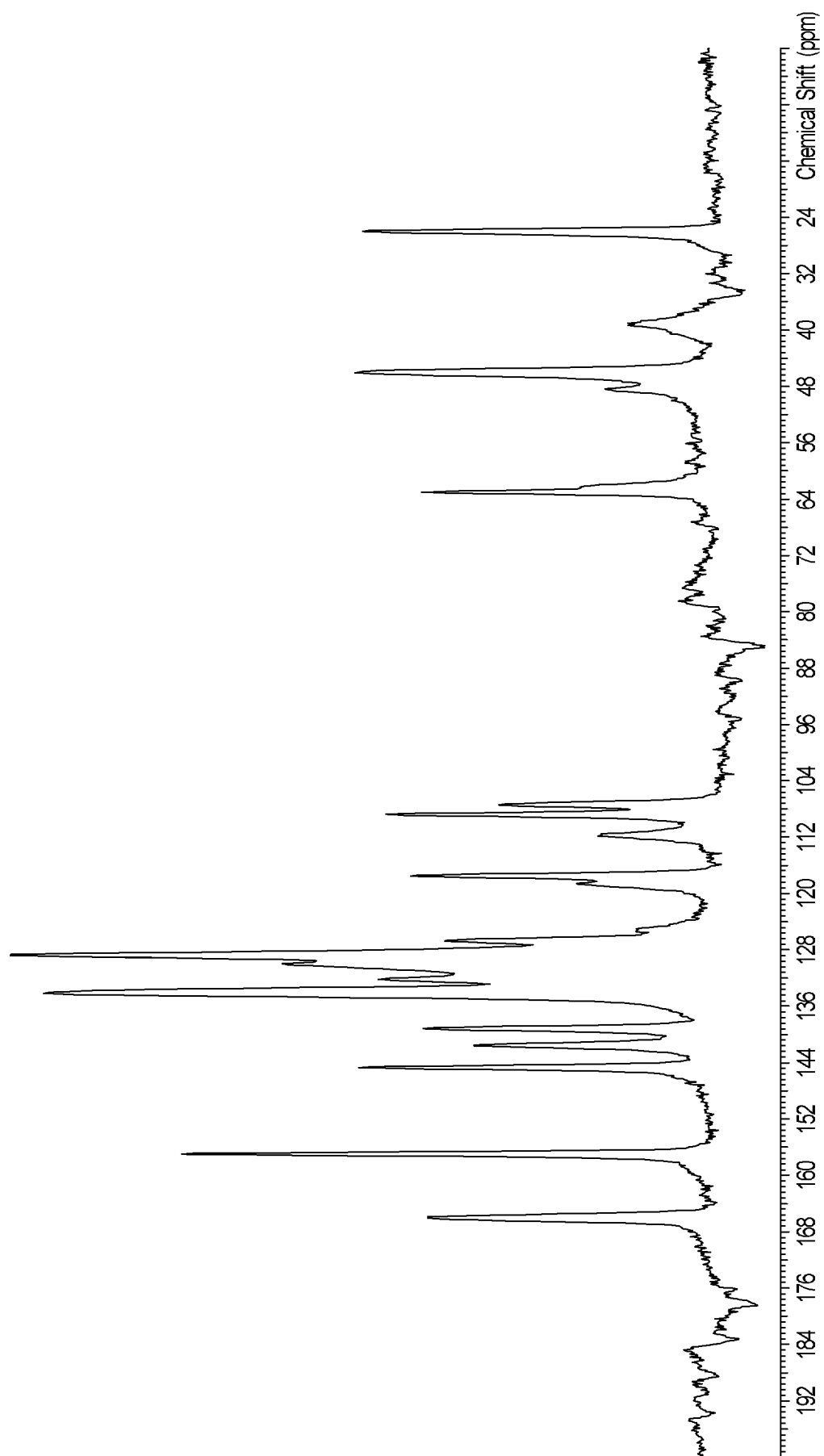
[Fig. 10]



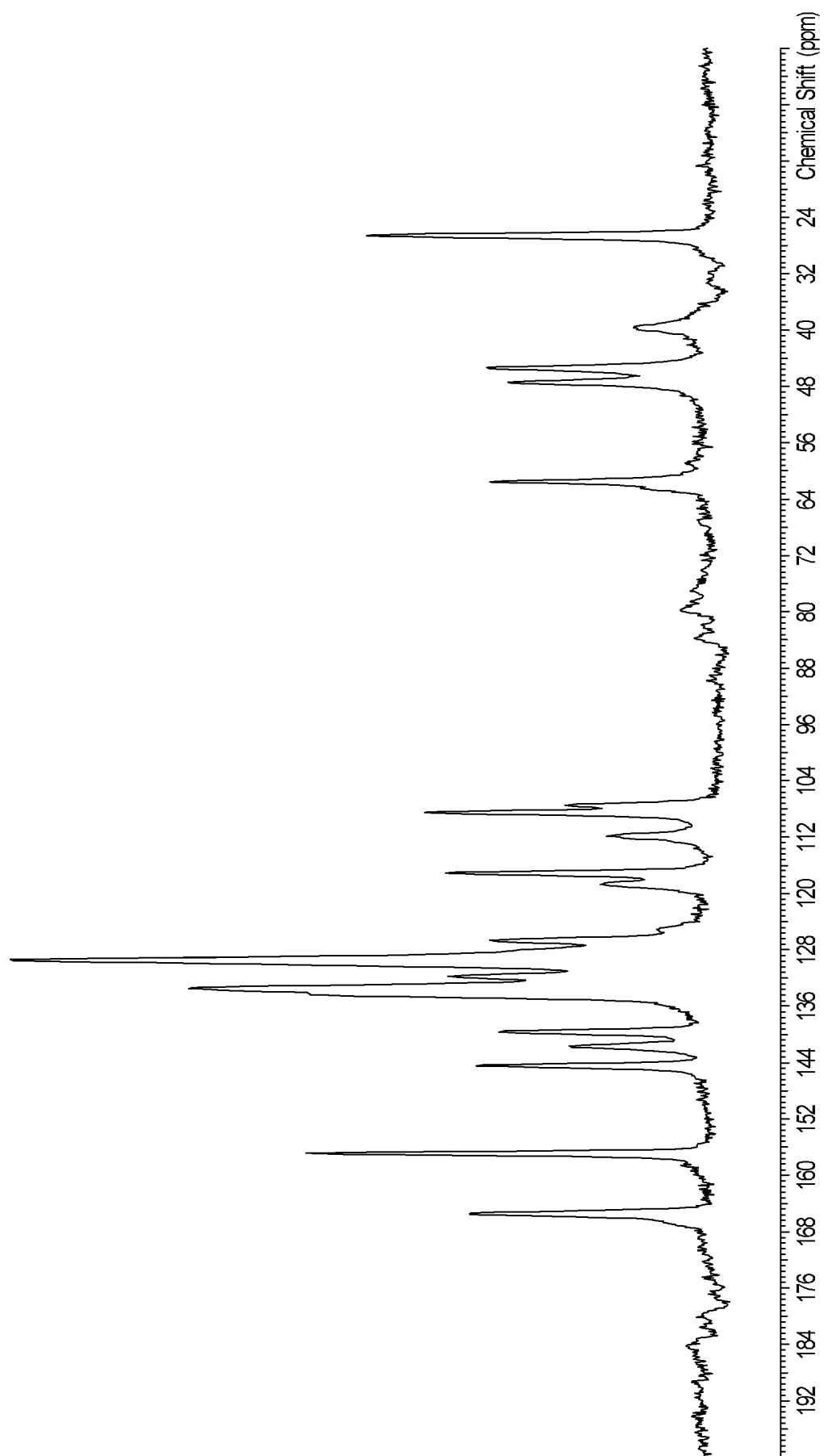
[Fig. 11]



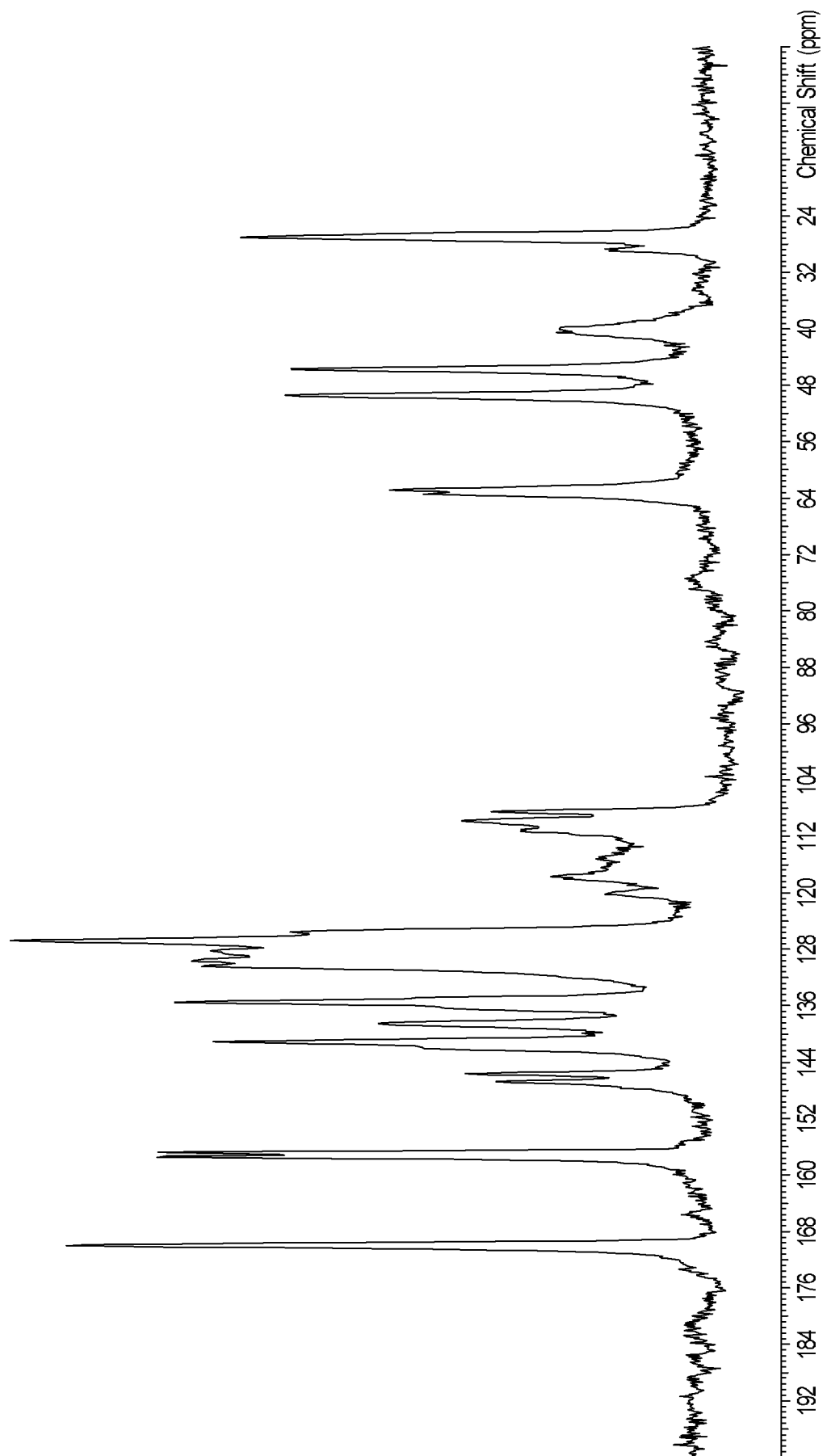
[Fig. 12]



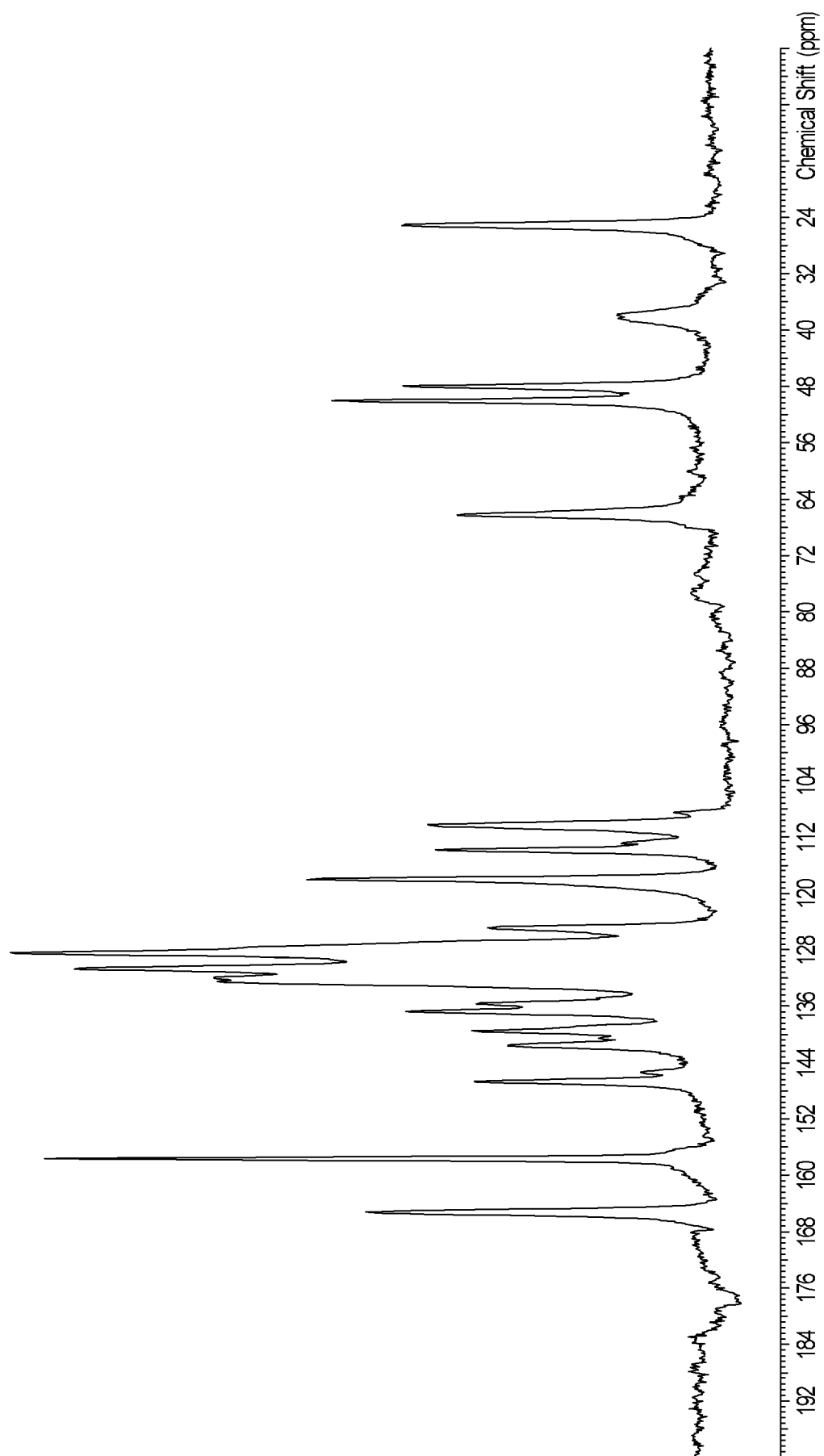
[Fig. 13]



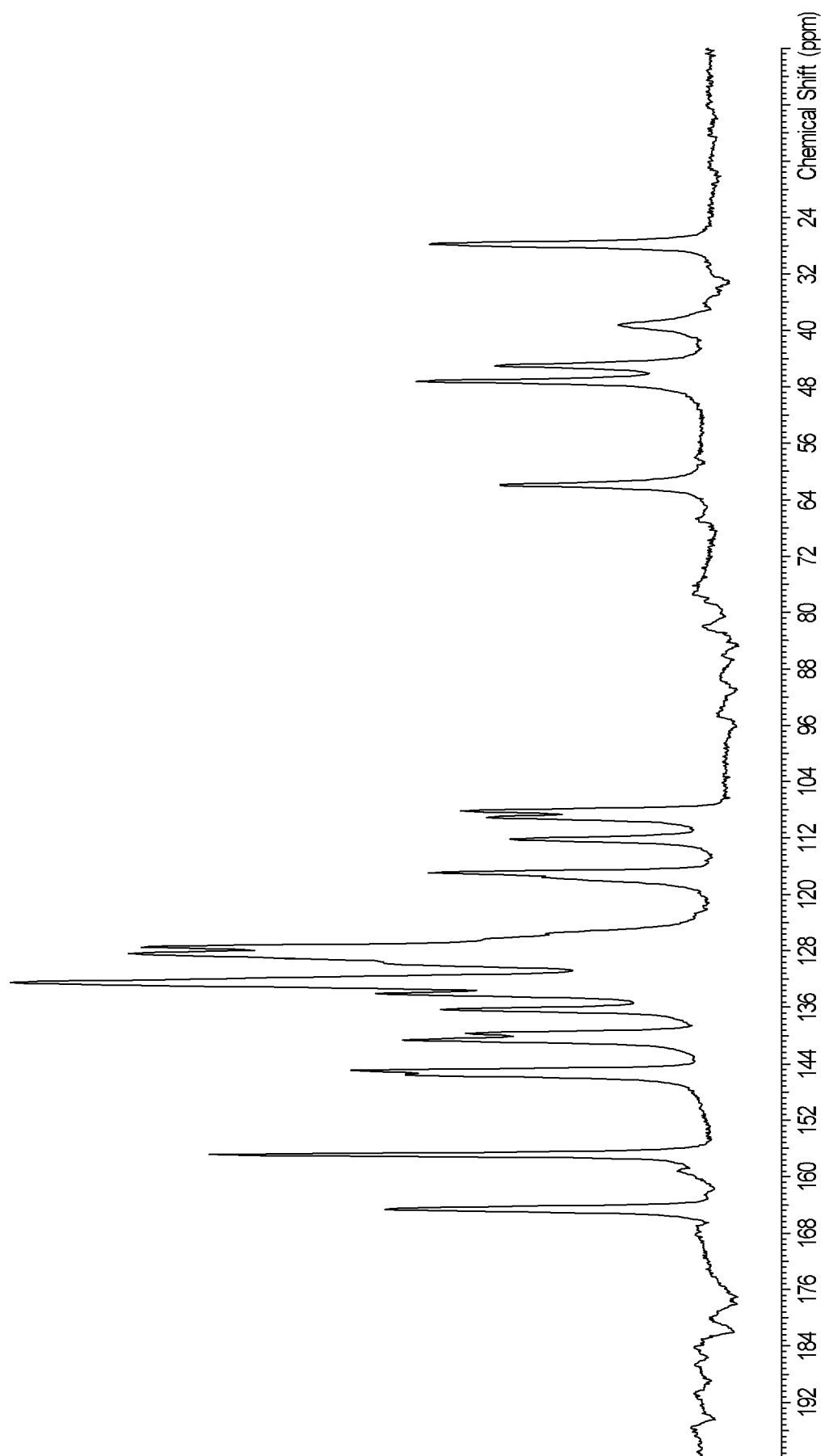
[Fig. 14]



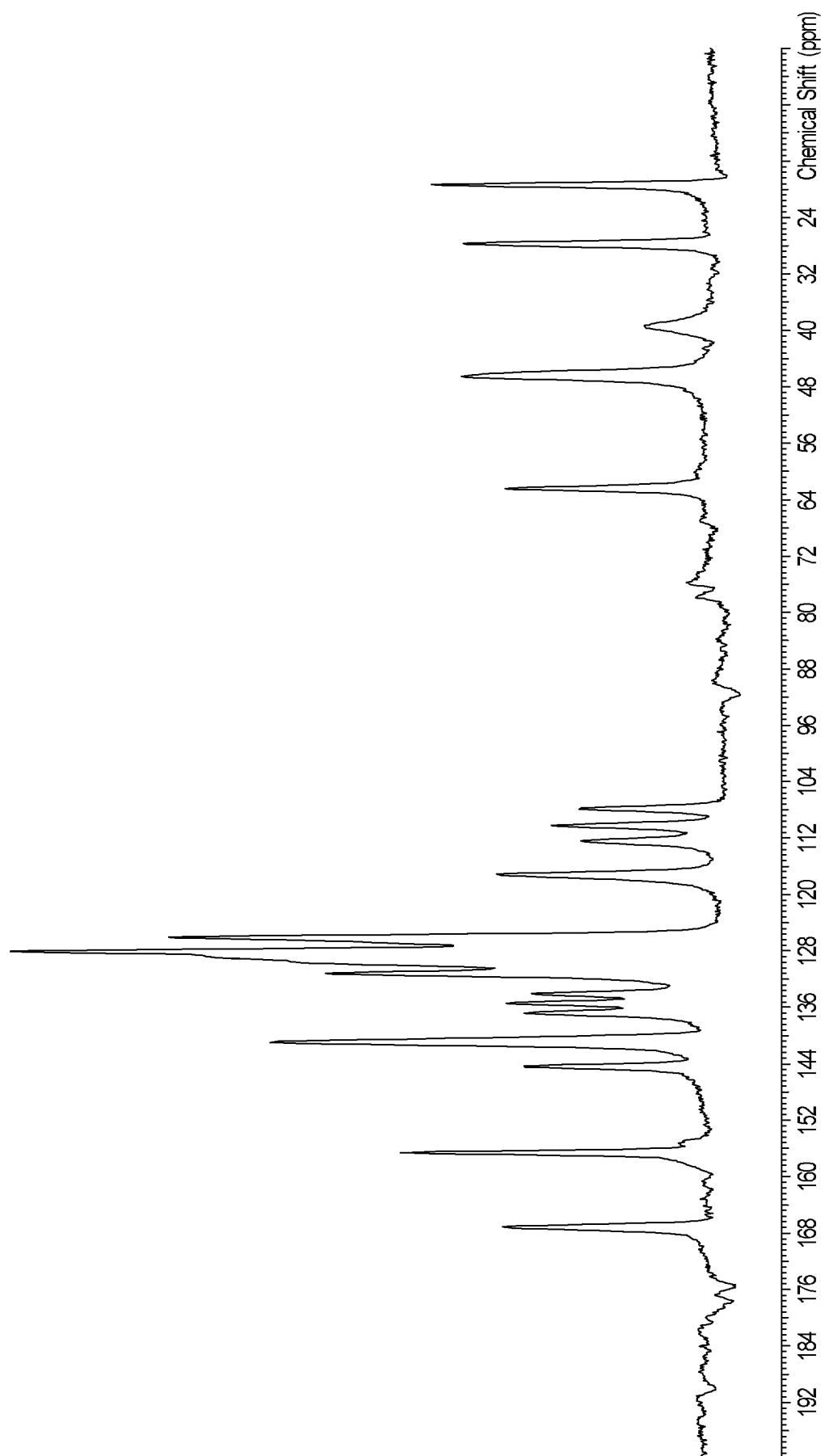
[Fig. 15]



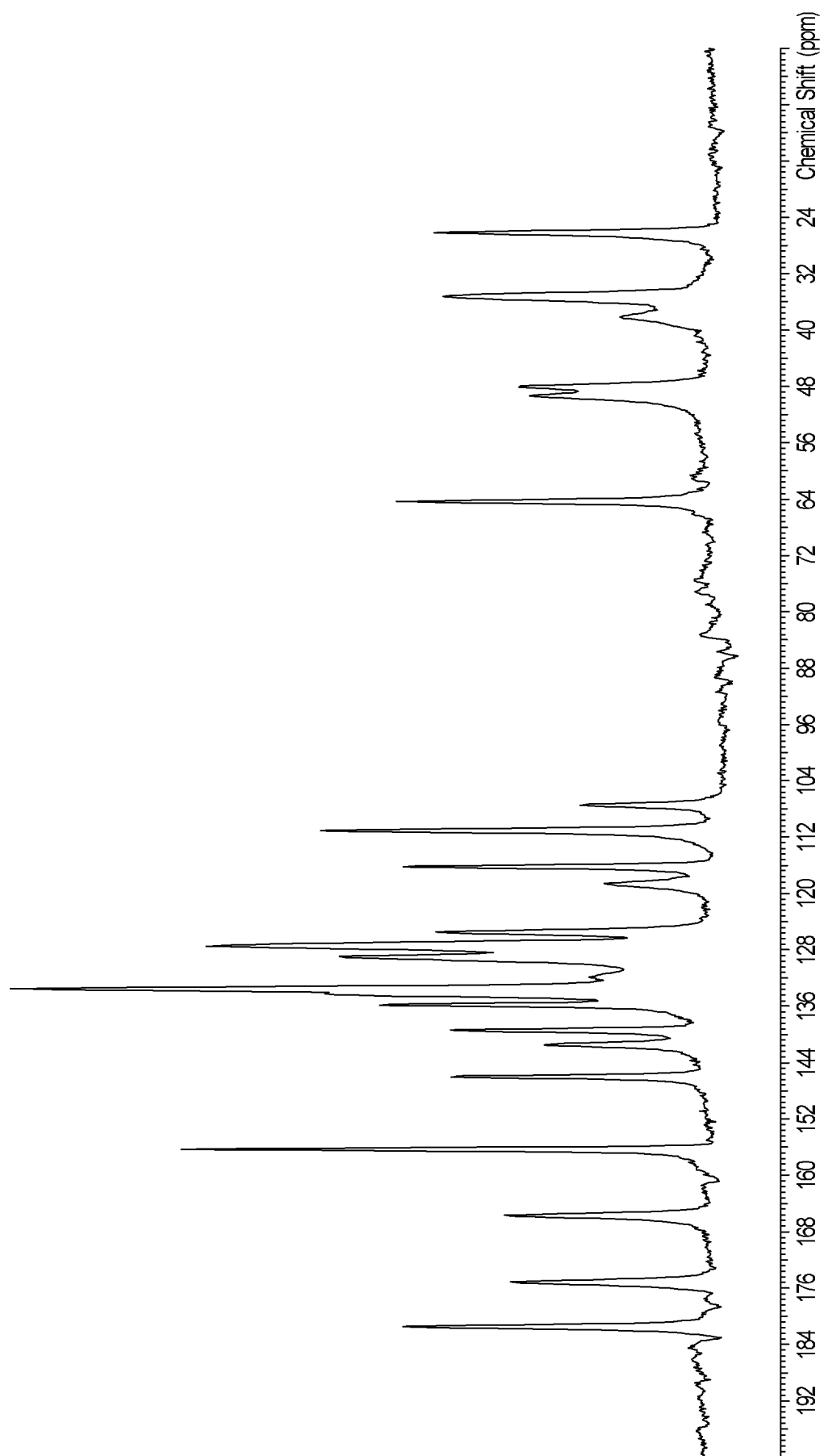
[Fig. 16]



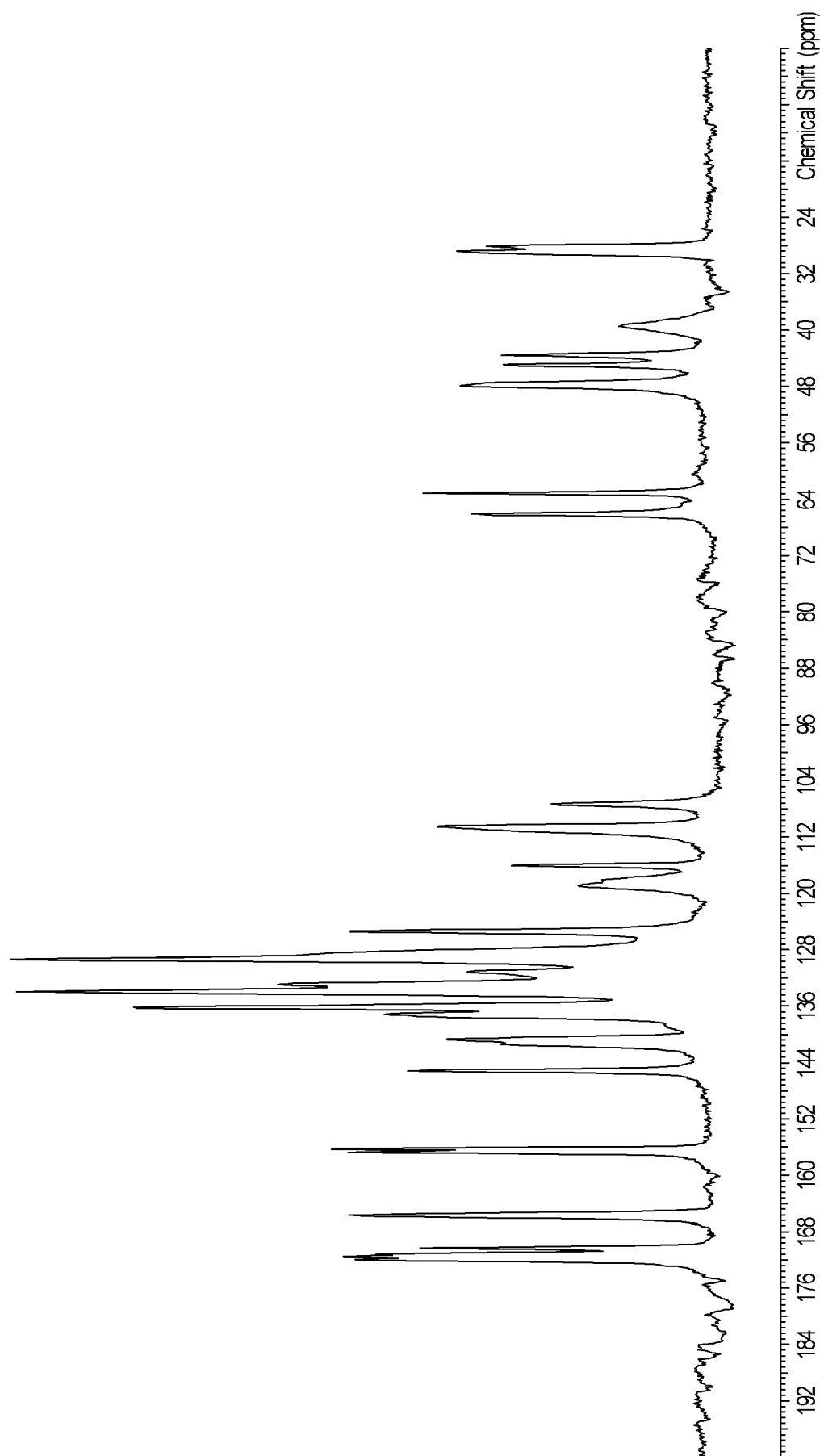
[Fig. 17]



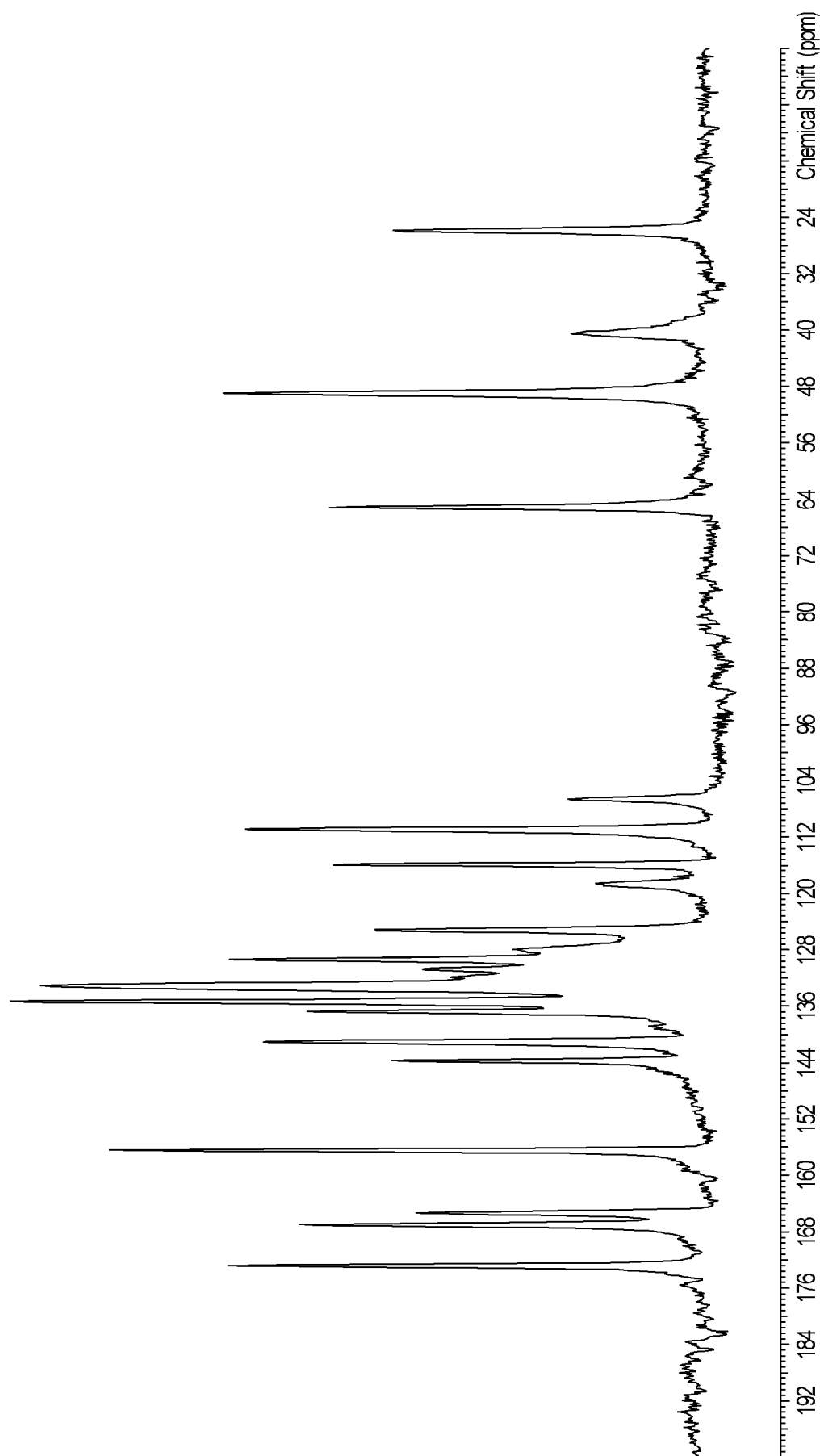
[Fig. 18]



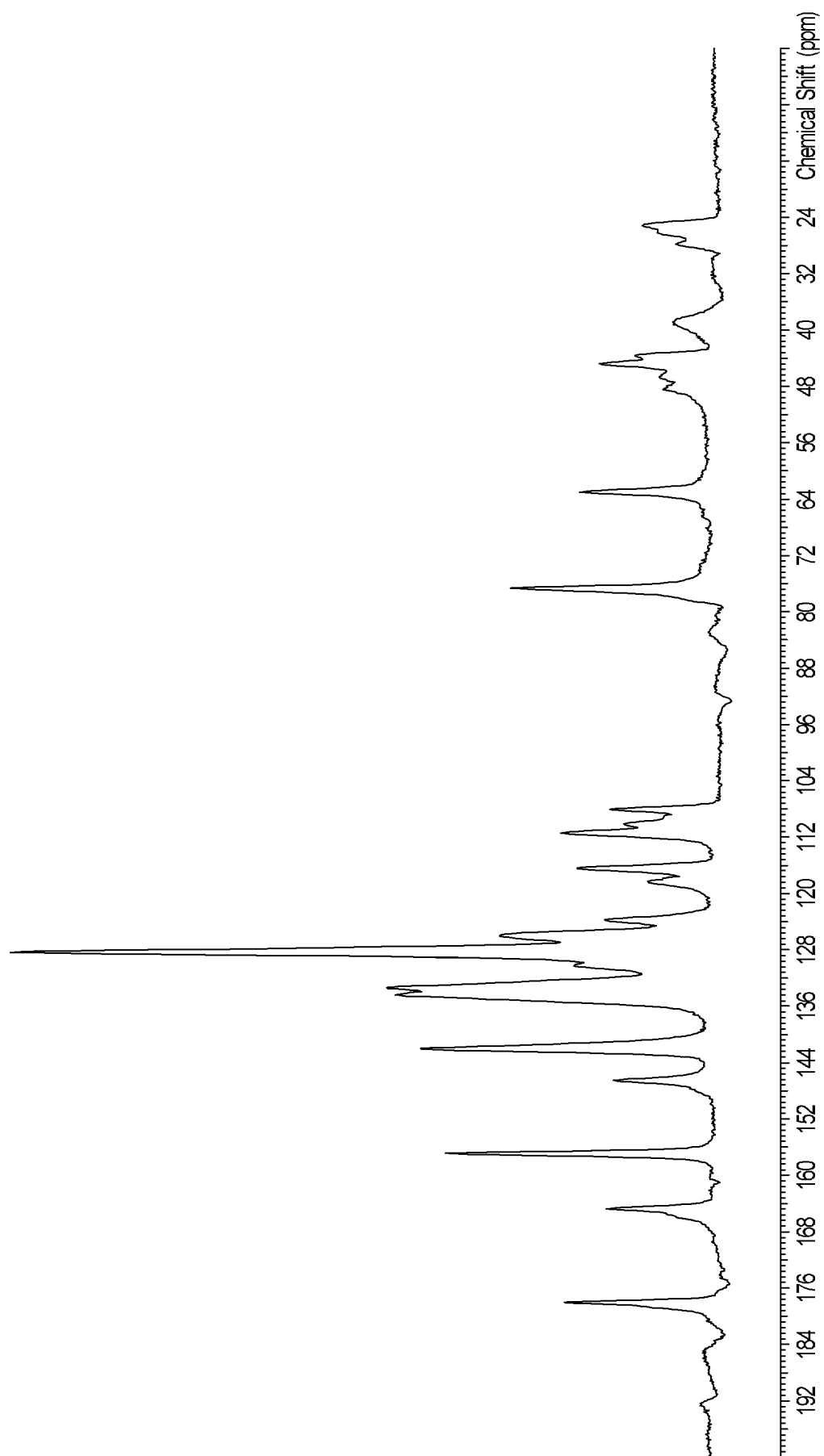
[Fig. 19]



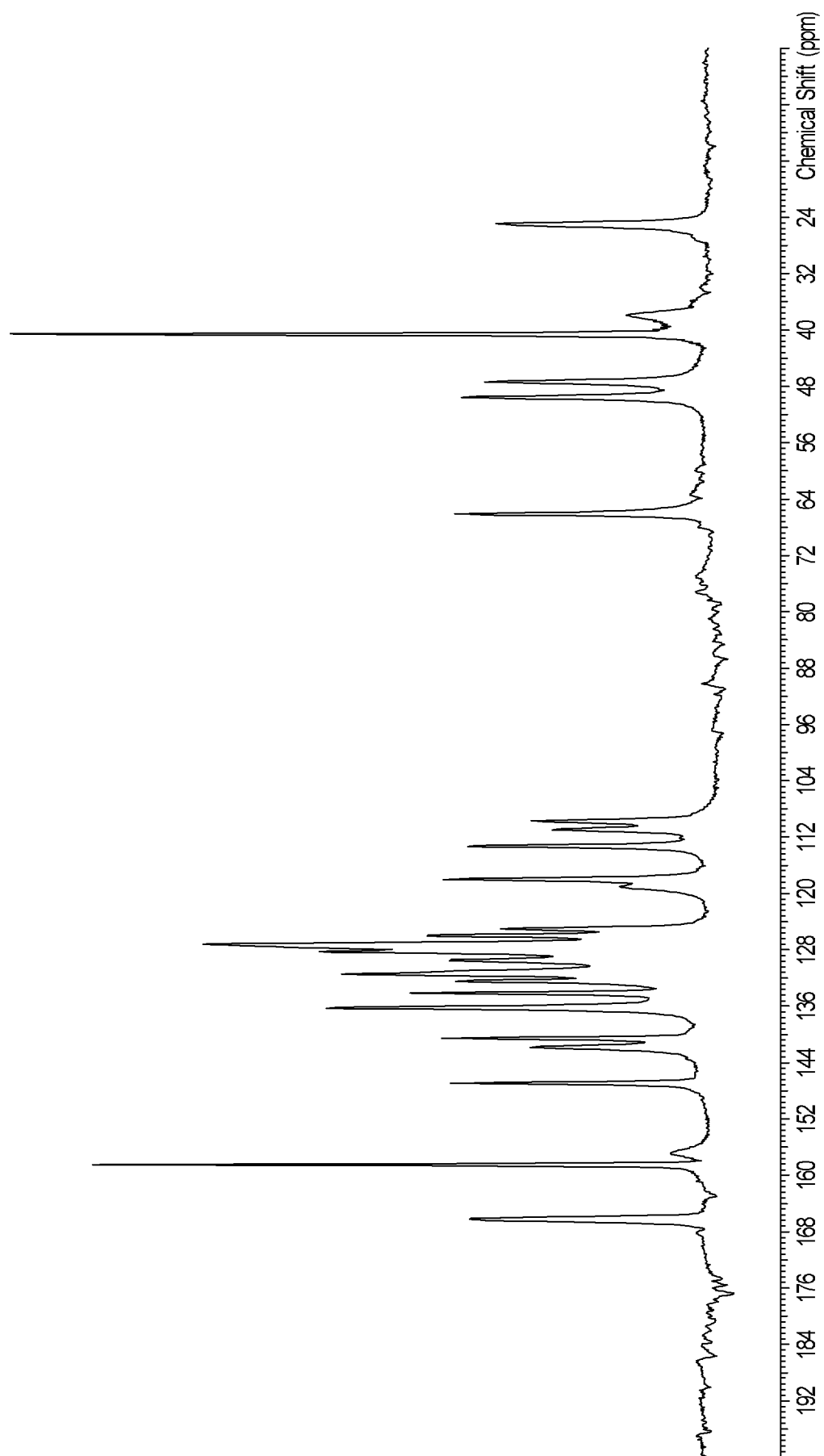
[Fig. 20]



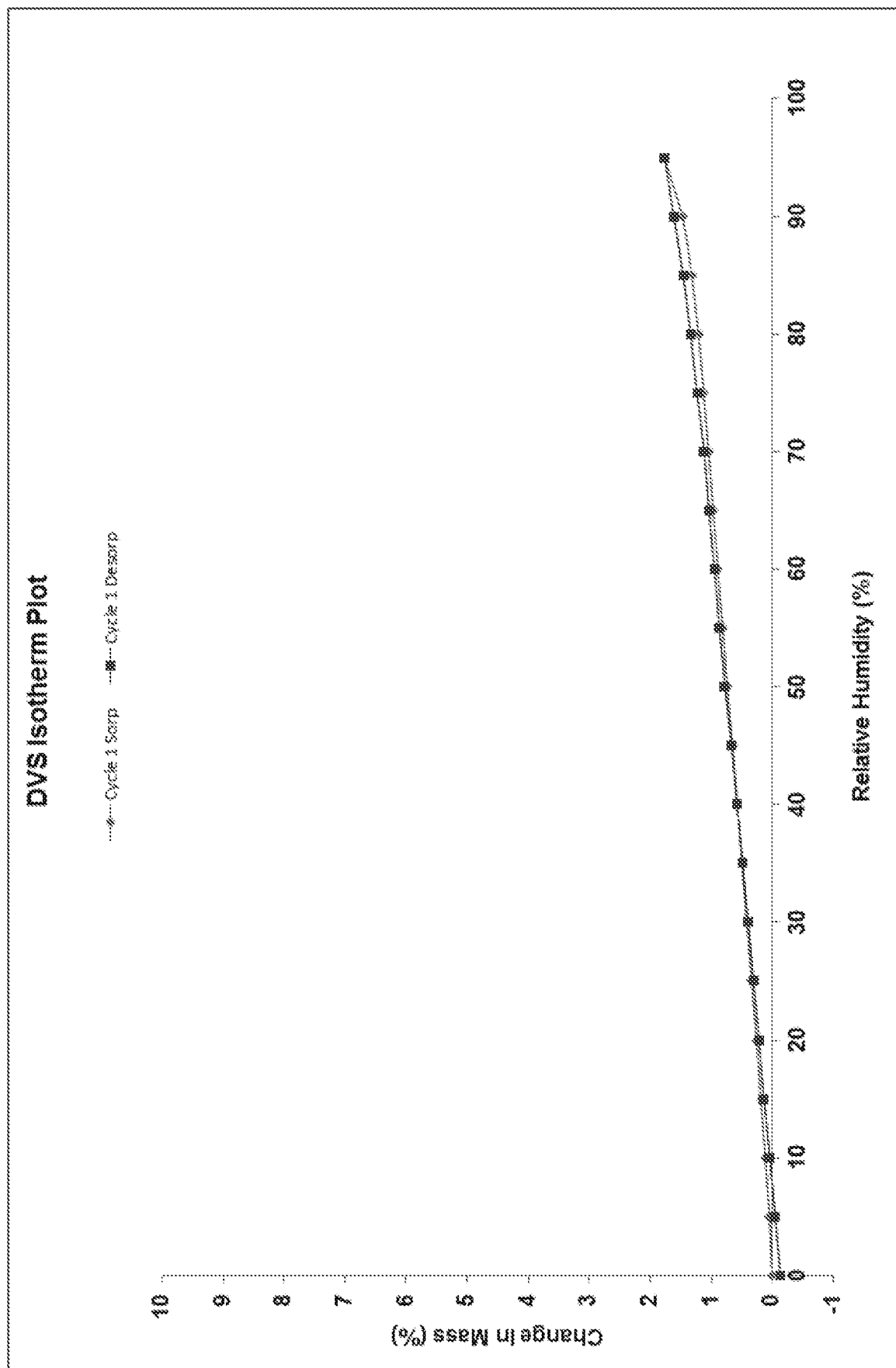
[Fig. 21]



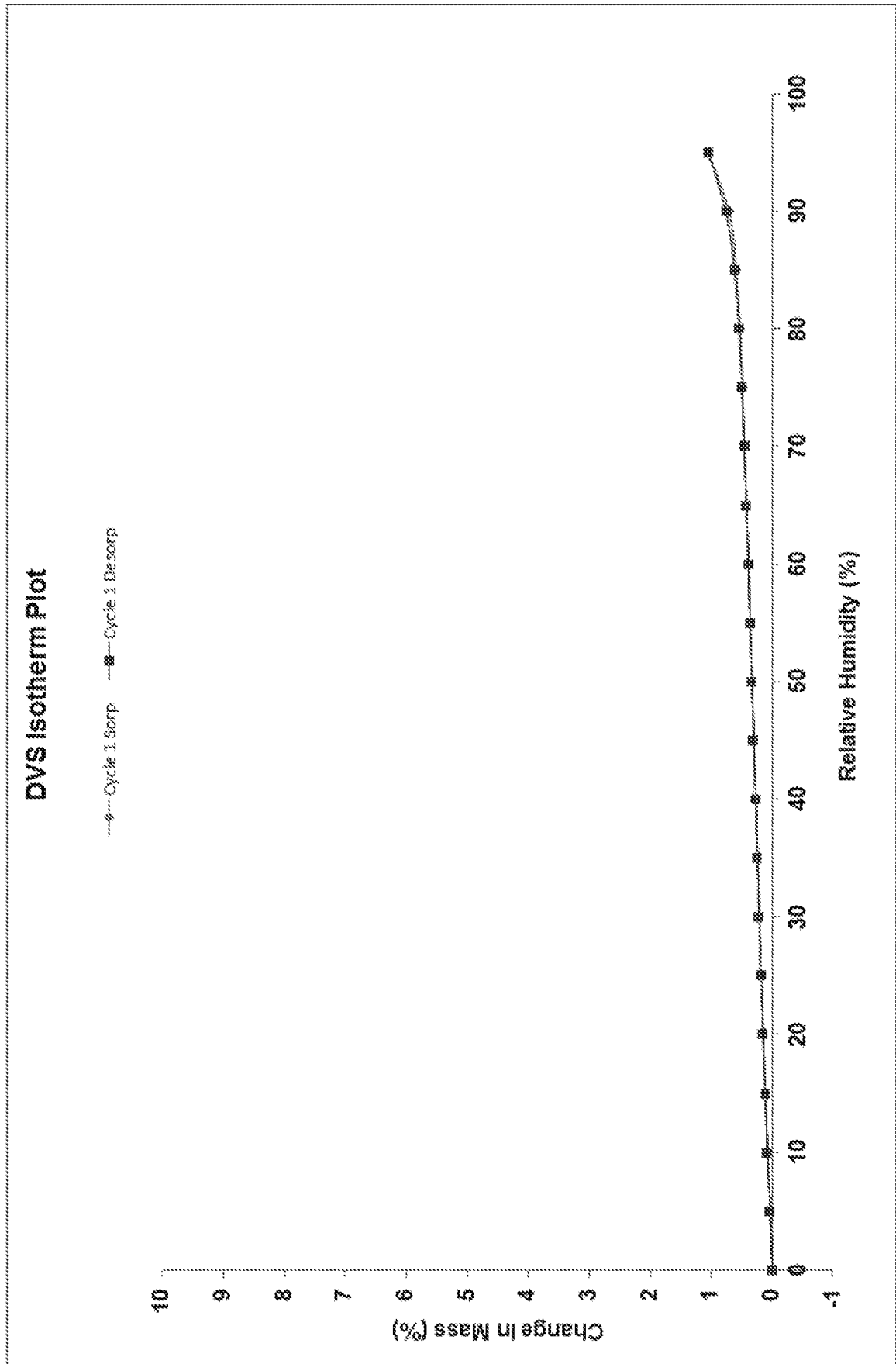
[Fig. 22]



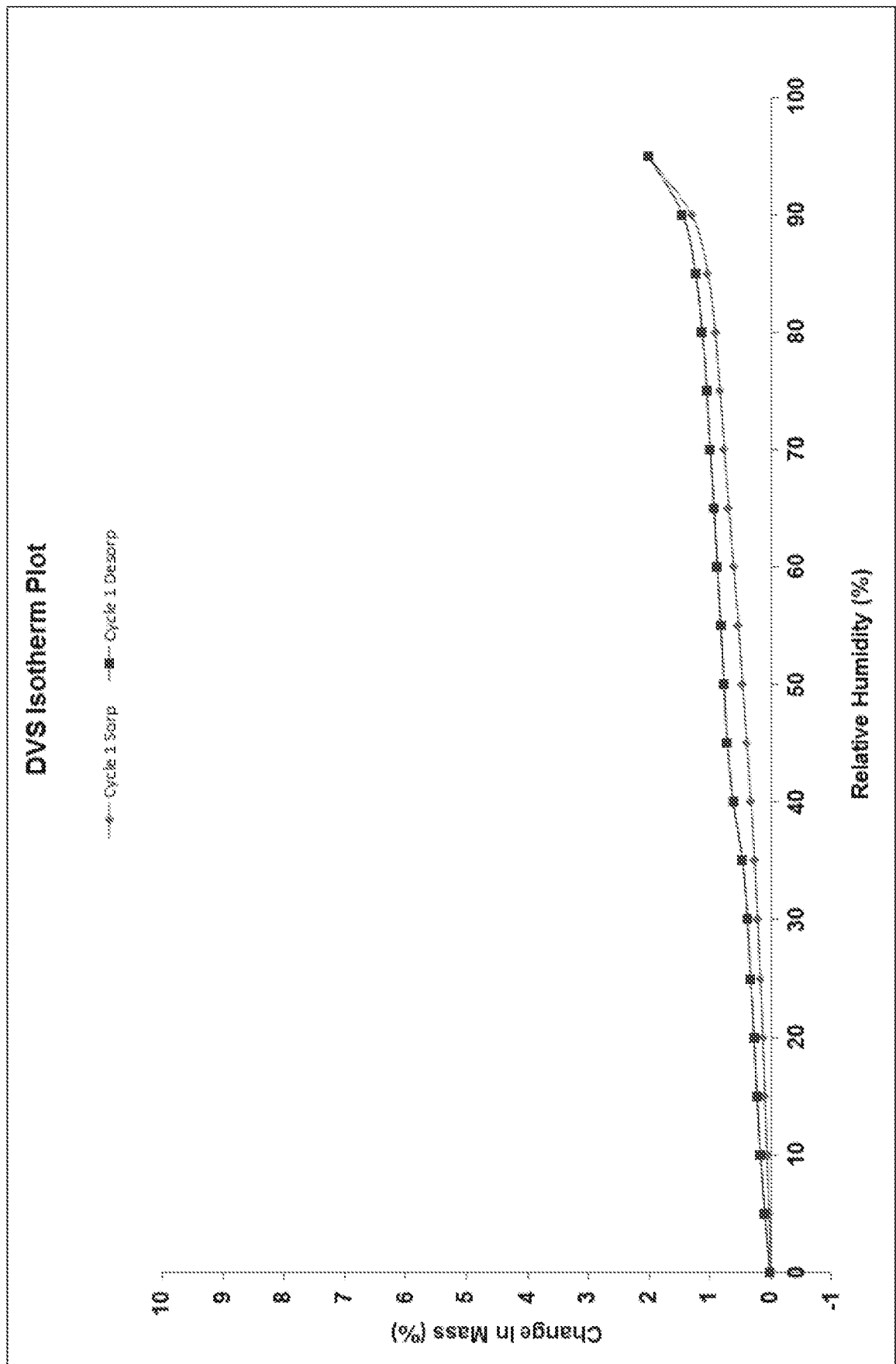
[Fig. 23]



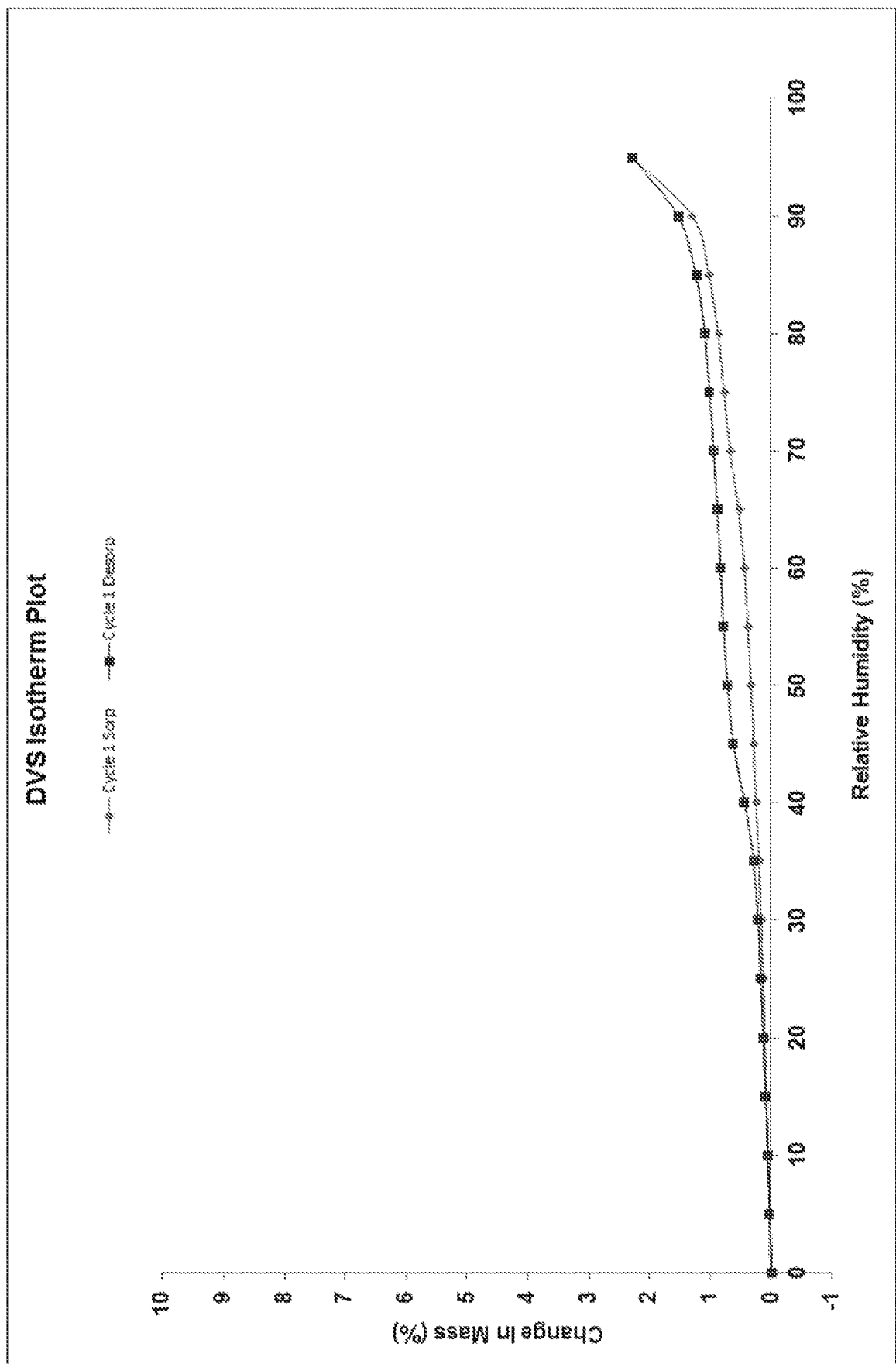
[Fig. 24]



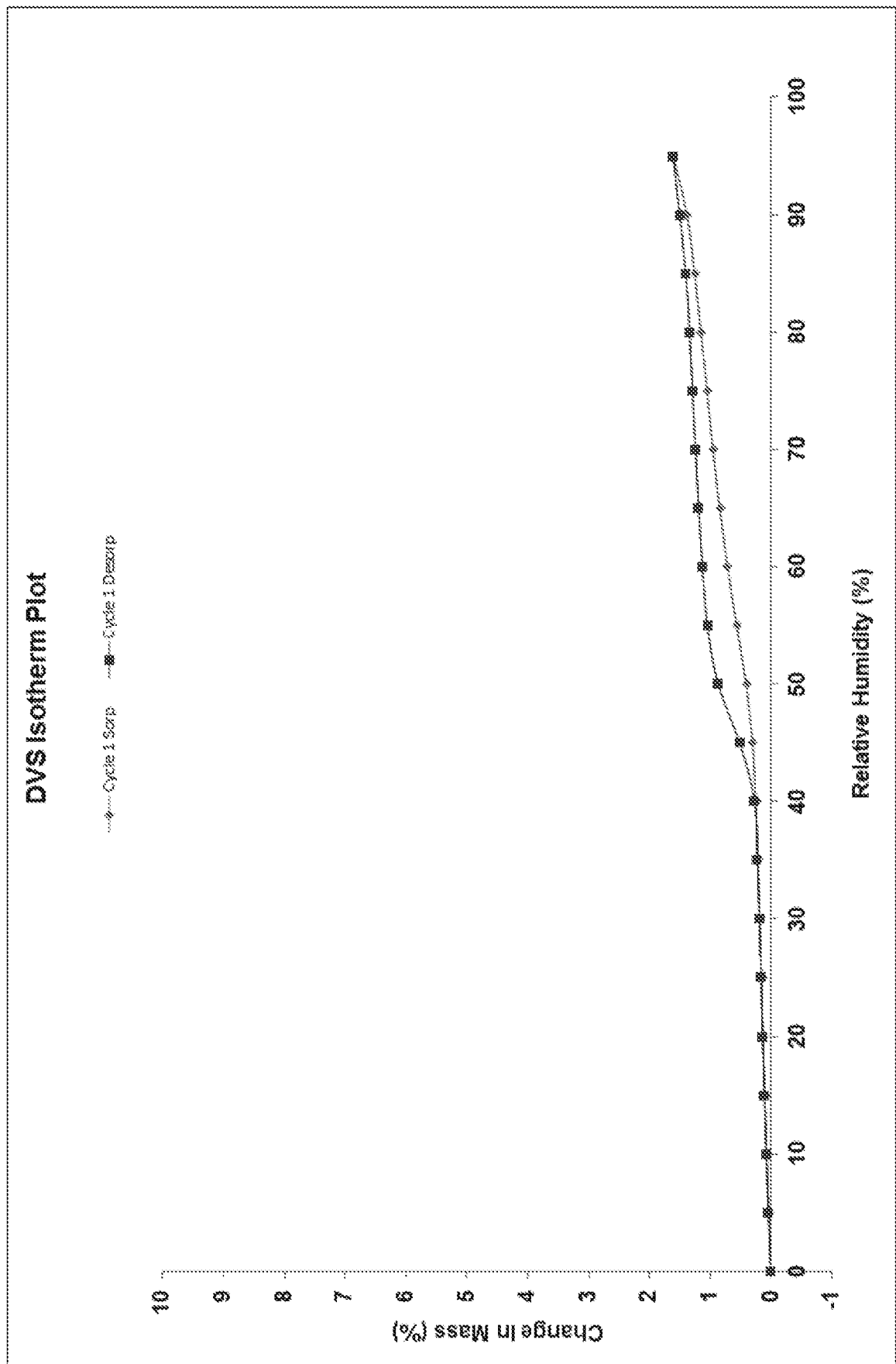
[Fig. 25]



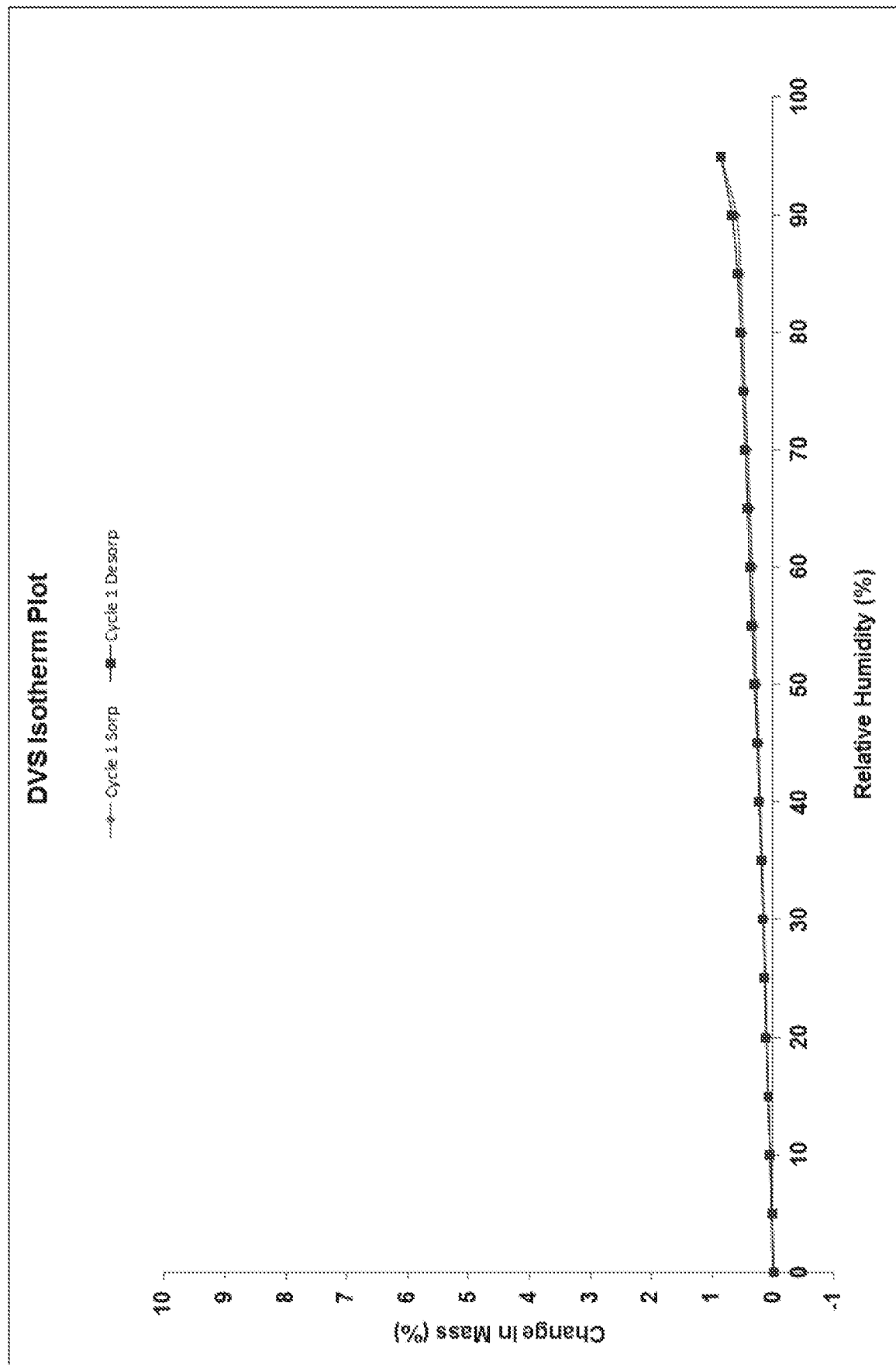
[Fig. 26]



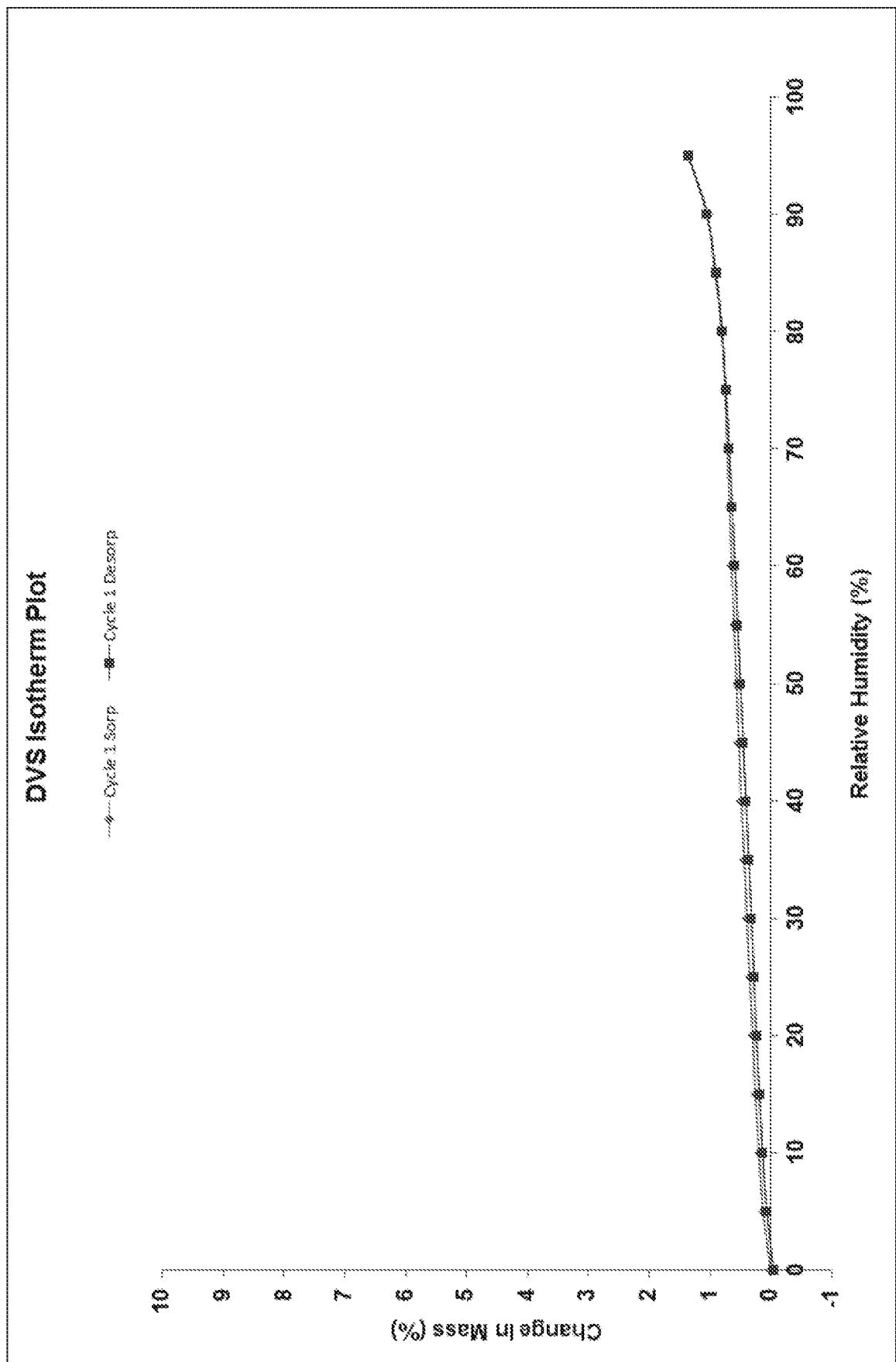
[Fig. 27]



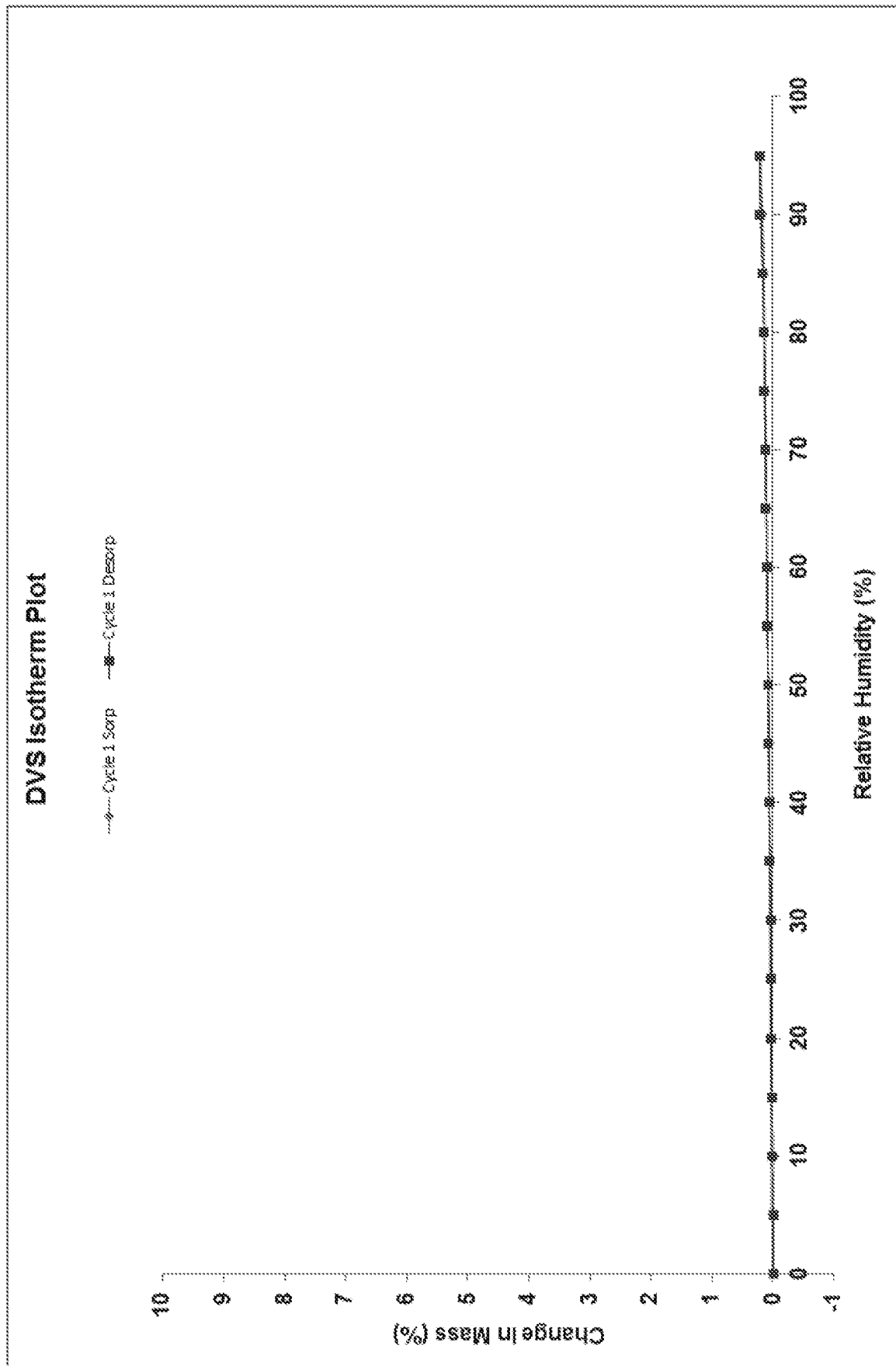
[Fig. 28]



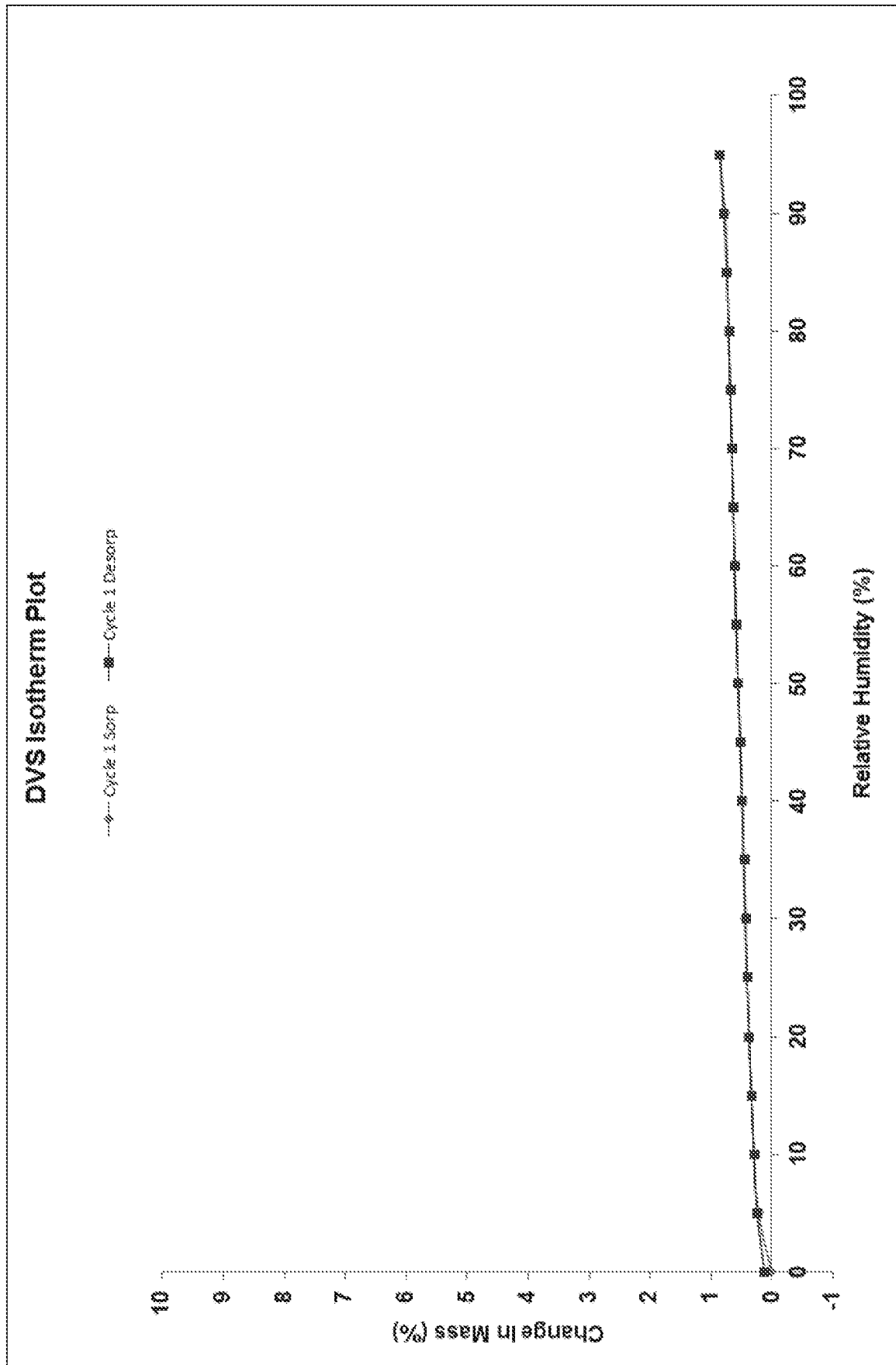
[Fig. 29]



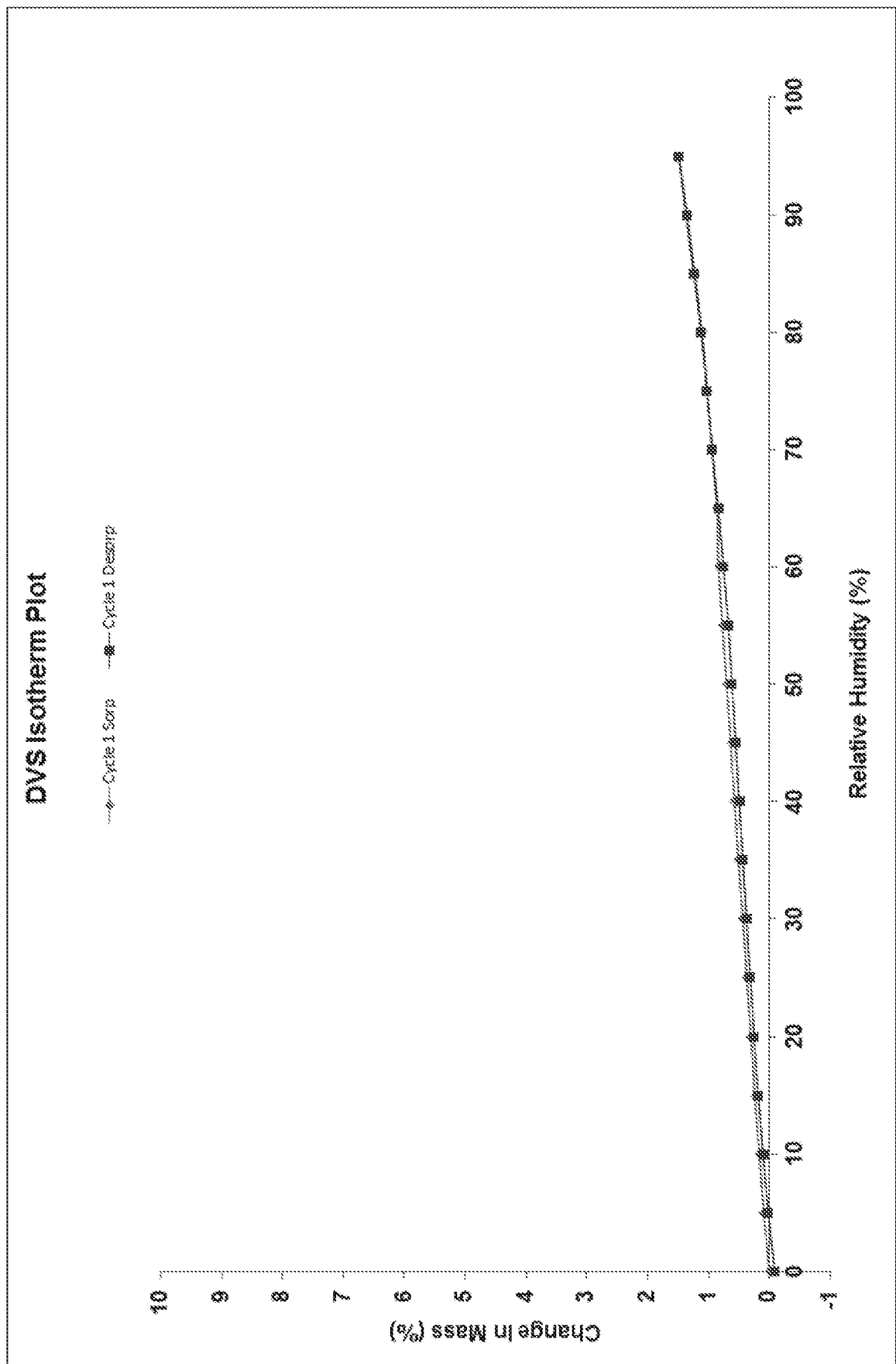
[Fig. 30]



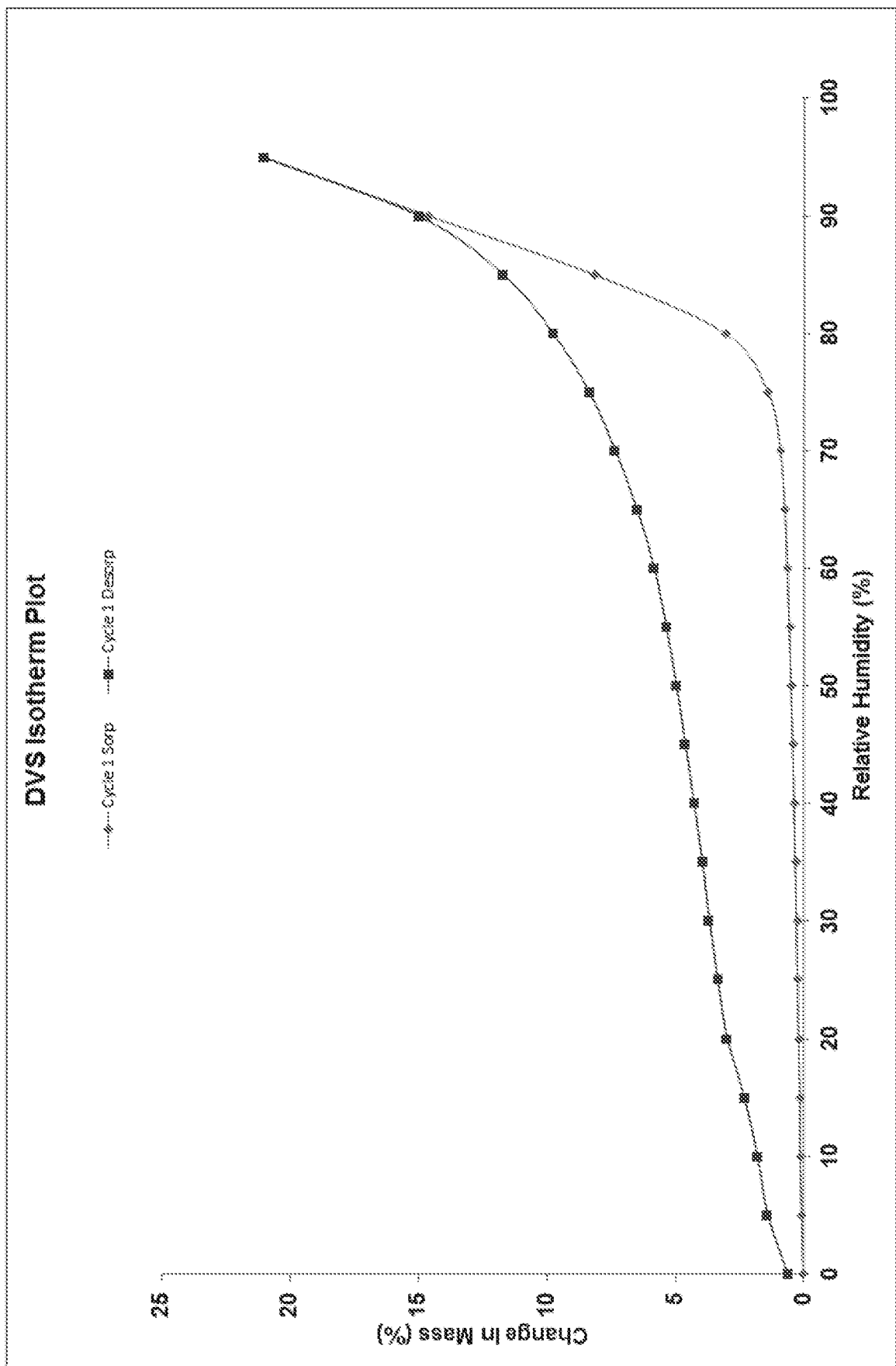
[Fig. 31]



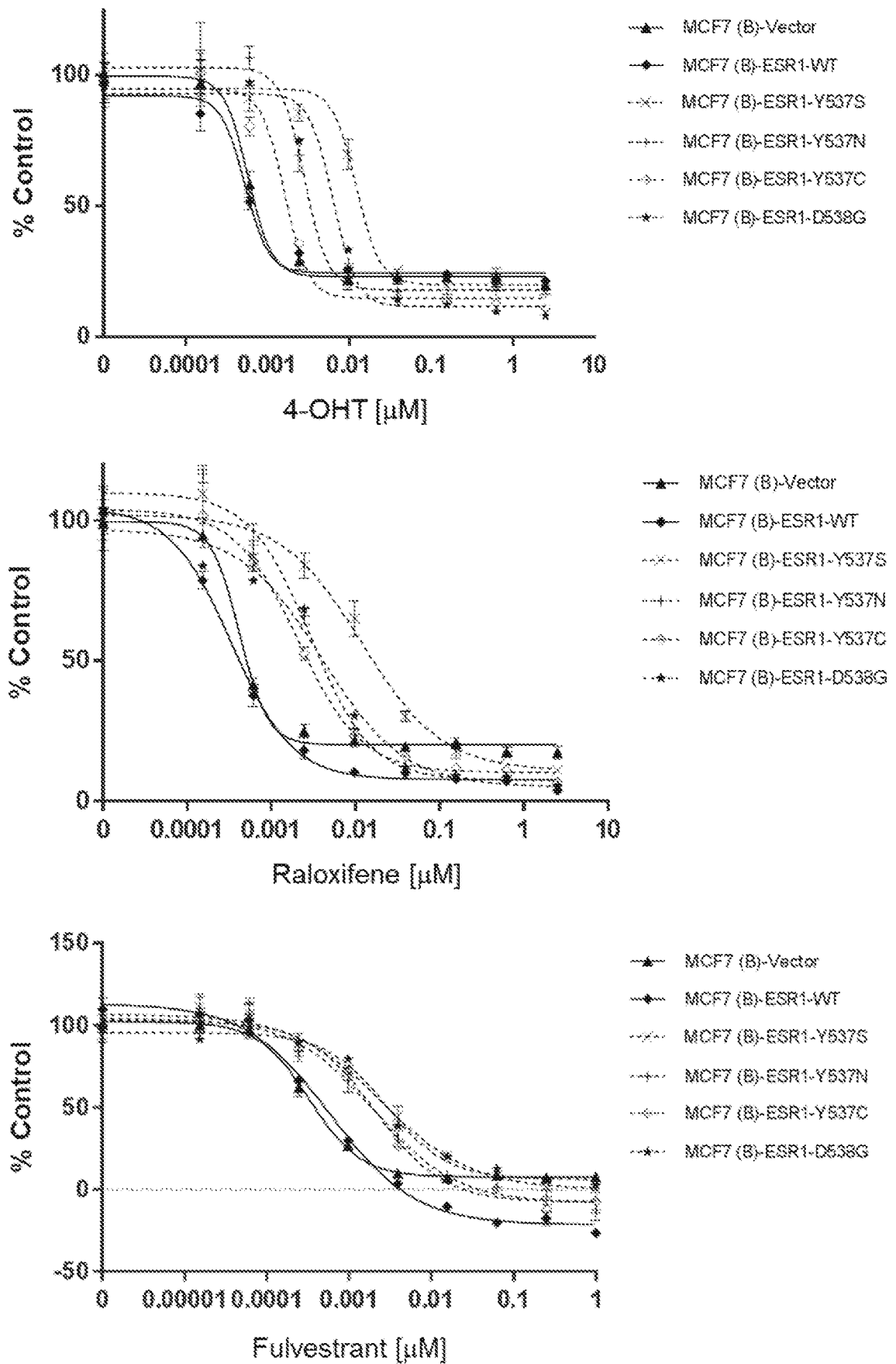
[Fig. 32]



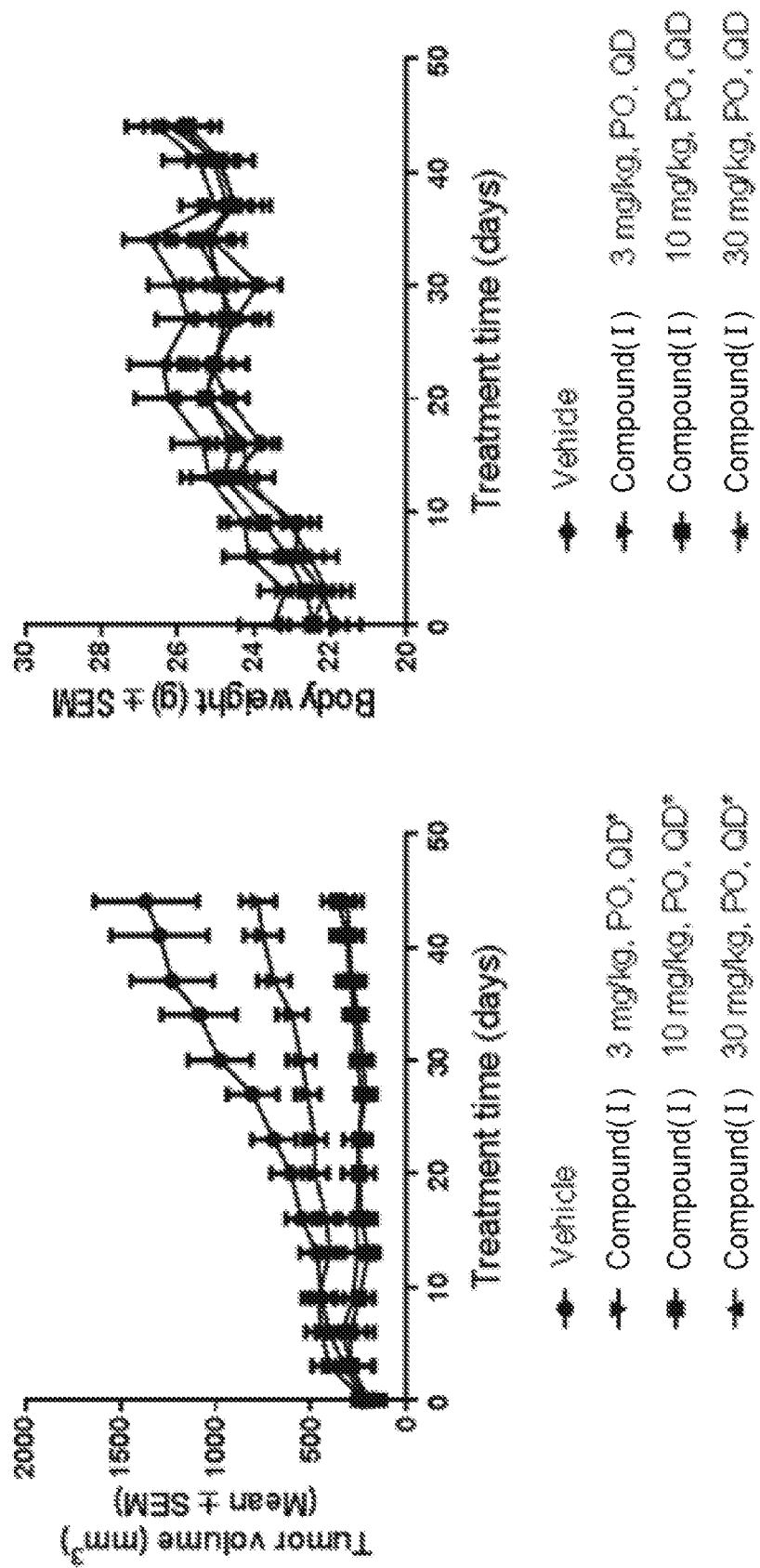
[Fig. 33]



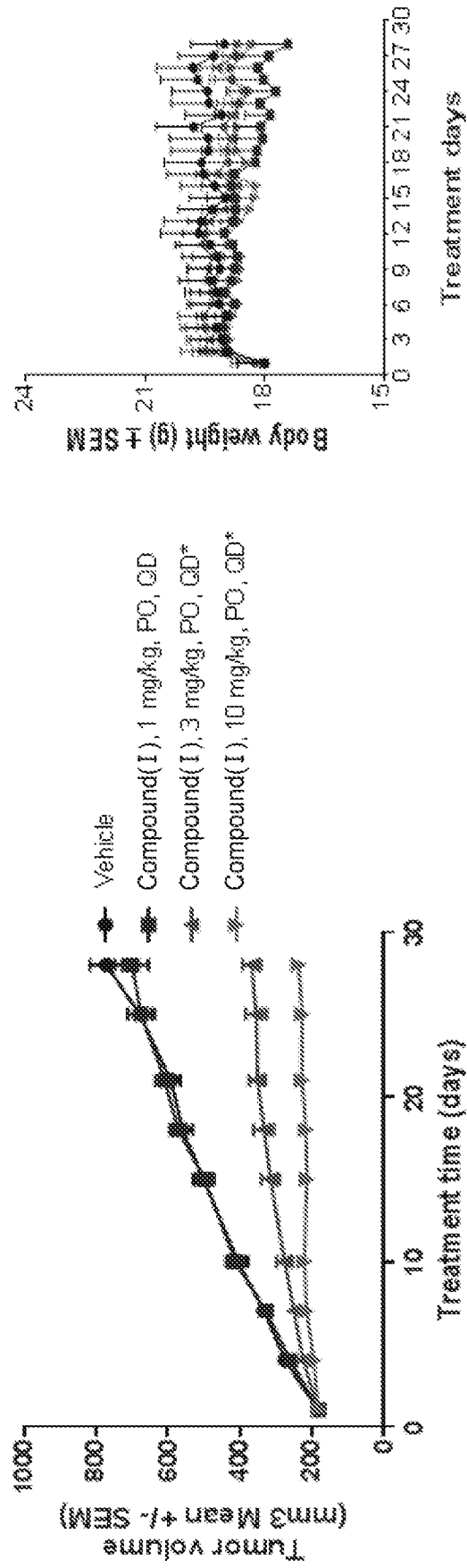
[Fig. 34]



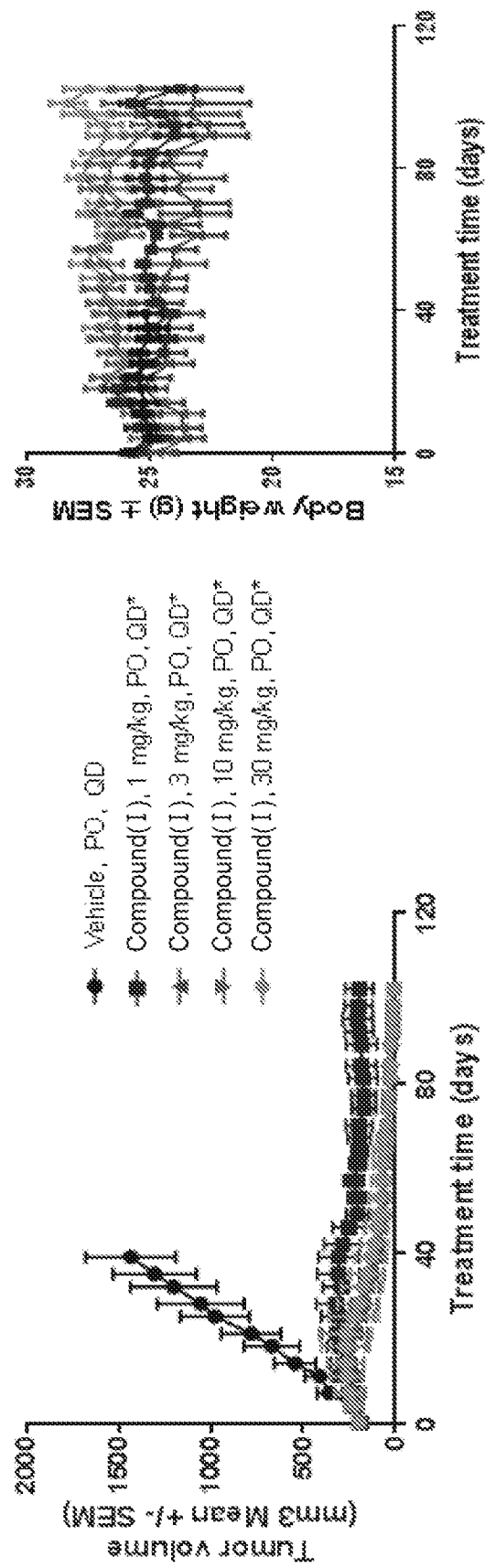
[Fig. 35]



[Fig. 36]



[Fig. 37]



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2019/019947

A. CLASSIFICATION OF SUBJECT MATTER		
Int.Cl. C07D231/56(2006.01)i, A61K31/416(2006.01)i, A61P35/00(2006.01)i		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
Int.Cl. C07D231/56, A61K31/416, A61P35/00		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Published examined utility model applications of Japan 1922-1996 Published unexamined utility model applications of Japan 1971-2019 Registered utility model specifications of Japan 1996-2019 Published registered utility model applications of Japan 1994-2019		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAplus/REGISTRY (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016/196346 A1 (EISAI R&D MANAGEMENT CO., LTD.) 2016.12.08, Claims, Compound 69 & JP 2018-516250 A & US 2016/0347717 A1 & US 2018/0127378 A1 & WO 2016/196337 A1 & EP 3302471 A1 & AU 2016271126 A1 & CA 2987321 A1 & KR 10-2018-0011274 A & CN 107847498 A	1-68
A	WO 2013/142266 A1 (SERAGON PHARMACEUTICALS, INC.) 2013.09.26, Claims, Examples & JP 2015-514072 A & US 2015/0105403 A1 & EP 2828243 A1 & CA 2866891 A1 & CN 104220426 A & KR 10-2014-0138296 A	1-68
☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
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Date of the actual completion of the international search		Date of mailing of the international search report
22.07.2019		06.08.2019
Name and mailing address of the ISA/JP		Authorized officer
Japan Patent Office		YOSHIKAI, Hirono
3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan		4P 6287
		Telephone No. +81-3-3581-1101 Ext. 3492

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2019/019947

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/037411 A2 (ARAGON PHARMACEUTICALS, INC.) 2012.03.22, Claims, Examples & JP 2013-544761 A & JP 2016-155832 A & US 2013/0231333 A1 & US 2016/0297767 A1 & US 2012/0071535 A1 & US 2013/0012561 A1 & WO 2012/037410 A2 & EP 2616445 A2 & EP 2735562 A1 & CN 103189361 A & KR 10-2013-0136986 A	1-68
P, X	US 2018/0141913 A1 (EISAI R & D MANAGEMENT CO., LTD.) 2018.05.24, Claims, Paragraphs [0125]-[0133], Example 21 & WO 2018/098305 A1	1-68
P, A	WO 2018/097273 A1 (EISAI R&D MANAGEMENT CO., LTD.) 2018.05.31, Claims, Examples & JP 2018-108981 A & US 2019/0144419 A1 & AU 2017363699 A1 & CA 3041986 A1 & CN 109790141 A	1-68