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(54) **MALATE SALT OF N-(4-{[6,7-BIS(METHYLOXY) QUINOLIN-4-YL]OXY}PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER**

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(57) **ABSTRACT**

Disclosed are malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including a (L)-malate salt, a (D)-malate salt, a (DL) malate salt, and mixtures thereof; and crystalline and amorphous forms of the malate salts. Also disclosed are pharmaceutical compositions comprising at least one malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide; and methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis (methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1, 1-dicarboxamide.

3 Claims, 27 Drawing Sheets

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Figure 1

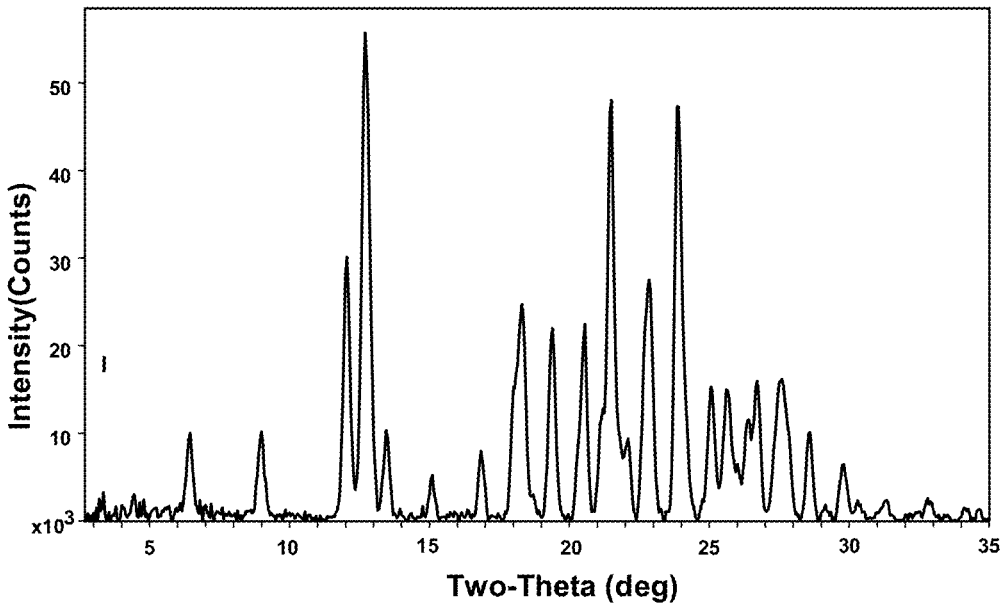

Intensity(Counts)
x10^3
50
40
30
20
10
5
10
15
20
25
30
35
Two-Theta (deg)

Figure 2

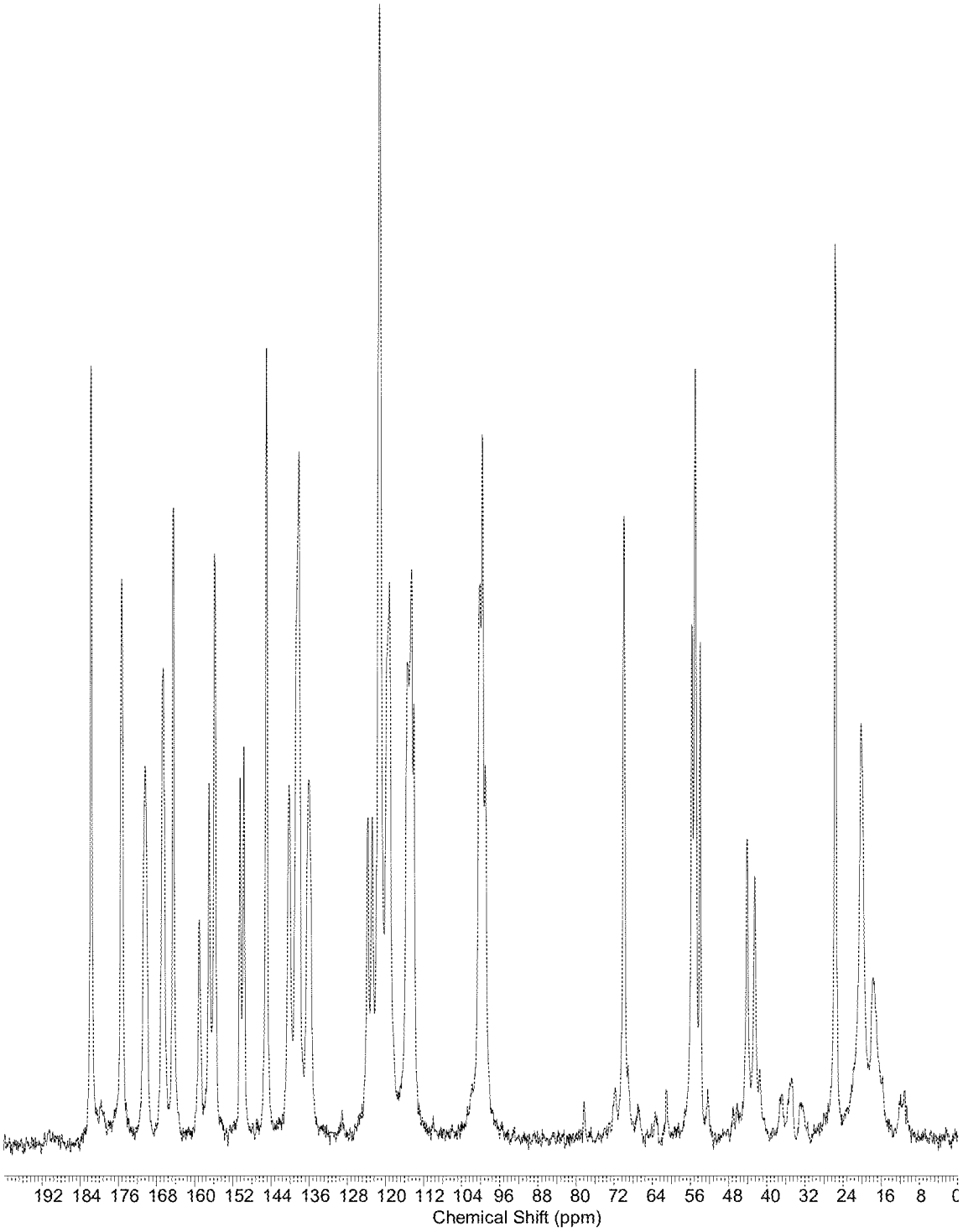

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

Figure 3

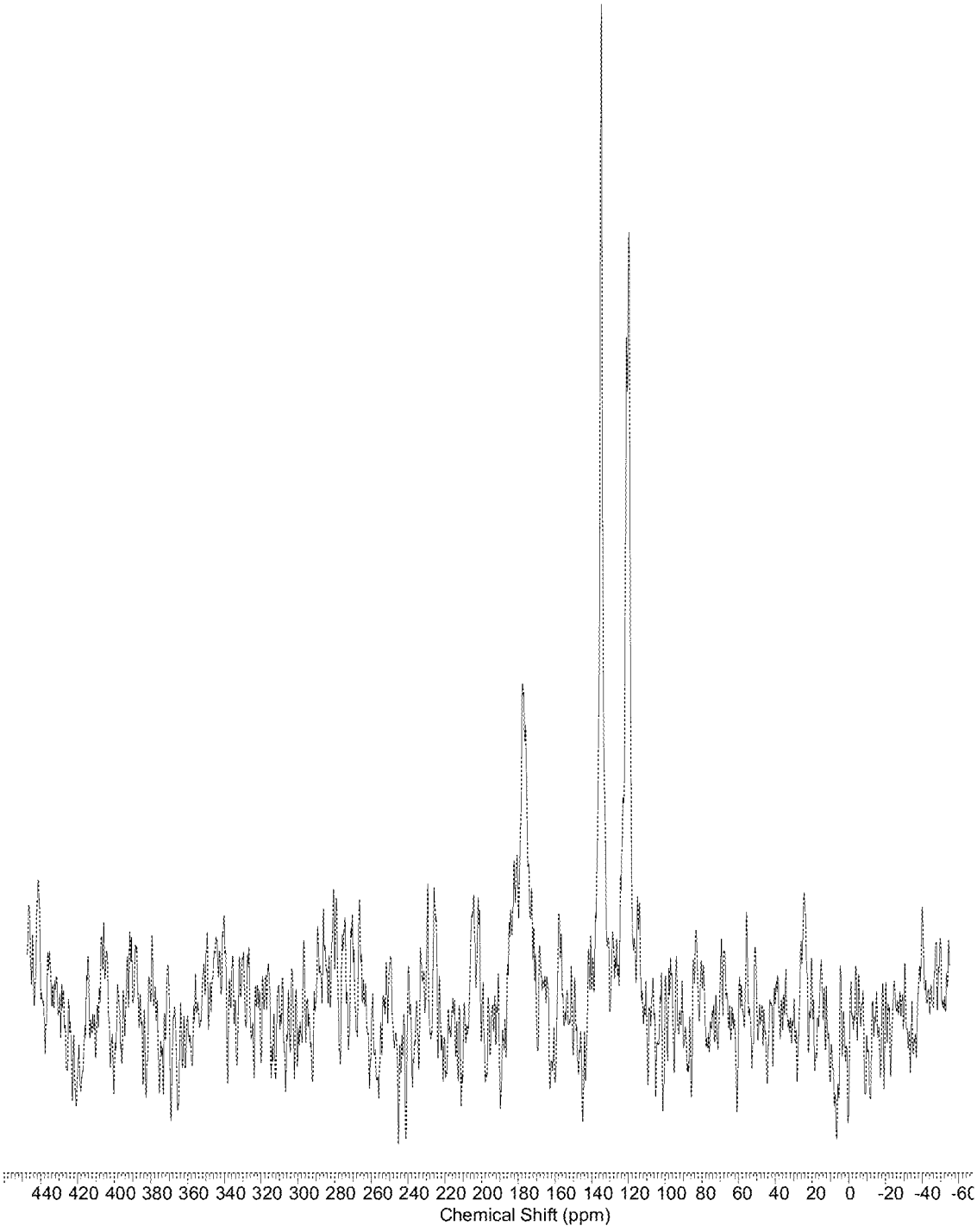

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 4

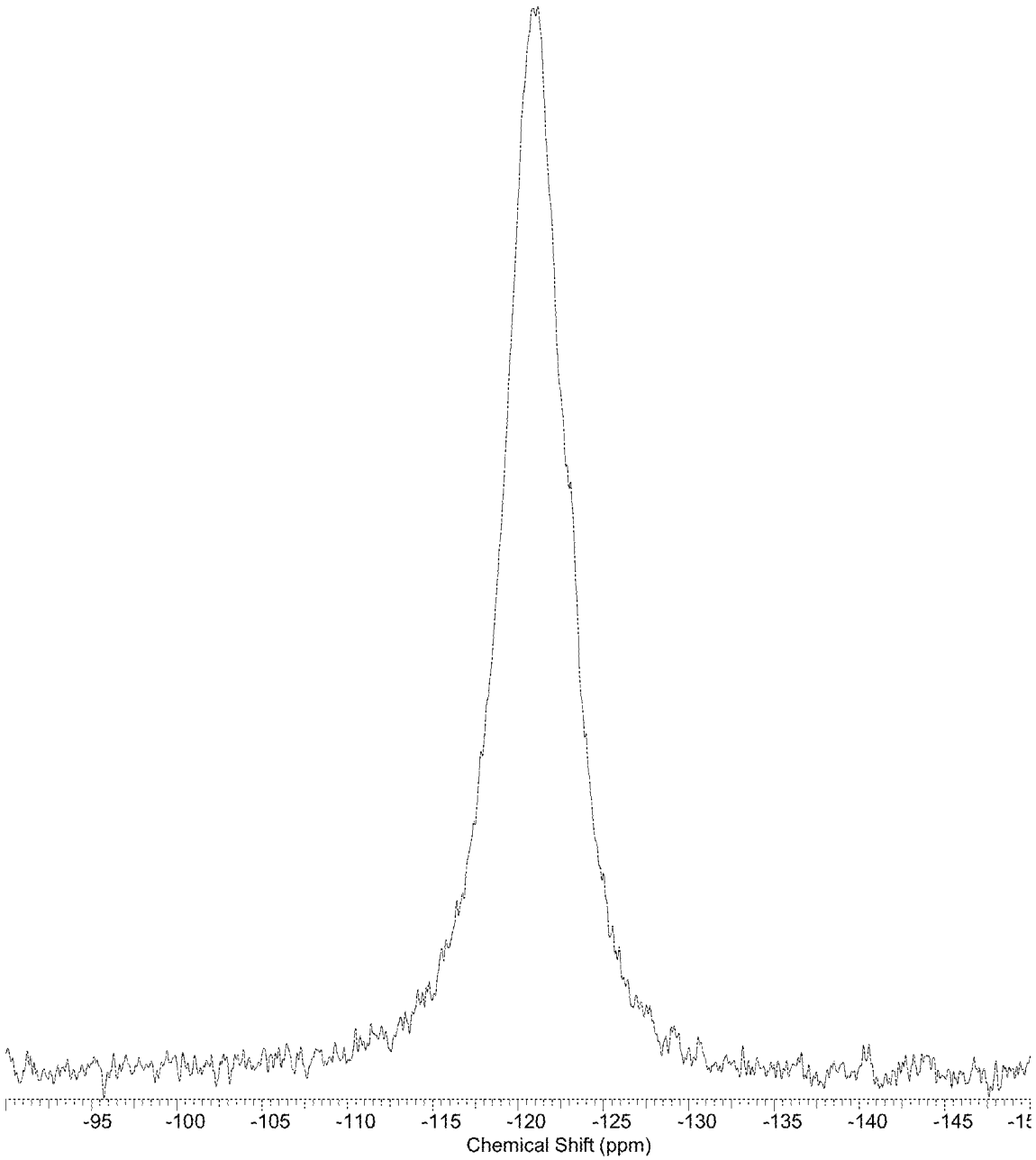


Figure 5

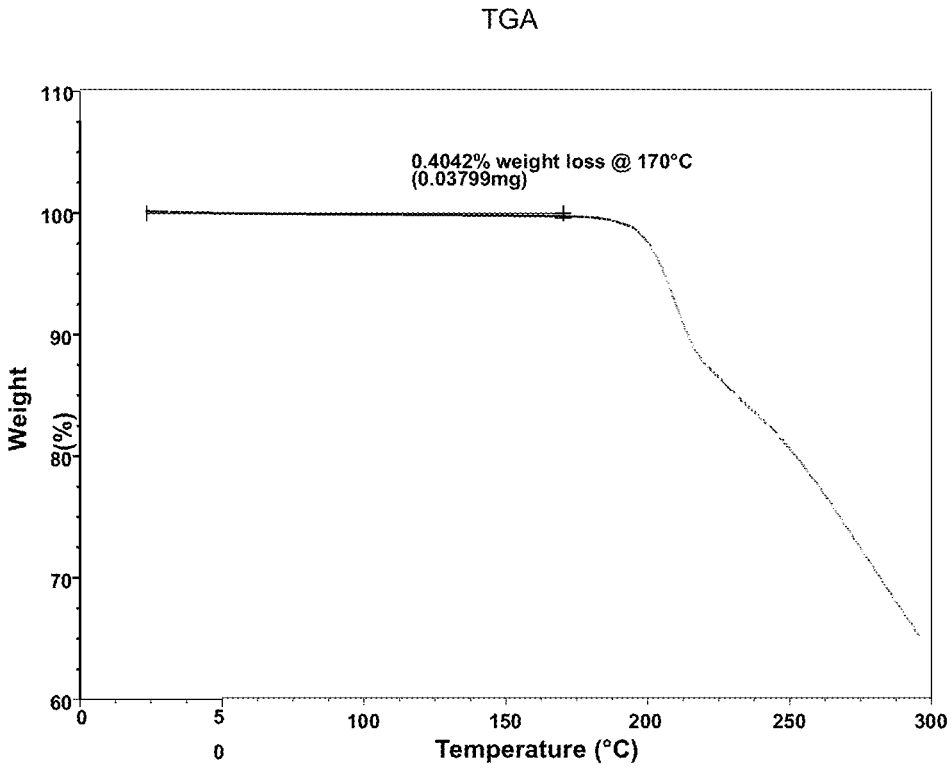

TGA
0.4042% weight loss @ 170°C
(0.03799mg)
Weight (%)
Temperature (°C)
110
100
90
80
70
60
0
50
100
150
200
250
300

Figure 6

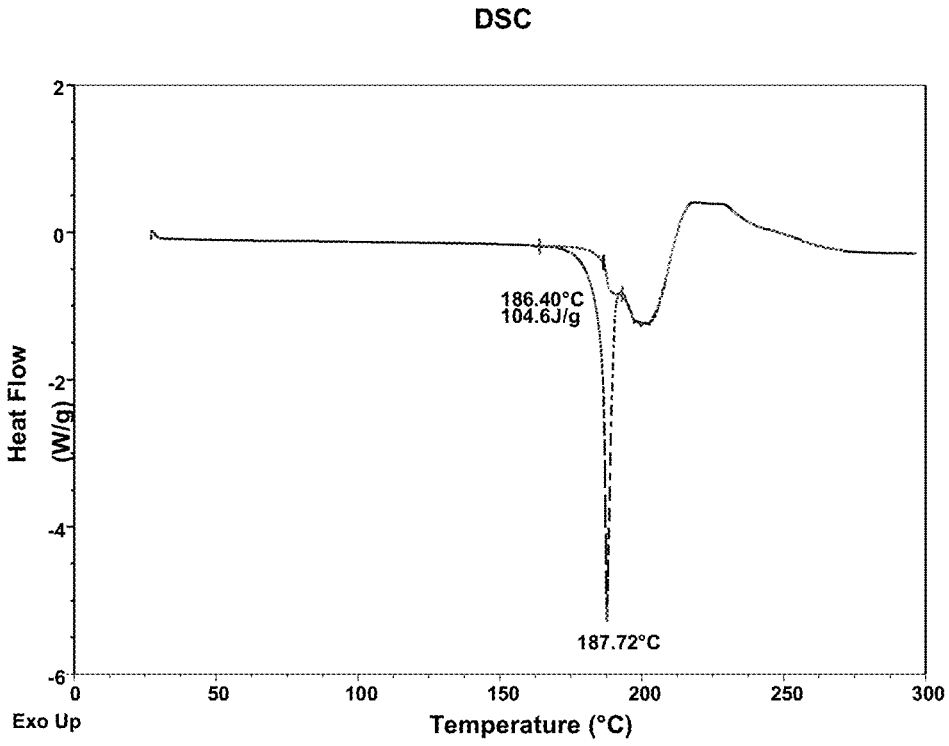
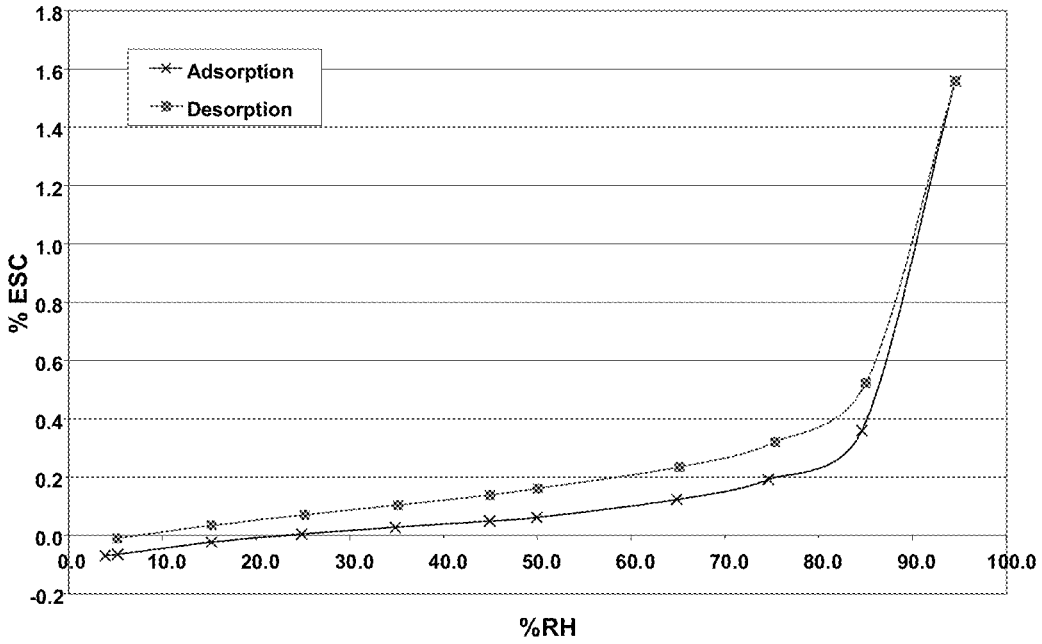

DSC
2
0
-2
-4
-6
Heat Flow (W/g)
186.40°C
104.6J/g
187.72°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)

Figure 7



Moisture Sorption of Compound (I), Form N-1

Figure 8

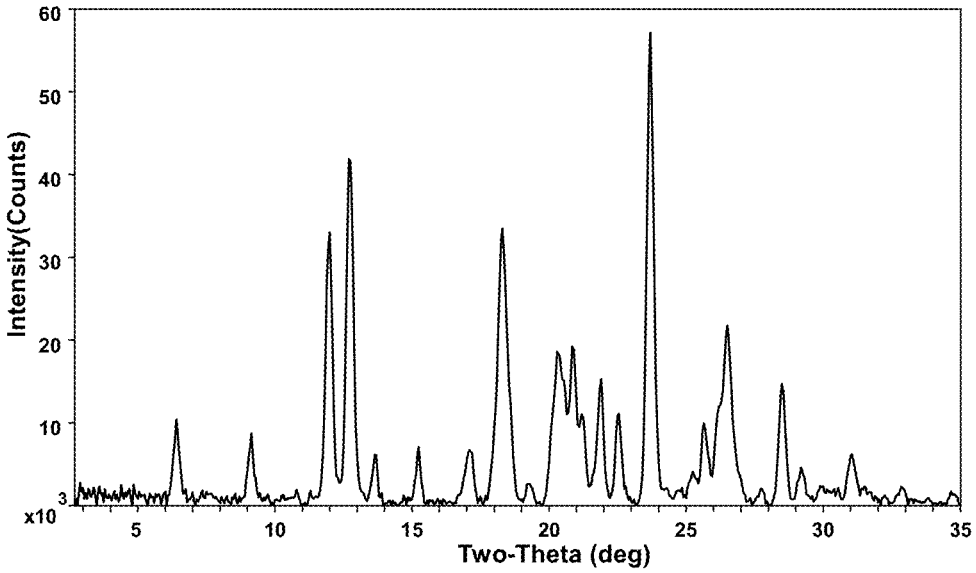

Intensity(Counts)
x10
3
10
20
30
40
50
60
5
10
15
20
25
30
35
Two-Theta (deg)

Figure 9

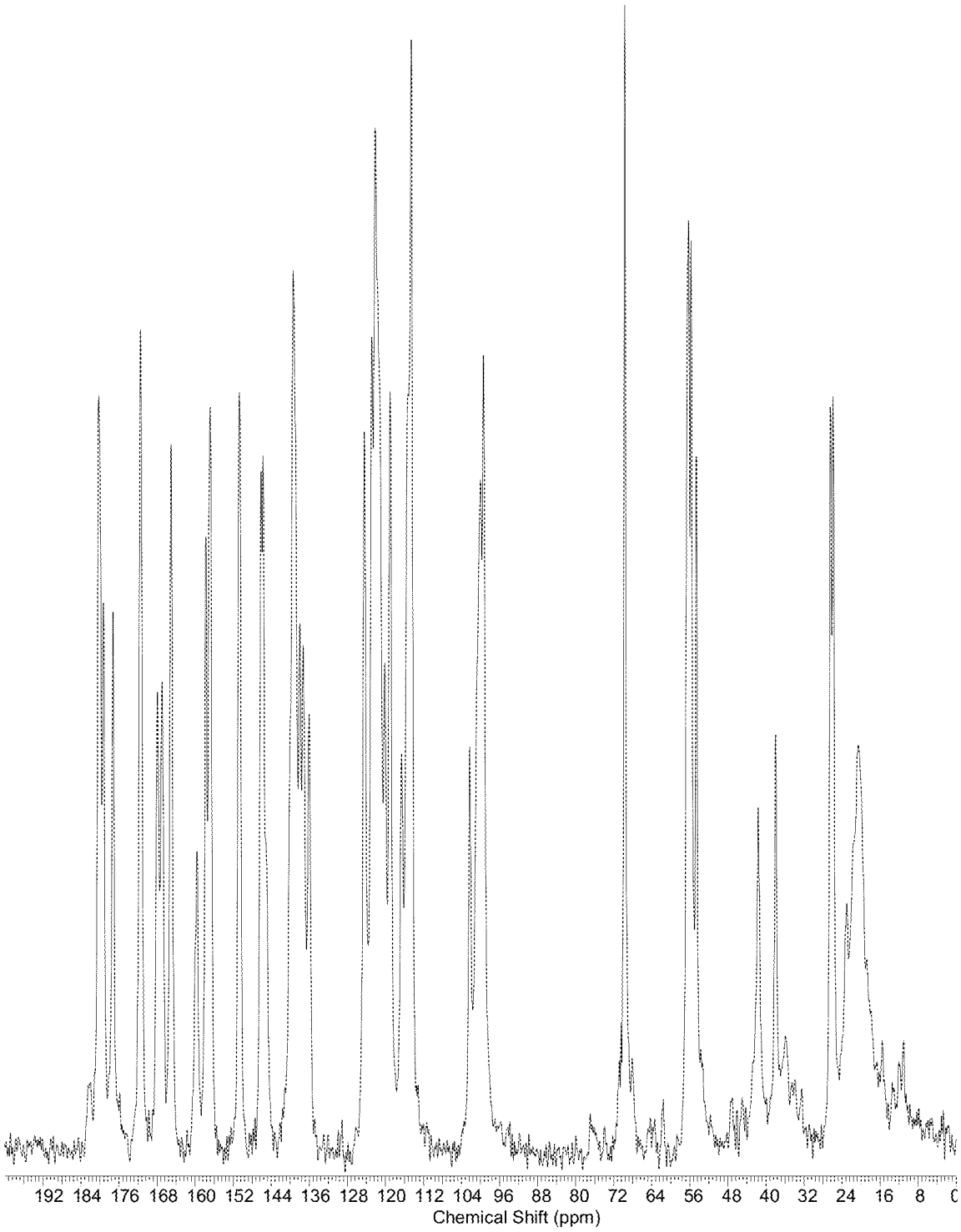

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

Figure 10

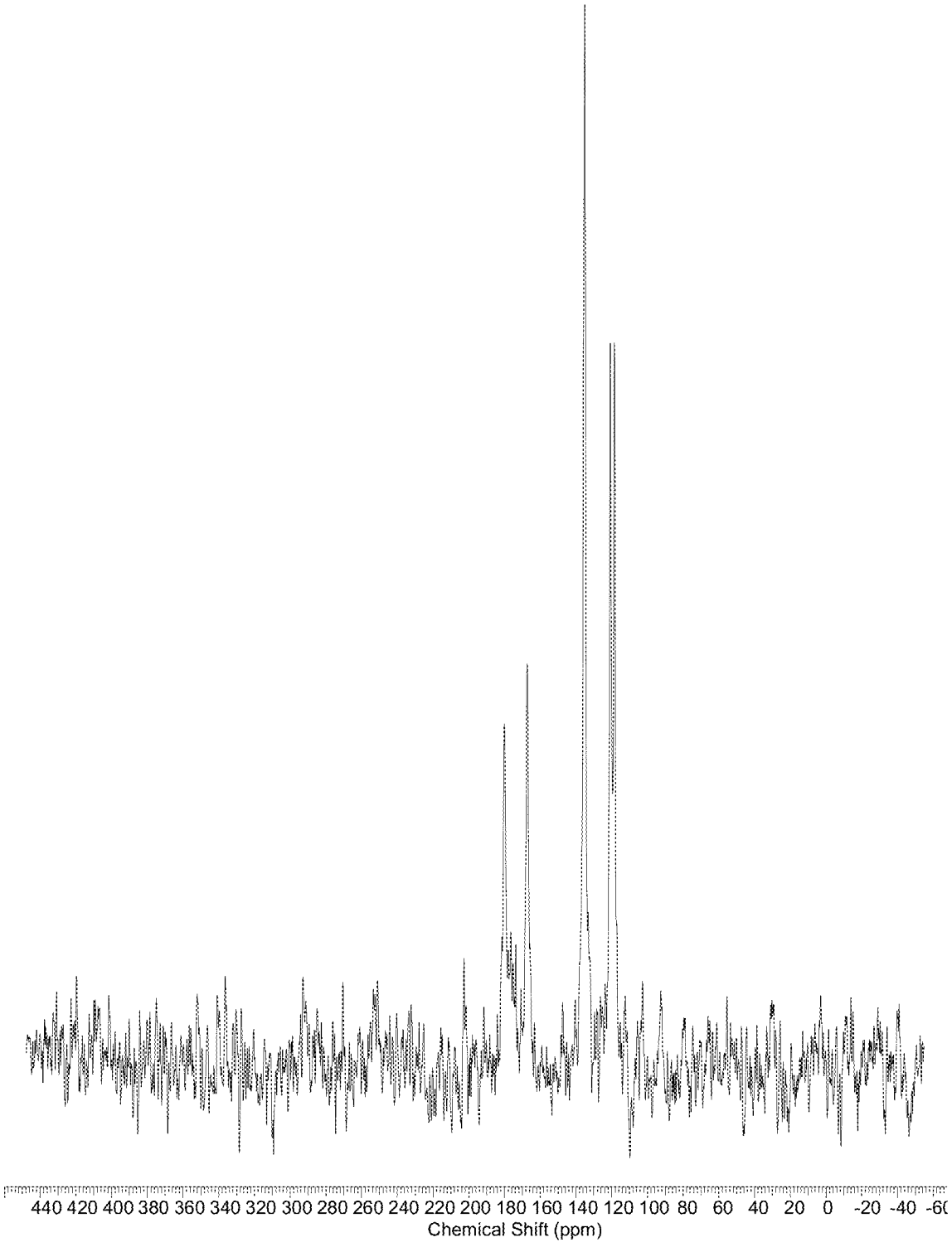

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -6(
Chemical Shift (ppm)

Figure 11

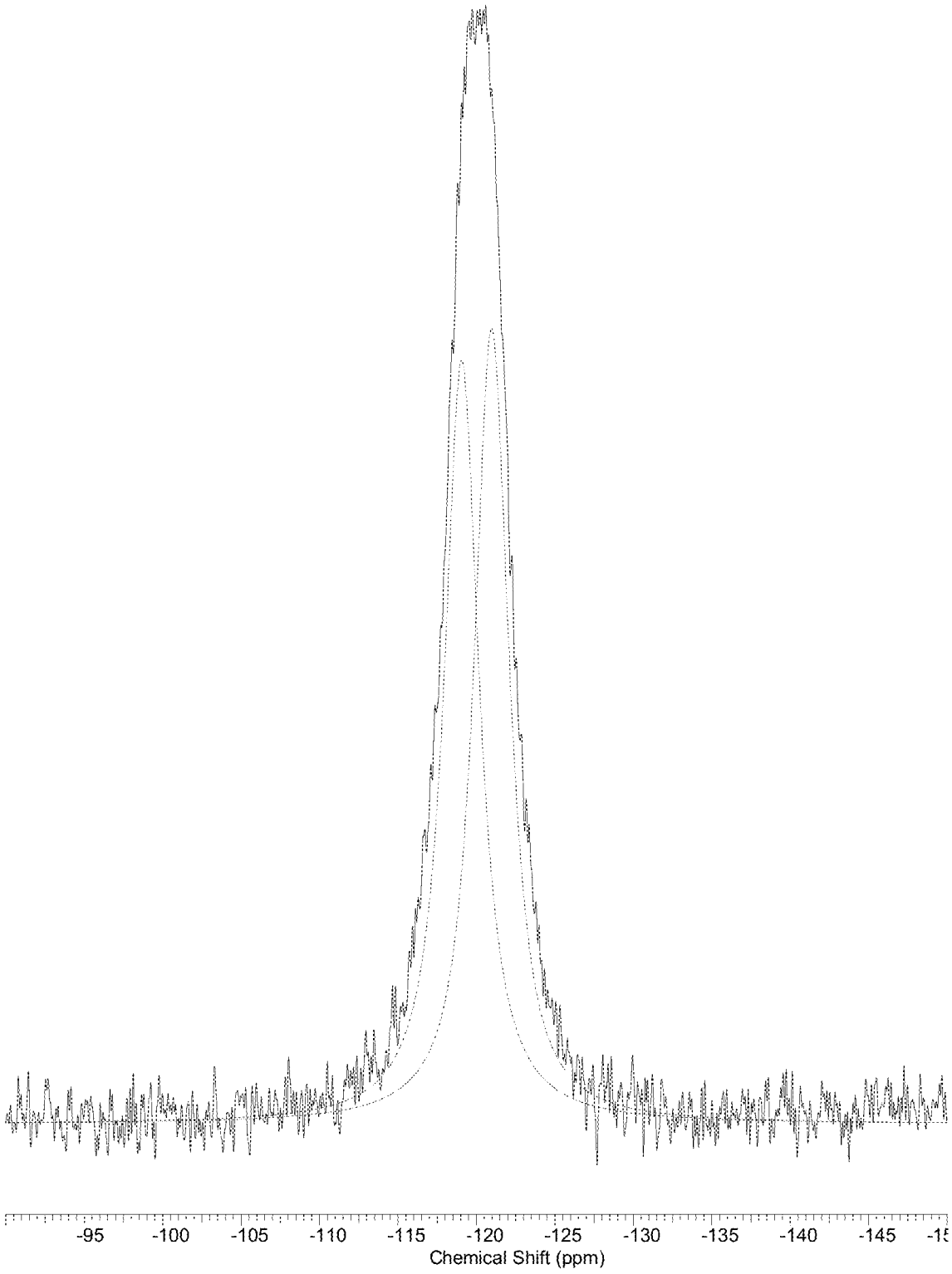


Figure 12

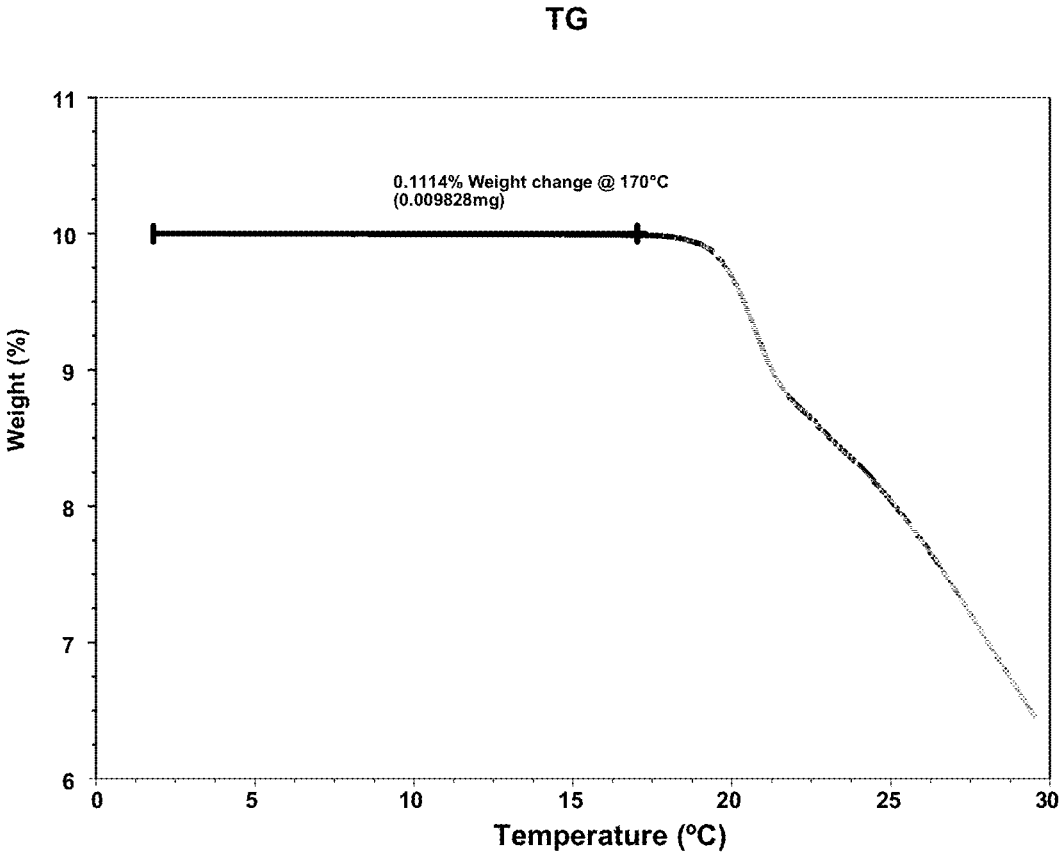

TG
0.1114% Weight change @ 170°C
(0.009828mg)
Weight (%)
Temperature (°C)
11
10
9
8
7
6
0
5
10
15
20
25
30

Figure 13

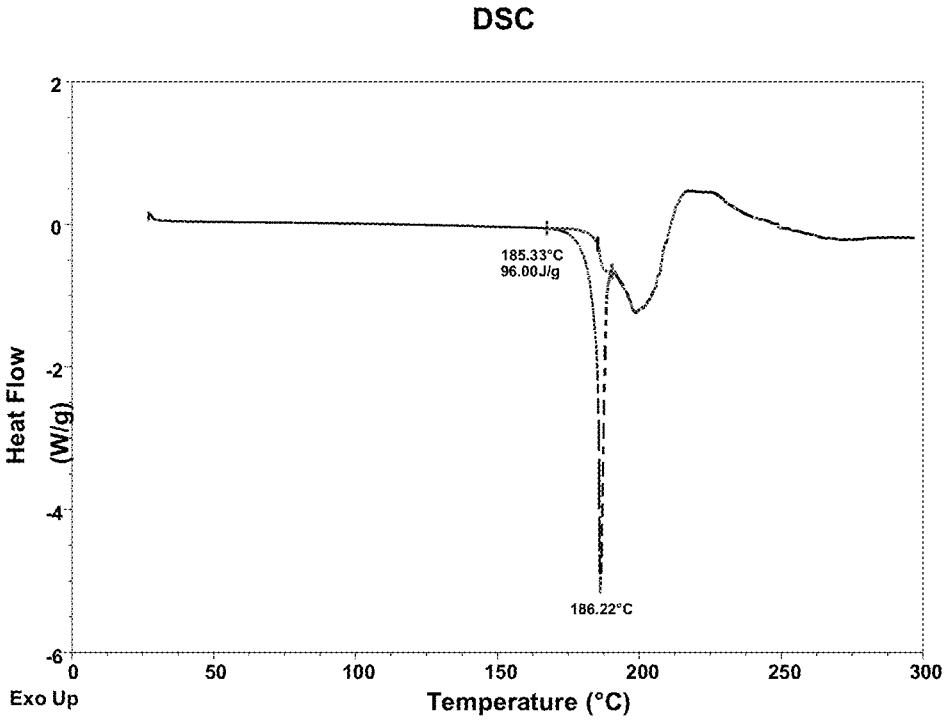

DSC
2
0
-2
-4
-6
Heat Flow (W/g)
185.33°C
96.00J/g
186.22°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)

Figure 14

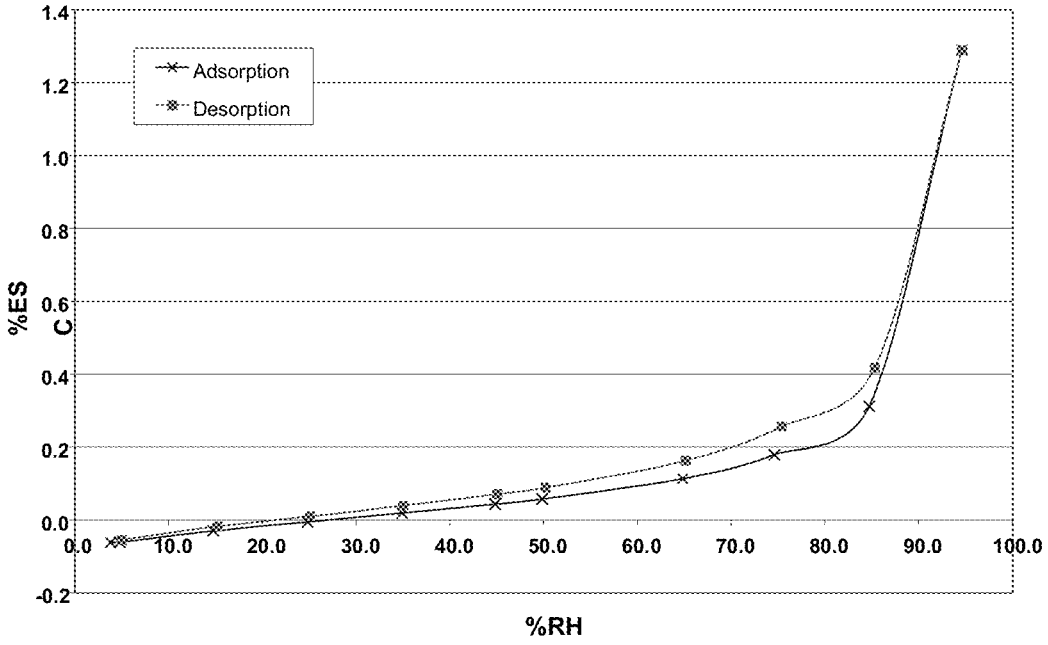

Adsorption
Desorption
%ES
C
%RH
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

Figure 15

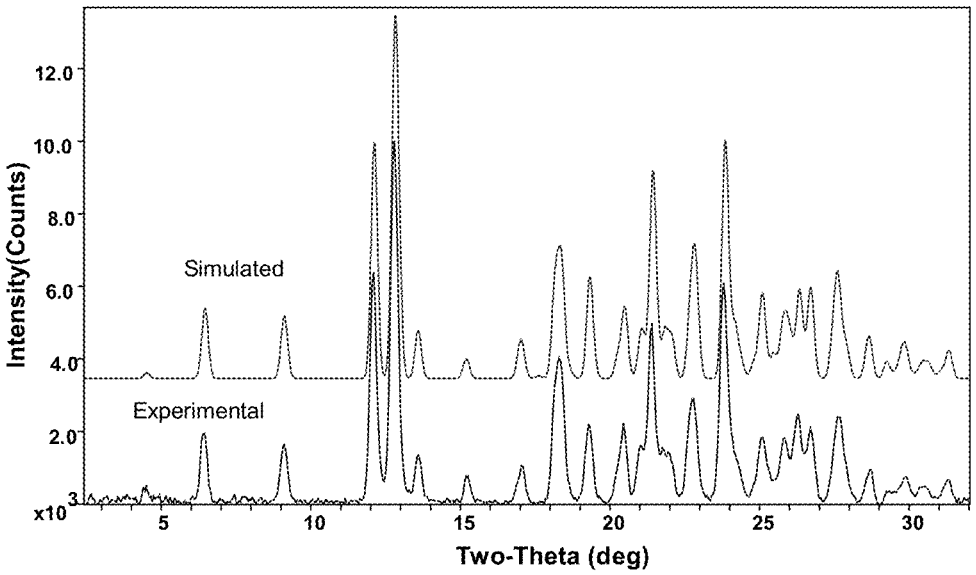

12.0
10.0
8.0
6.0
4.0
2.0
x10 3
Intensity(Counts)
Simulated
Experimental
5
10
15
20
25
30
Two-Theta (deg)

Figure 16

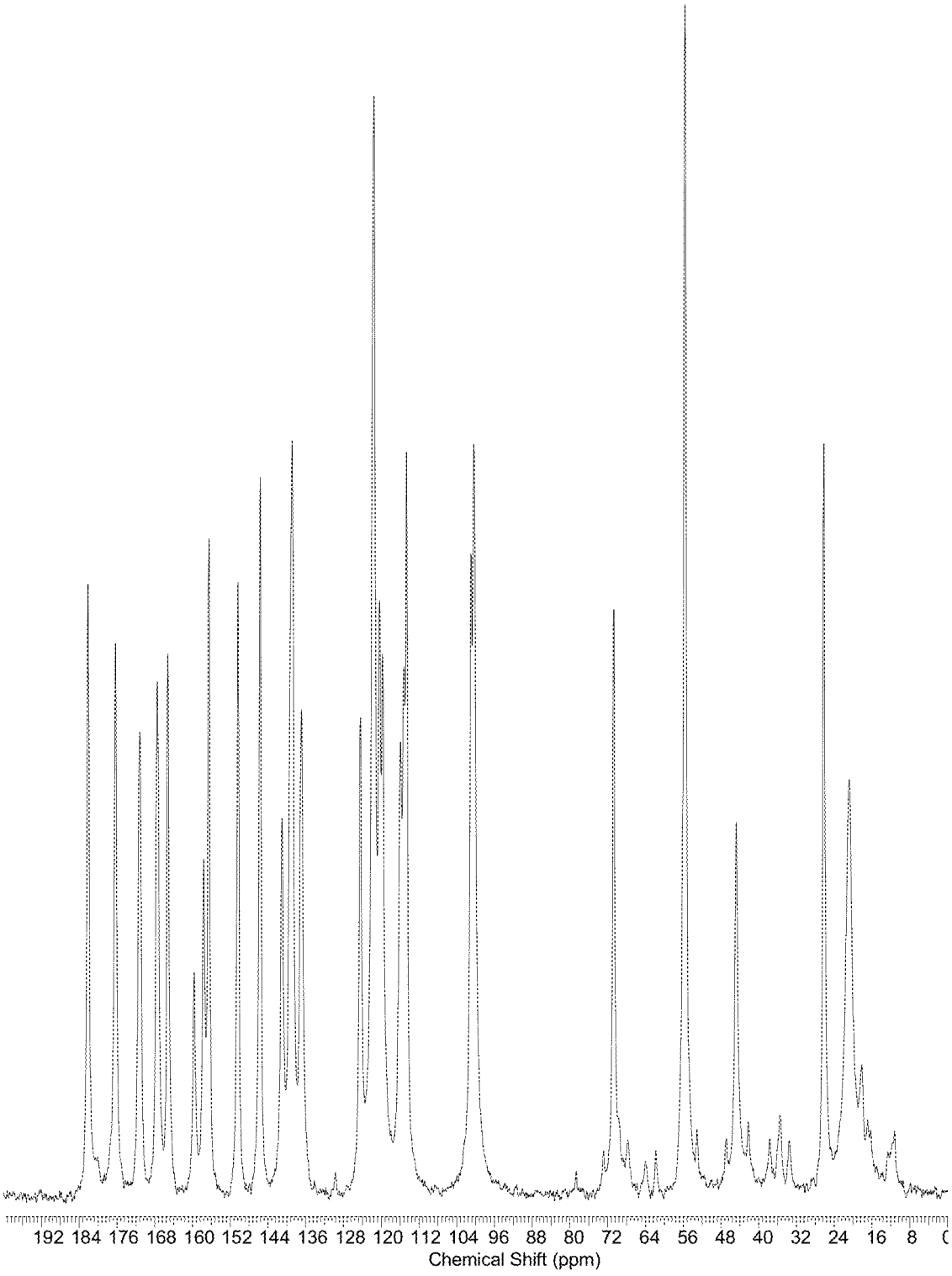

192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

Figure 17

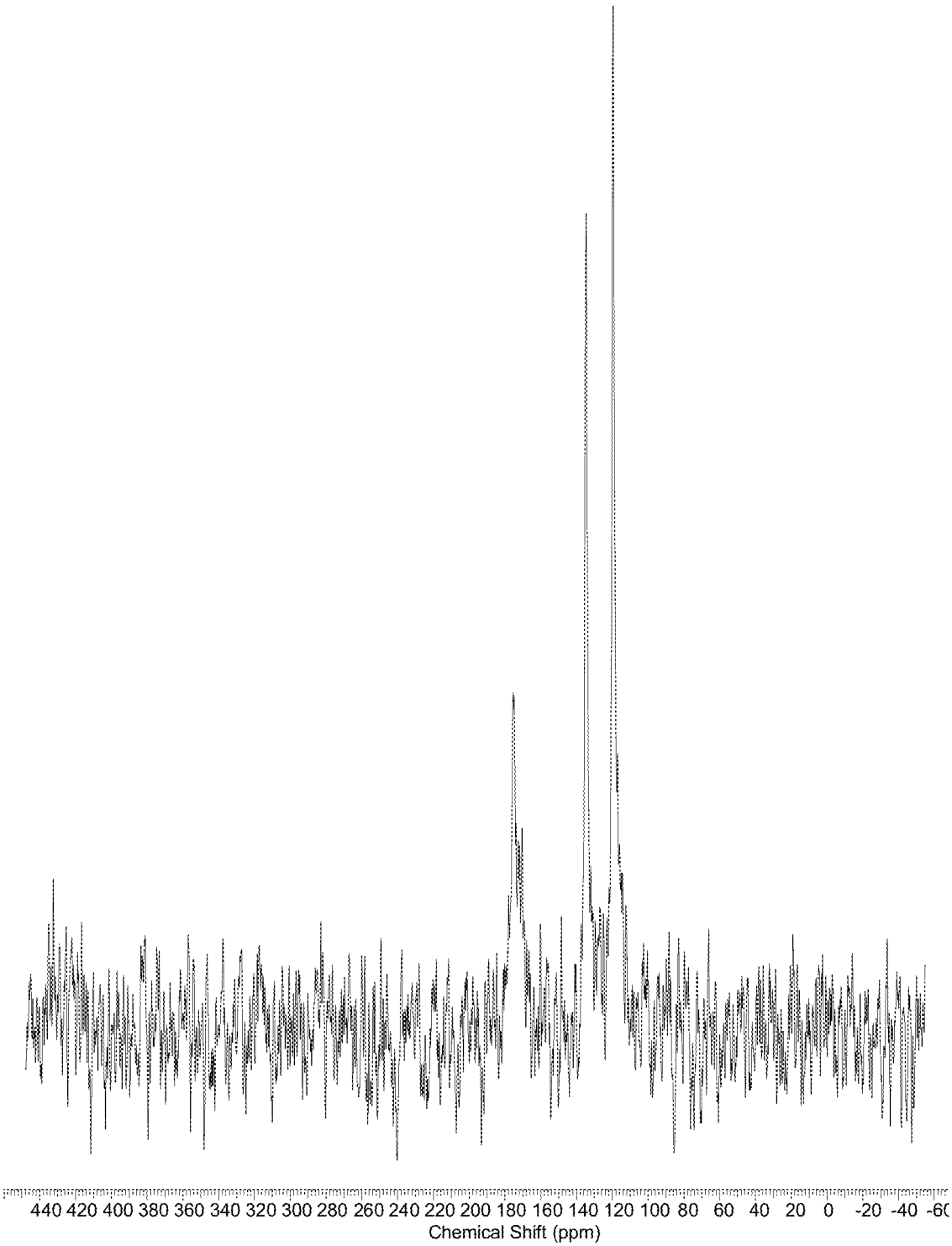

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -6(
Chemical Shift (ppm)

Figure 18

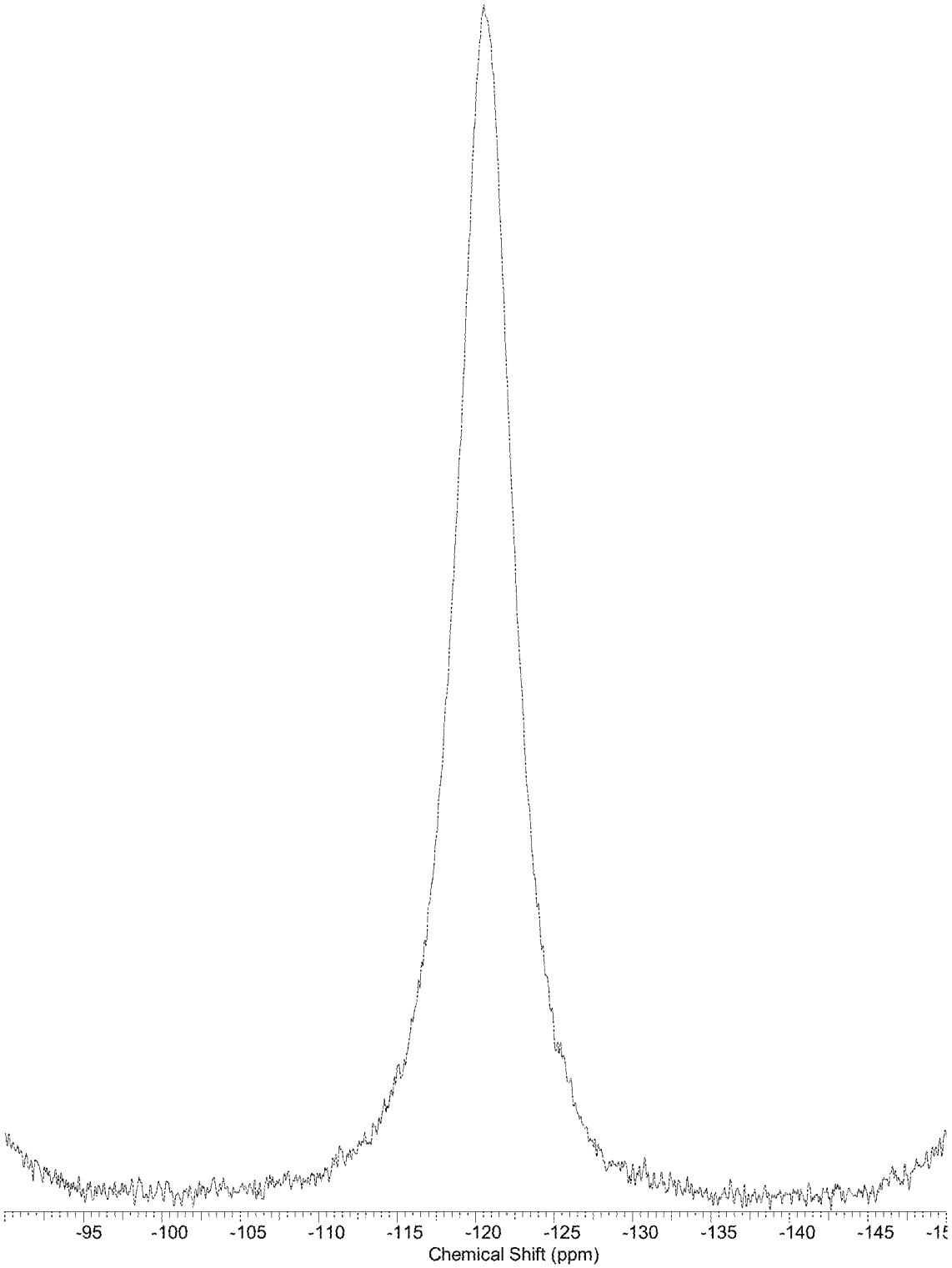


Figure 19

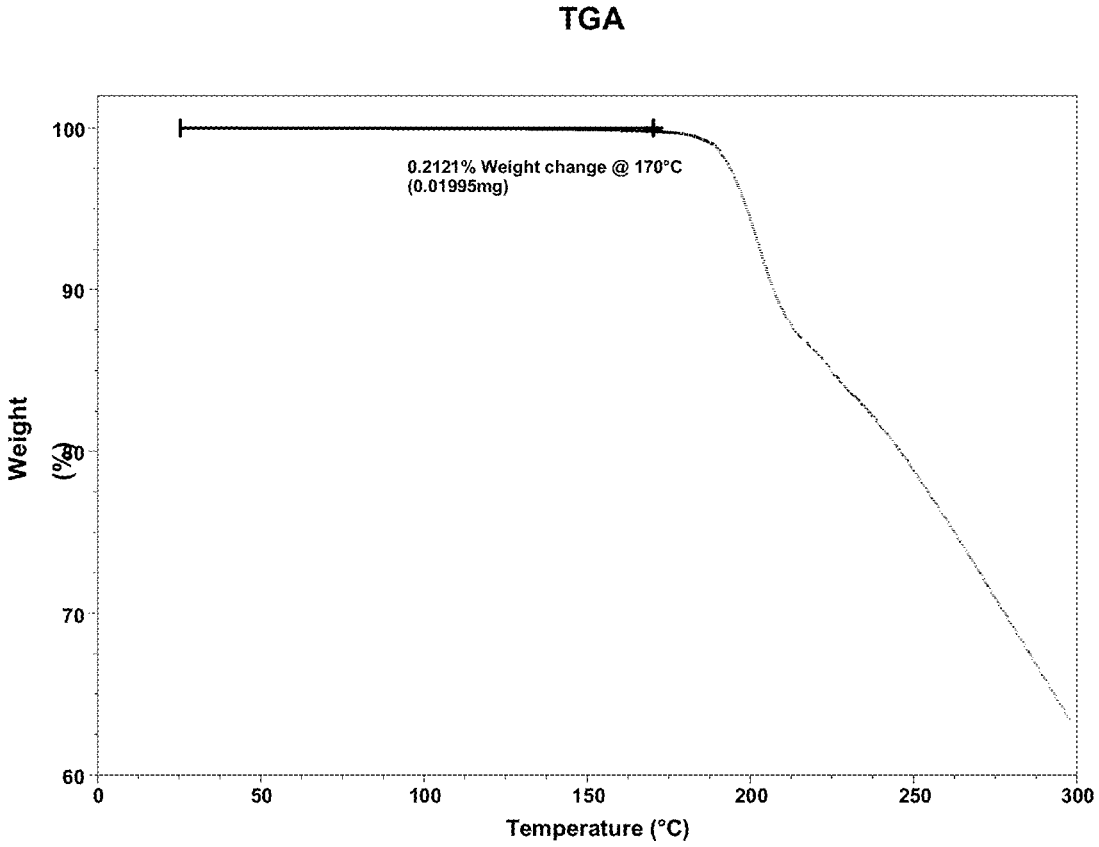

TGA
0.2121% Weight change @ 170°C
(0.01995mg)
Weight (%)
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

Figure 20

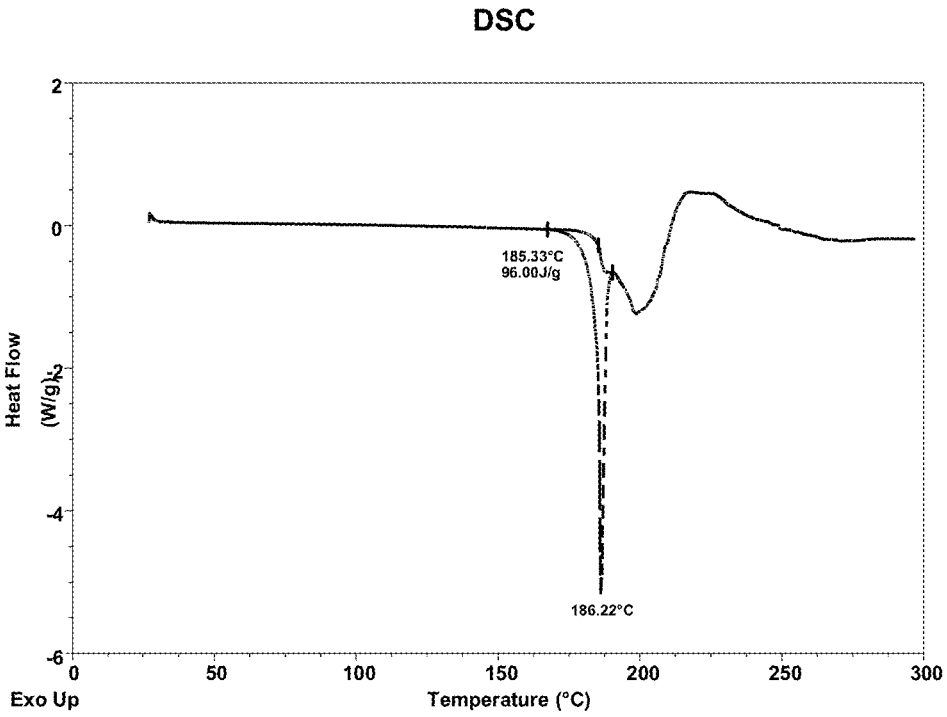

DSC
2
0
-2
-4
-6
Heat Flow
(W/g)
185.33°C
96.00J/g
186.22°C
0
50
100
150
200
250
300
Exo Up
Temperature (°C)

Figure 21

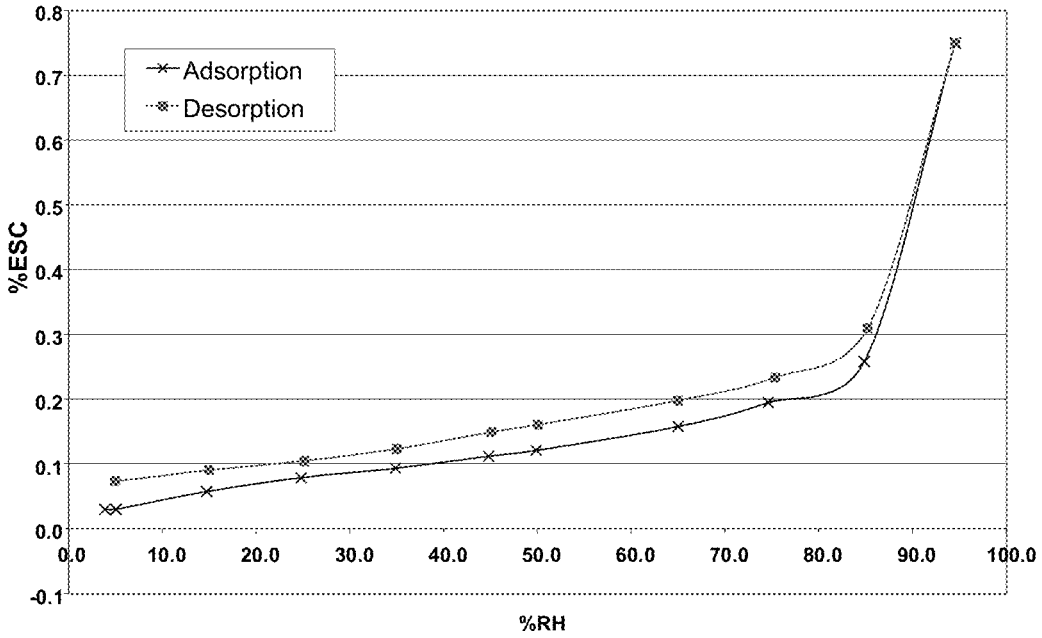

Adsorption
Desorption
%ESC
%RH
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
0.0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
100.0

Figure 22

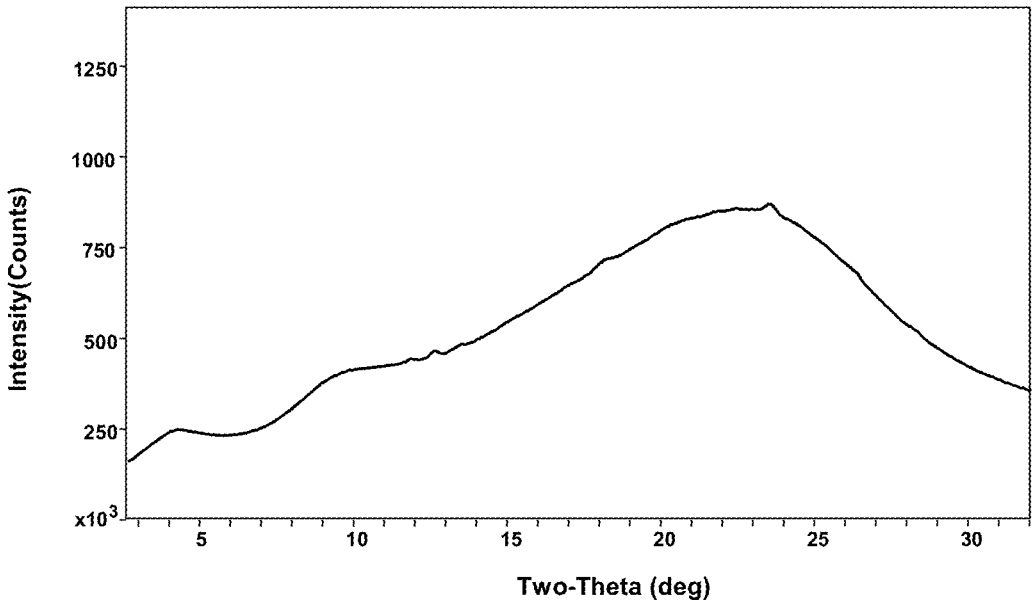

1250
1000
750
500
250
x10^3
Intensity(Counts)
5
10
15
20
25
30
Two-Theta (deg)

Figure 23

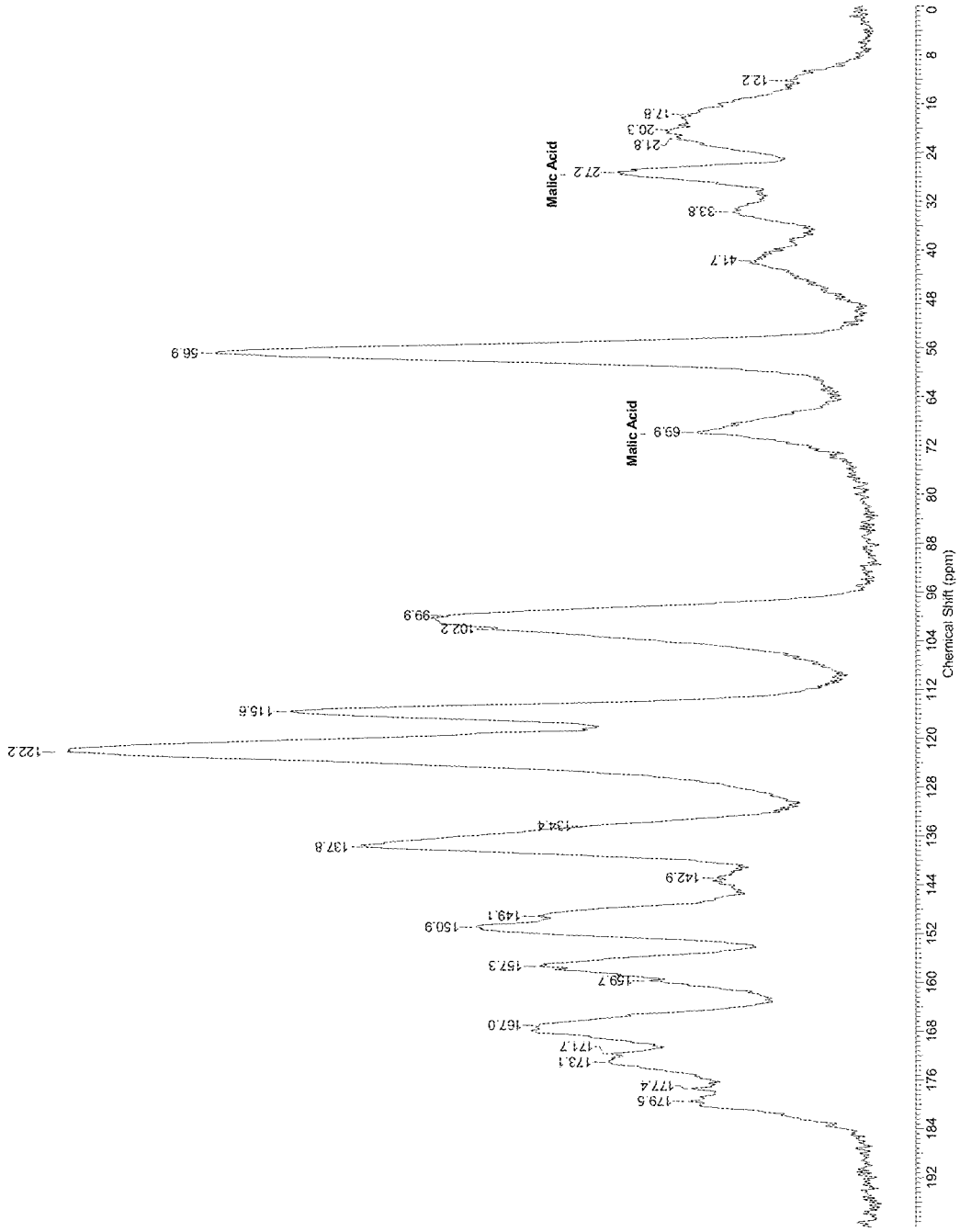

Malic Acid
Malic Acid
12.2
17.8
20.3
21.8
27.2
33.8
41.7
56.9
69.9
99.9
102.2
115.6
122.2
134.4
137.8
142.9
149.1
150.9
157.3
159.7
167.0
171.7
173.1
177.4
179.5
Chemical Shift (ppm)

Figure 24

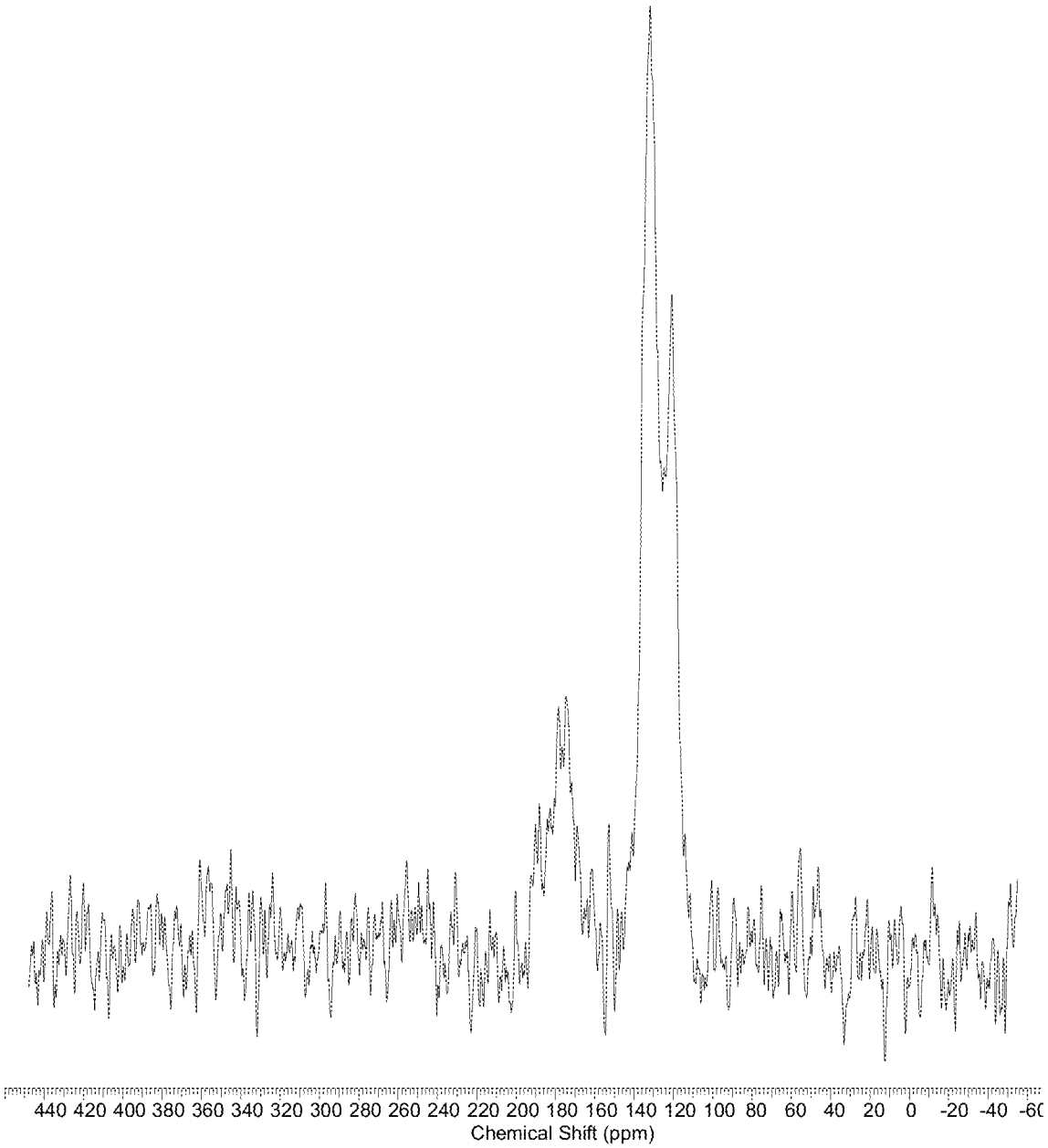

440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40 -60
Chemical Shift (ppm)

Figure 25

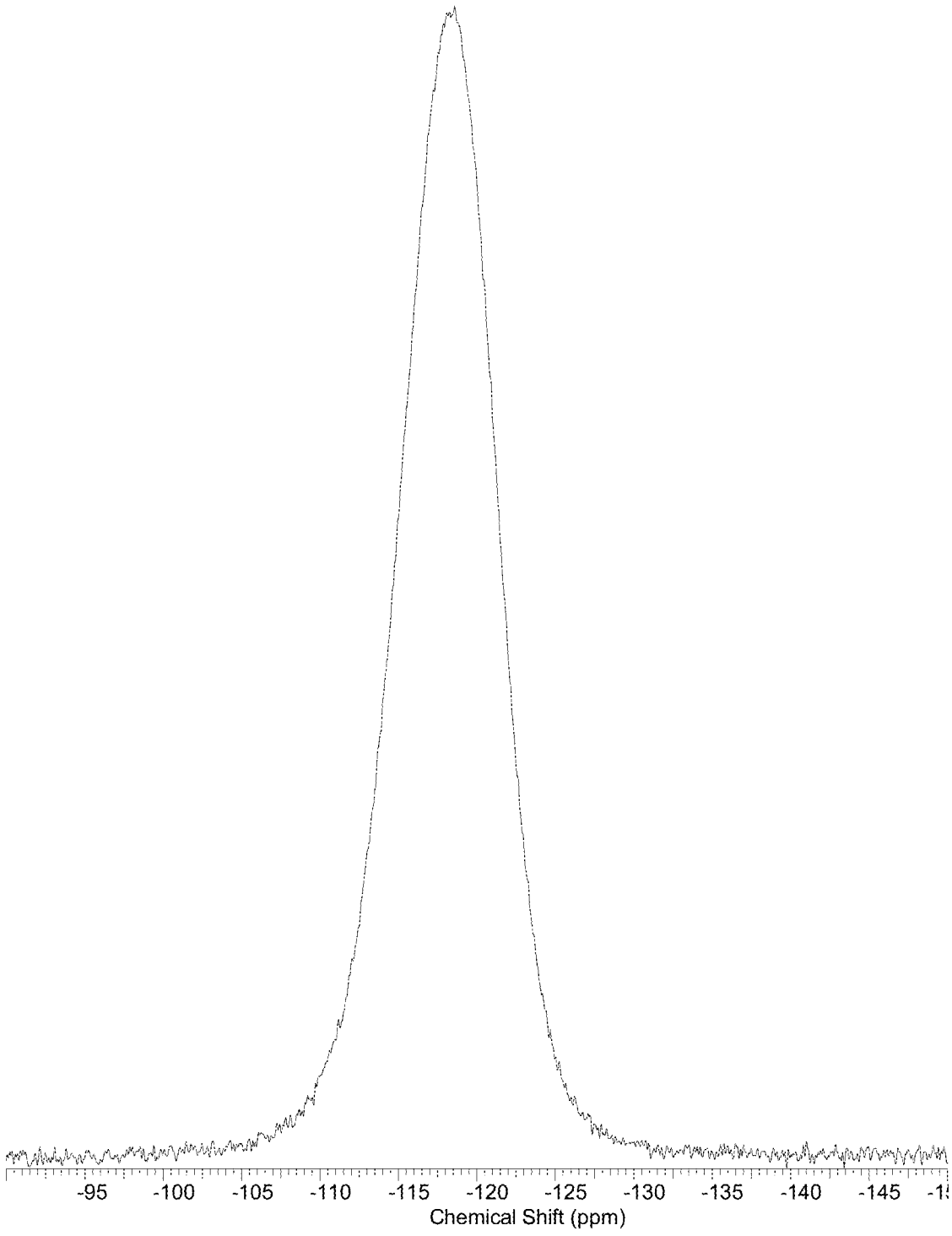


Figure 26

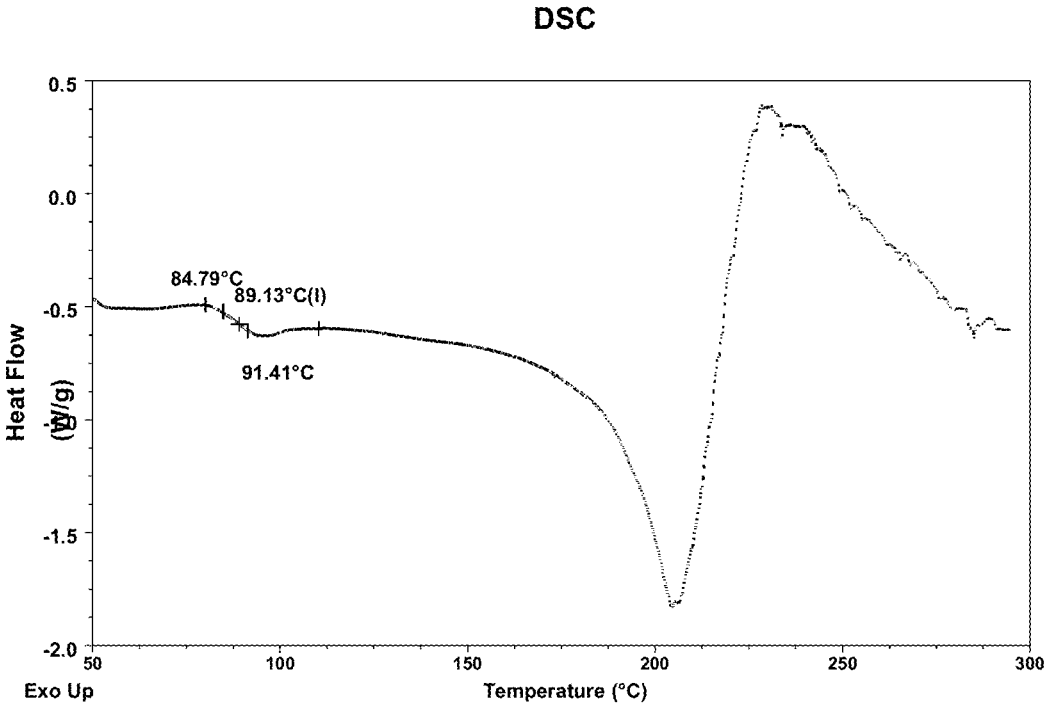
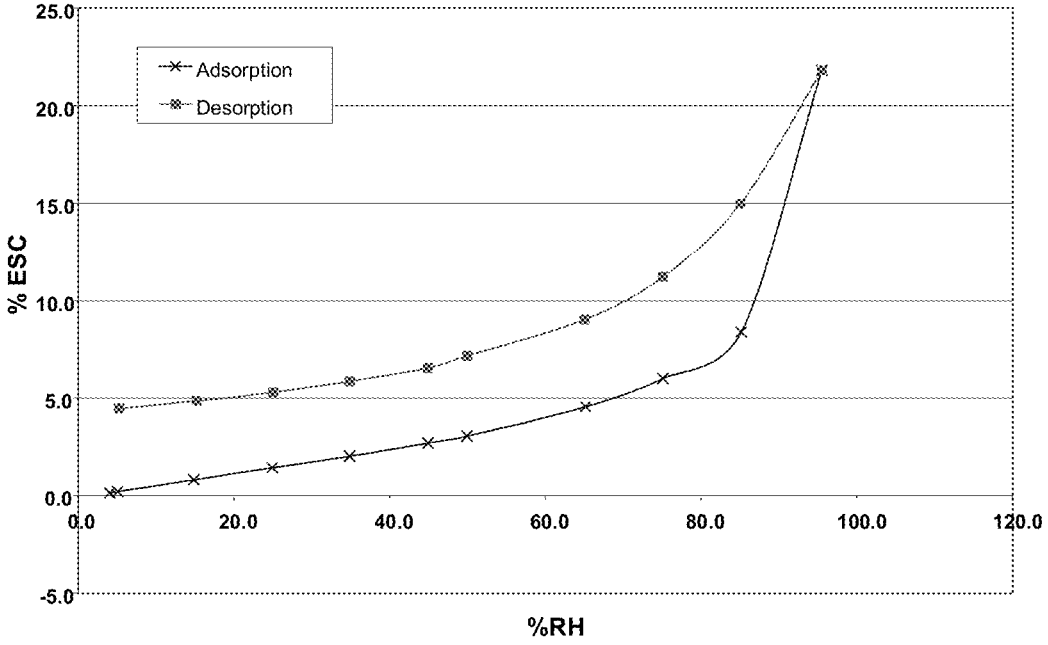

DSC
0.5
0.0
-0.5
-1.5
-2.0
Heat Flow (W/g)
Exo Up
84.79°C
89.13°C(I)
91.41°C
50
100
150
200
250
300
Temperature (°C)

Figure 27


Adsorption
Desorption
% ESC
%RH
25.0
20.0
15.0
10.0
5.0
0.0
-5.0
0.0
20.0
40.0
60.0
80.0
100.0
120.0

MALATE SALT OF N-(4-{[6,7-BIS(METHYLOXY) QUINOLIN-4-YL]OXY}PHENYL)-N'-(4-FLUOROPHENYL)CYCLOPROPANE-1,1-DICARBOXAMIDE, AND CRYSTALLINE FORMS THEREOF FOR THE TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. Ser. No. 17/149,365, filed Jan. 14, 2021, which is a continuation application of U.S. Ser. No. 17/070,514, filed Oct. 14, 2020, which is a continuation application of U.S. Ser. No. 16/796,250, filed Feb. 20, 2020, which is a continuation application of U.S. Ser. No. 15/617,725, filed Jun. 8, 2017, which is a division of U.S. Ser. No. 14/340,871, filed Jul. 25, 2014, which is a division of U.S. Ser. No. 13/145,054, filed Oct. 20, 2011, which claims priority under 35 U.S.C. § 371 to Patent Cooperation Treaty application PCT/US2010/021194, filed Jan. 15, 2010, which claims the benefit of U.S. provisional application No. 61/145,421, filed Jan. 16, 2009, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. The malate salts of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide include one of (1) the (L)-malate salt, (2) the (D)-malate salt, (3) the (D,L)-malate salt, and (4) mixtures thereof. The disclosure also relates to pharmaceutical compositions comprising at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

The disclosure also relates to pharmaceutical compositions comprising a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

The disclosure also relates to methods of treating cancer comprising administering at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

The disclosure further relates to methods of treating cancer comprising administering a crystalline or an amorphous form of at least one malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide.

BACKGROUND

Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. One mechanism that can be exploited in cancer treatment is the modulation of protein kinase activity because signal transduction through protein kinase activation is responsible for many of the characteristics of tumor cells. Protein kinase signal transduction is of particular relevance in, for example,

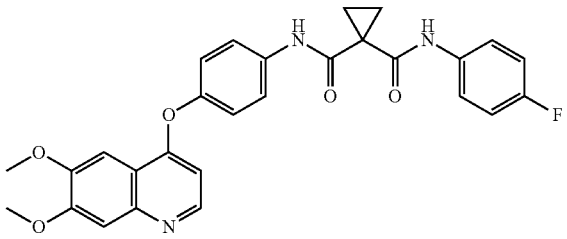
thyroid, gastric, head and neck, lung, breast, prostate, and colorectal cancers, as well as in the growth and proliferation of brain tumor cells.

Protein kinases can be categorized as receptor type or non-receptor type. Receptor-type tyrosine kinases are comprised of a large number of transmembrane receptors with diverse biological activity. For a detailed discussion of the receptor-type tyrosine kinases, see Plowman et al., DN&P 7(6): 334-339, 1994. Since protein kinases and their ligands play critical roles in various cellular activities, deregulation of protein kinase enzymatic activity can lead to altered cellular properties, such as uncontrolled cell growth associated with cancer. In addition to oncological indications, altered kinase signaling is implicated in numerous other pathological diseases, including, for example, immunological disorders, cardiovascular diseases, inflammatory diseases, and degenerative diseases. Therefore, protein kinases are attractive targets for small molecule drug discovery. Particularly attractive targets for small-molecule modulation with respect to antiangiogenic and antiproliferative activity include receptor type tyrosine kinases Ret, c-Met, and VEGFR2.

The kinase c-Met is the prototypic member of a subfamily of heterodimeric receptor tyrosine kinases (RTKs) which include Met, Ron and Sea. The endogenous ligand for c-Met is the hepatocyte growth factor (HGF), a potent inducer of angiogenesis. Binding of HGF to c-Met induces activation of the receptor via autophosphorylation resulting in an increase of receptor dependent signaling, which promotes cell growth and invasion. Anti-HGF antibodies or HGF antagonists have been shown to inhibit tumor metastasis in vivo (See: Maulik et al Cytokine & Growth Factor Reviews 2002 13, 41-59). c-Met, VEGFR2 and/or Ret overexpression has been demonstrated on a wide variety of tumor types including breast, colon, renal, lung, squamous cell myeloid leukemia, hemangiomas, melanomas, astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components). The Ret protein is a transmembrane receptor with tyrosine kinase activity. Ret is mutated in most familial forms of medullary thyroid cancer. These mutations activate the kinase function of Ret and convert it into an oncogene product.

Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 20016, 1005-1024). Kinase KDR (refers to kinase insert domain receptor tyrosine kinase) and flt-4 (fms-like tyrosine kinase-4) are both vascular endothelial growth factor (VEGF) receptors. Inhibition of EGF, VEGF and ephrin signal transduction will prevent cell proliferation and angiogenesis, two key cellular processes needed for tumor growth and survival (Matter A. Drug Disc. Technol. 2001 6, 1005-1024). EGF and VEGF receptors are desirable targets for small molecule inhibition.

Accordingly, small-molecule compounds that specifically inhibit, regulate and/or modulate the signal transduction of kinases, particularly including Ret, c-Met and VEGFR2 described above, are particularly desirable as a means to treat or prevent disease states associated with abnormal cell proliferation and angiogenesis. One such small-molecule is N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, which has the chemical structure:



WO 2005/030140 describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (Example 12, 37, 38, and 48) and also discloses the therapeutic activity of this molecule to inhibit, regulate and/or modulate the signal transduction of kinases, (Assays, Table 4, entry 289). Example 48 is on paragraph [0353] in WO 2005/030140.

Besides therapeutic efficacy, the drug developer endeavors to provide a suitable form of the therapeutic agent that has properties relating to processing, manufacturing, storage stability, and/or usefulness as a drug. Accordingly, the discovery of a form that possesses some or all of these desired properties is vital to drug development.

Applicants have found a salt form of the drug N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms

SUMMARY

This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

Another aspect relates to crystalline and amorphous forms of the malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide as described herein, pharmaceutical compositions thereof as described herein, and uses thereof as described herein.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** shows the experimental XRPD pattern for crystalline Compound (I), Form N-1 at 25° C.

FIG. **2** shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1.

FIG. **3** shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1.

FIG. **4** shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1.

FIG. **5** shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-1.

FIG. **6** shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-1.

FIG. **7** shows the moisture sorption of crystalline Compound (I), Form N-1.

FIG. **8** shows the experimental XRPD pattern for crystalline Compound (I), Form N-2 at 25° C.

FIG. **9** shows the solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2.

FIG. **10** shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2.

FIG. **11** shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2.

FIG. **12** shows the thermal gravimetric analysis (TGA) of crystalline Compound (I), Form N-2.

FIG. **13** shows the differential scanning calorimetry (DSC) of crystalline Compound (I), Form N-2.

FIG. **14** shows the moisture sorption of crystalline Compound (I), Form N-2.

FIG. **15** shows the experimental and simulated XRPD patterns for crystalline Compound (III), Form N-1 at room temperature.

FIG. **16** shows the solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1.

FIG. **17** shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1.

FIG. **18** shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1.

FIG. **19** shows the thermal gravimetric analysis (TGA) of crystalline Compound (III), Form N-1.

FIG. **20** shows the differential scanning calorimetry (DSC) of crystalline Compound (III), Form N-1.

FIG. **21** shows the moisture sorption of crystalline Compound (III), Form N-1.

FIG. **22** shows the XRPD pattern of amorphous Compound (I) at room temperature.

FIG. **23** shows the solid state ^{13}C NMR spectrum of amorphous Compound (I).

FIG. **24** shows the solid state ^{15}N NMR spectrum of amorphous Compound (I).

FIG. **25** shows the solid state ^{19}F NMR spectrum of amorphous Compound (I).

FIG. **26** shows the differential scanning calorimetry (DSC) of amorphous Compound (I).

FIG. **27** shows the moisture sorption of amorphous Compound (I).

DETAILED DESCRIPTION

This disclosure relates to improvements of the physiochemical properties of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, whereby this compound may be suitable for drug development. Disclosed herein are malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. New solid state forms of those salts are also disclosed. The malate salts as well as their crystalline and amorphous forms disclosed herein each represent separate aspects of the disclosure. Although the malate salts and their solid state forms are described herein, the invention also relates to novel compositions containing the disclosed salts and solid state forms. Therapeutic uses of the salts and solid state forms described as well as therapeutic compositions containing them represent separate aspects of the disclosure. The techniques used to characterize the salts and their solid state forms are described in the examples below. These techniques, alone or in combination, may be used to characterize the salts and their solid state forms disclosed herein. The salts and their solid state forms may be also characterized by reference to the disclosed figures.

N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide was found to have an enzyme Ret IC_{50} value of about 5.2 nM (nanomolar) and an enzyme c-Met IC_{50} value of about 1.3

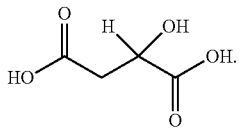
nM (nanomolar). The assay that was used to measure this c-Met activity is described in paragraph [0458] in WO2005-030140.

RET biochemical activity was assessed using a Luciferase-Coupled Chemiluminescent Kinase assay (LCCA) format as described in WO2005-030140. Kinase activity was measured as the percent ATP remaining following the kinase reaction. Remaining ATP was detected by luciferase-luciferin-coupled chemiluminescence. Specifically, the reaction was initiated by mixing test compounds, 2 μM ATP, 1 μM poly-EY and 15 nM RET (baculovirus expressed human RET kinase domain M700-D1042 with a $(His)_6$ tag on the N-terminus) in a 20 uL assay buffer (20 mM Tris-HCL pH 7.5, 10 mM $MgCl_2$, 0.01% Triton X-100, 1 mM DTT, 3 mM $MnCl_2$). The mixture was incubated at ambient temperature for 2 hours after which 20 uL luciferase-luciferin mix was added and the chemiluminescent signal read using a Wallac Victor^2 reader. The luciferase-luciferin mix consists of 50 mM HEPES, pH 7.8, 8.5 ug/mL oxalic acid (pH 7.8), 5 mM DTT, 0.4% Triton X-100, 0.25 mg/mL coenzyme A, 63 μM AMP, 28 μg/mL luciferin and 40,000 units of light/mL luciferase.

Malate Salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

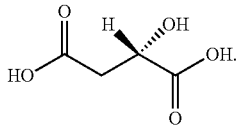
This disclosure relates to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. These malate salts are a combination of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide with malic acid which forms a 1:1 malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Malic acid has the following structure:



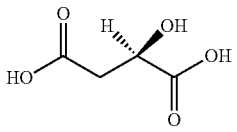
Due to its chiral carbon, two enantiomers of malic acid exist, (L)-malic acid and (D)-malic acid.

(L)-malic acid has the following structure:



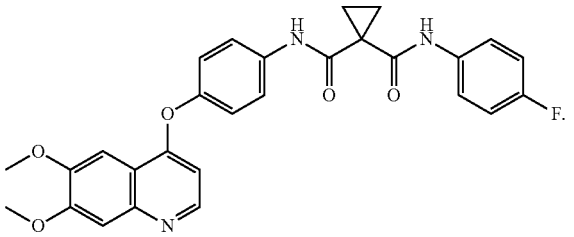
There are various names or designations for the (L)-malic acid that are known in the art. These include butanedioic acid, hydroxy-, (2S)-(9CI); butanedioic acid, hydroxy-, (S)-; malic acid, L-(8CI); malic acid, 1-(3CI); (−)-(S)-malic acid; (−)-Hydroxysuccinic acid; (−)-(L)-malic acid; (−)-malic acid; (2S)-2-hydroxybutanedioic acid; (2S)-2-hydroxysuccinic acid; (S)-malic acid; apple acid; L-(−)-malic acid; (L)-malic acid; NSC 9232; S-(−)-malic acid; and S-2-hydroxybutanedioic acid.

(D) malic acid has the following structure:



There are various names or designations for the (D)-malic acid that are known in the art. These include butanedioic acid, 2-hydroxy-, (2R)-, butanedioic acid, hydroxy-, (2R)-(9CI); butanedioic acid, hydroxy-, (R)-; (+)-malic acid; (2R)-2-hydroxybutanedioic acid; (2R)-malic acid; (R)-(+)-malic acid; (R)-malic acid; D-(+)-2-hydroxysuccinic acid; D-(+)-malic acid; and D-malic acid.

As discussed above, the chemical structure of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide is



There are no chiral carbons in its chemical structure. There are various names for N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide which are publicly known, and some of these various names or designations include 1,1-cyclopropanedicarboxamide, N'-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N-(4-fluorophenyl)- and 1,1-cyclopropanedicarboxamide, N-[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]-N'-(4-fluorophenyl)-(9CI).

N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide can be prepared according to any of several different methodologies, either on a gram scale (<1 kg) or a kilogram scale (>1 kg). A gram-scale method is set forth in WO 2005-030140, which describes the synthesis of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Examples 25, 37, 38, and 48), which is hereby incorporated by reference. Alternatively, N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, including the active compound(s), can be prepared on a kilogram scale using the procedure set forth in Example 1 below.

This disclosure relate to malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide:

- the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (I));
- the (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (Compound (II)); and
- the (DL)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (Compound (III)).

Each has improved properties over N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and its other salts. The names used herein to characterize a specific form, e.g. "N-2" etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere identifiers that are to be interpreted in accordance with the characterization information presented herein.

The malate salts of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, and particularly Compound (I), have a preferred combination of pharmaceutical properties for development. Under the conditions of 25° C./60% relative humidity (RH) and 40° C./60% RH, Compound (I) showed no change in assay, purity, moisture and dissolution. The DSC/TGA showed the Compound (I) to be stable up to 185° C. No solvent losses were observed. The uptake of water by the (L)-malate salt was reversible with a slight hysteresis. The amount of water taken up was calculated at about 0.60 wt % at 90% RH. The (L)-malate salt was synthesized with good yield and purity >90% and had sufficient solubility for use in a pharmaceutical composition. The amount of water associated with this salt was calculated at about 0.5 wt % by Karl Fischer analysis and correlates with TGA and GVS analysis. The (D)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) will have the same properties as the (L)-malate salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide).

The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide. For example, the hydrochloride salt of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide exhibits undesirable moisture sensitivity, changing phase upon exposure to high humidity (75% humidity) and high temperature (40° C.). The maleate salt had low solubility. The tartrate salt had low crystallinity and low solubility. The phosphate salt exhibited an 8% weight gain due to absorption of H_2O—the highest among the salts tested.

The water solubility of the various salts was determined using 10 mg solids per mL water. The salts were prepared in a salt screen by reacting an acetone solution of the freebase with stock tetrahydrofuran (THF) solutions of a range of acids in about a 1:1 molar ratio. Table 1 below summarizes the water solubility and other data relating to the free base and each salt.

TABLE 1

	Solubility (mg/ml)	
Free base	<<0.001	very low solubility
Propionate	<<0.001	no salt formation; mixture of free base and acid
Acetate	<<0.001	no salt formation; mixture of free base and acid
Succinate	0.010	no salt formation; mixture of free base and acid
Benzoate	0.005	no salt formation; mixture of free base and acid
L-Lactate	0.015	Amorphous, salt
Pyrro-glutamate	0.44	Amorphous, salt
Glycolate	0.016	Amorphous, salt
L-Ascorbate	0.053	low crystallinity
Sulfate	0.004	Crystalline salt, low solubility
Tosylate	0.007	Crystalline salt, low solubility
Malonate	0.003	Crystalline salt, low solubility
2,5 dihydroxy-benzoate	<<0.001	Crystalline Salt, low solubility
Fumarate	0.008	Crystalline Salt, low solubility
Citrate	0.002	Crystalline Salt, low solubility
Mesylate	0.175	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Esylate	0.194	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Benzene-sulfonate	0.039	Crystalline Salt; possible sulfonic acid formation when made with alcohol
Chloride	0.070	Crystalline but Hygroscopic; possible hydrate formation. Change in XRPD pattern upon exposure to humidity.
Maleate	0.005	Crystalline salt, possible hydrate formation; low solubility; different XRPD pattern observed upon scale up (possible polymorphism issue)
Phosphate	0.026	Crystalline but Hygroscopic.
L-Tartrate	0.014	Low degree of crystallinity; Hygroscopic.
(L)-Malate	0.059	Crystalline; non-Hygroscopic with no indication of hydrate formation. Suitable solubility, and chemical/physical stability.

Another aspect of this disclosure relates to crystalline forms of Compound (I), which include the N-1 and/or the N-2 crystalline form of Compound (I) as described herein. Each of form of Compound (I) is a separate aspect of the disclosure. Similarly, another aspect of this disclosure relates to crystalline forms of Compound (II), which include the N-1 and/or the N-2 crystalline form of Compound (II) as described herein. Each of which is also a separate aspect of the disclosure. As is known in the art, the crystalline (D) malate salt will form the same crystalline form and have the same properties as crystalline Compound (I). See WO 2008/083319, which discusses the properties of crystalline enantiomers. Mixtures of the crystalline forms of Compounds (I) and (II) are another aspect of the disclosure.

The crystalline N-1 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 18.1, 42.9, 44.5, 70.4, 123.2, 156.2, 170.8, 175.7, and 182.1 ppm, ±0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. **2**;

(iii) an x-ray powder diffraction pattern (CuKα λ=1.5418 Å) comprising four or more peaks selected from: 6.4, 9.0, 12.0, 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6 °2θ±0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. **1**;

(v) a solid state ^{15}N NMR spectrum with peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. **3**.

Other solid state properties which may be used to characterize the crystalline N-1 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below. For crystalline Compound (I), the solid state phase and the degree of crystallinity remained unchanged after exposure to 75% RH at 40° C. for 1 week.

The crystalline N-2 forms of Compounds (I) and (II) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with peaks at 23.0, 25.9, 38.0, 54.4, 56.11, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ±0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. **9**;

(ii) an x-ray powder diffraction pattern (CuKα λ=1.5418 Å) comprising four or more peaks selected from: 6.4, 9.1, 12.0, 12.8, 13.7, 17.1, 20.9, 21.9, 22.6, and 23.7 °2θ±0.2 °2θ, wherein measurement of the crystalline form is at an ambient room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. **8**;

(v) a solid state ^{15}N NMR spectrum with peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. **10**.

Other solid state properties which may be used to characterize the crystalline N-2 forms of Compounds (I) and (II) are shown in the figures and discussed in the examples below.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-1 form.

In another embodiment, the disclosure relates to a crystalline form of Compound (I), as described herein in any of the aspects and/or embodiments, is substantially pure N-2 form.

The disclosure also relates to amorphous forms of Compounds (I) and (II). The preparation and solid state properties and characteristics of the amorphous form of Compound (I) are described in the examples below. The amorphous forms of Compounds (I) and (II) represent another aspect of the disclosure.

One further aspect of the disclosure relates to mixtures of Compound (I) and Compound (II). The mixtures may have from greater than zero weight % to less than 100 weight % Compound (I) and from less than 100 weight % to greater zero weight % Compound (II), based on the total weight of Compound (I) and Compound (II). In other embodiments, the mixture comprises from about 1 to about 99 weight % Compound (I) and from about 99 to about 1 weight % Compound (II), based on the total weight of Compound (I) and Compound (II) in said mixture. In a further embodiment, the mixture comprises from about 90 weight % to less than 100 weight % Compound (I) and from greater than zero weight % to about 10 weight % Compound (II), based on the total weight of Compound (I) and Compound (II). Accordingly, the mixture may have 1-10% by weight of Compound (I); 11-20% by weight of Compound (I); 21-30% by weight of Compound (I); 31-40% by weight of Compound (I); 41-50% by weight of Compound (I); 51-60% by weight of Compound (I); 61-70% by weight of Compound (I); 71-80% by weight of Compound (I); 81-90% by weight of Compound (I); or 91-99% by weight of Compound (I) with the remaining weight percentage of malate salt being that of Compound (II).

Another aspect of this disclosure relates to crystalline forms of (DL)-malate salt of N-(4-{[6,7-bis(methyloxy) quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, Compound (III). The (DL)-malate salt is prepared from racemic malic acid. The crystalline N-1 form of Compound (III) as described here may be characterized by at least one of the following:

(i) a solid state ^{13}C NMR spectrum with four or more peaks selected from 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, 182.1 ppm, ±0.2 ppm;

(ii) a solid state ^{13}C NMR spectrum substantially in accordance with the pattern shown in FIG. **16**;

(iii) a powder x-ray diffraction pattern (CuKα λ=1.5418 Å) comprising four or more 2θ values selected from: 12.8, 13.5, 16.9, 19.4, 21.5, 22.8, 25.1, and 27.6, ±0.2 °2θ, wherein measurement of the crystalline form is at temperature of room temperature;

(iv) an x-ray powder diffraction (XRPD) spectrum substantially in accordance with the pattern shown in FIG. **15**;

(v) a solid state ^{15}N NMR spectrum with peaks at 119.6, 134.7, and 175.5 ppm, ±0.2 ppm; and/or

(vi) a solid state ^{15}N NMR spectrum substantially in accordance with the pattern shown in FIG. **17**.

Other solid state properties which may be used to characterize the crystalline N-1 form of Compound (III) are shown in the figures and discussed in the examples below. In one embodiment, the N-1 Form of Compound (III) is characterized by unit cell parameters approximately equal to the following:

Cell dimensions: a=14.60 Å
b=5.20 Å
c=39.09 Å
α=90.0°
β=90.4°
γ=90.0°
Space group: $P2_1/n$
Molecules of Compound (I)/unit cell: 4
Volume=2969 $Å^3$
Density (calculated)=1.422 g/cm^3

The unit cell parameters of Form N-1 of Compound (III) were measured at a temperature of approximately 25° C., e.g., ambient or room temperature.

Each of the N-1 and N-2 crystalline forms of Compounds (T) and (IT) and the crystalline form N-1 of Compound (III) have unique characteristics that can distinguish them one from another. These characteristics can be understood by comparing the physical properties of the solid state forms which are presented in the Examples below. For example, Table 2 lists characteristic XRPD peak positions (°2θ±0.2 °2θ) for crystalline Compound (III), Form N-1 and Forms N-1 and N-2 of crystalline Compound (I). Amorphous forms do not display reflection peaks in their XRPD patterns.

TABLE 2

Characteristic diffraction peak positions (degrees 2θ ± 0.2) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.

Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
6.4	6.4	6.4
9.0	9.1	9.1
12.0	12.0	12.1
12.8	12.8	12.8
13.5	13.7	13.6
16.9	17.1	17.1
19.4*	20.9*	19.3
21.5*	21.9*	21.4
22.8*	22.6	22.8

TABLE 2-continued

Characteristic diffraction peak positions (degrees 2θ ± 0.2) @ RT, based on pattern collected with a diffractometer (CuKα) with a spinning capillary.		
Compound (I) Form N-1	Compound (I) Form N-2	Compound (III) Form N-1
25.1*	23.7	25.1
27.6*	—	27.6

*unique reflections between Compound (I), Form N-1 and Compound (I), Form N-2.

The unique reflections between Forms N-1 and N-2 of crystalline Compound (II) are designated by an asterisk (*). As discussed above, Compound (II) is an enantiomer of Compound (I) and thus, Compound (II), Form N-1 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-1. Likewise, Compound (II), Form N-2 will have the same characteristic reflection pattern and unique peaks as those listed in Table 2 for Compound (I), Form N-2. Compounds (I) and (II) are distinct from one another based on their absolute stereochemistry, i.e., the (L)-malate salt versus the (D)-malate salt, respectively. Crystalline Compound (III), Form N-1, is distinct as the (D,L)-malate salt.

The characteristic peaks from the solid state NMR may also serve to distinguish the crystalline and amorphous forms disclosed herein. For example, Table 3 lists characteristic solid state ^{13}C NMR peaks for crystalline Compound (III), Form N-1; crystalline Compound (I). Forms N-1 and N-2, and the amorphous form of Compound (I).

TABLE 3

Solid State Carbon-13 NMR Resonances (ppm, ±0.2 ppm)			
(I) Form N-1	(I), Form N-2	(III), Form N-1	(I), Amorphous
18.1	23.0	20.8	27.2
42.9	25.9	26.2	33.8
44.5	38.0	44.8	142.9
54.4	54.4	70.7	—
56.1	56.1	114.7	—
70.4	41.7	141.1	—
123.2	69.7	145.7	—
156.2	102.0	176.3	—
170.8	122.5	182.1	—
175.7	177.3	—	—
182.1	179.3	—	—
—	180.0	—	—
—	180.3	—	—

The solid state ^{19}F and ^{15}N NMR spectra, discussed below, provide data for similar comparison and characterization. As discussed above, being an enantiomer of Compound (I), crystalline Forms N-1 and N-2 and the amorphous form of Compound (II) will have the same solid state NMR resonances, and unique peaks between them, as those listed in Table 3 for Forms N-1 and N-2 of crystalline Compound (I).

Pharmaceutical Compositions and Methods of Treatment

Another aspect of this disclosure relates to a pharmaceutical composition comprising at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient. The amount of Compound (I), Compound (II), Compound (III), or the combinations thereof in the pharmaceutical composition can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may individually be present in the pharmaceutical composition as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a solid or dispersion pharmaceutical composition comprising at least one of a therapeutically effective amount of a crystalline form of Compound (I), Compound (II), Compound (III), or combinations thereof, and a pharmaceutically acceptable excipient.

Another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms, with crystalline Compound (I), Form N-1 or N-2 being preferred. Accordingly another aspect of this disclosure relates to a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, the method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating cancer, as discussed above, where the cancer treated is stomach cancer, esophageal carcinoma, kidney cancer, liver cancer, ovarian carcinoma, cervical carcinoma, large bowel cancer, small bowel cancer, brain cancer (including astrocytic tumor, which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components), lung cancer (including non-small cell lung cancer), bone cancer, prostate carcinoma, pancreatic carcinoma, skin cancer, bone cancer, lymphoma, solid tumors, Hodgkin's disease, non-Hodgkin's lymphoma or thyroid cancer thyroid cancer (including medullary thyroid cancer).

Tyrosine kinase inhibitors have also been used to treat non-small cell lung cancer (NSCLC). Gefitinib and erlotinib are angiogenesis inhibitors that target receptors of an epidermal growth factor called tyrosine kinase. Erlotinib and Gefitinib are currently being used for treating NSCLC. Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}-phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof, optionally in combination with Erlotinib or Gefitinib. In another embodiment, the combination is with Erlotinib.

Another aspect of this disclosure relates to a method of treating non-small cell lung cancer (NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating a method of treating non-small cell lung cancer

(NSCLC) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of Erlotinib or Gefitinib in combination with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above. In another embodiment, the combination administered in this method is Erlotinib with at least one of Compound (I), Compound (II), Compound (III), or combinations thereof.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

Another aspect of this disclosure relates to a method of treating an astrocytic tumor (which includes glioblastoma, giant cell glioblastoma, gliosarcoma, and glioblastoma with oligodendroglial components in a subject) in a subject, the method comprising administering to the subject in need of the treatment a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating an astrocytic tumor comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, or a pharmaceutically acceptable salt thereof. The amount administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a method of treating thyroid cancer (including medullary thyroid cancer) in a subject, the method comprising administering to the subject in need of the treatment at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms. Accordingly another aspect of this disclosure relates to a method of treating thyroid cancer comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (II), Compound (III) or combinations thereof such as discussed above.

Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, at least one of Compound (I), Compound (II), Compound (III) or combinations thereof. The amount of Compound (I), Compound (II), or combinations thereof administered can be a therapeutically effective amount. Compound (I), Compound (II), or Compound (III) may be individually administered as one of the solid state forms discussed above or combinations thereof. The crystalline forms are preferred solid state forms.

Accordingly another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities comprising administering to a subject in need thereof a therapeutically effective amount of at least one of Compound (I), Compound (II), Compound (III), or combinations thereof, wherein Compound (I), Compound (II), or Compound (III) is present in a crystalline form. In another aspect of this disclosure, this method of treatment may be practiced by administering a pharmaceutical composition of at least one of Compound (I), Compound (U), Compound (III) or combinations thereof such as discussed above. Another aspect of this disclosure relates to a method of treating diseases or disorders associated with uncontrolled, abnormal, and/or unwanted cellular activities. This method administers, to a subject in need thereof, a crystalline form of Compound (I), Compound (II), or any combination of Compound (I) and (II). The amount of Compound (I), Compound (II), or any combination of Compound (I) and (II) administered can be a therapeutically effective amount.

Another aspect of this disclosure relates to a use of the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to any of the above embodiments for the manufacture of a medicament for the treatment of a disease or disorder discussed above. When dissolved, a crystalline or amorphous form according to this disclosure loses its solid state structure, and is therefore referred to as a solution of, for example, Compound (I). At least one crystalline form disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form according to the disclosure is dissolved and/or suspended.

A pharmaceutical composition such as discussed above may be any pharmaceutical form which contains active Compound (I), Compound (II) and/or Compound (III), including the solid state forms thereof (hereinafter referred to as active compound(s). The pharmaceutical composition may be, for example, a tablet, capsule, liquid suspension, injectable, topical, or transdermal. The pharmaceutical compositions generally contain about 1% to about 99% by weight of the active compound(s), or a crystalline form of the active compound(s), and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of active compound, with the rest being suitable pharmaceutical excipients or other adjuvants, as discussed below.

A "therapeutically effective amount of the active compounds, or a crystalline or amorphous form of the active compound(s), according to this disclosure to inhibit, regulate and/or modulate the signal transduction of kinases (discussed here concerning the pharmaceutical compositions)

refers to an amount sufficient to treat a patient suffering from any of a variety of cancers associated with abnormal cell proliferation and angiogenesis. A therapeutically effective amount according to this disclosure is an amount therapeutically useful for the treatment or prevention of the disease states and disorders discussed herein. Compounds (I), (II), and/or (III) (including their solid state forms), possess therapeutic activity to inhibit, regulate and/or modulate the signal transduction of kinases such as described in WO2005-030140. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl] oxy}phenyl)-N'-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide.

The actual amount required for treatment of any particular patient will depend upon a variety of factors including the disease state being treated and its severity; the specific pharmaceutical composition employed; the age, body weight, general health, sex and diet of the patient; the mode of administration; the time of administration; the route of administration; and the rate of excretion of the active compound(s), or a crystalline form of the active compound(s), according to this disclosure; the duration of the treatment; any drugs used in combination or coincidental with the specific compound employed; and other such factors well known in the medical arts. These factors are discussed in Goodman and Gilman's "The Pharmacological Basis of Therapeutics", Tenth Edition, A. Gilman, J. Hardman and L. Limbird, eds., McGraw-Hill Press, 155-173, 2001, which is incorporated herein by reference. The active compound(s), or a crystalline form of active compound(s), according to this disclosure and pharmaceutical compositions comprising them, may be used in combination with anticancer or other agents that are generally administered to a patient being treated for cancer. They may also be co-formulated with one or more of such agents in a single pharmaceutical composition.

Depending on the type of pharmaceutical composition, the pharmaceutically acceptable carrier may be chosen from any one or a combination of carriers known in the art. The choice of the pharmaceutically acceptable carrier depends partly upon the desired method of administration to be used. For a pharmaceutical composition of this disclosure, that is, one of the active compound(s), or a crystalline form of the active compound(s), of this disclosure, a carrier should be chosen so as to substantially maintain the particular form of the active compound(s), whether it would be crystalline or not. In other words, the carrier should not substantially alter the form the active compound(s) are. Nor should the carrier be otherwise incompatible with the form of the active compound(s), such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

The pharmaceutical compositions of this disclosure may be prepared by methods know in the pharmaceutical formulation art, for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). In a solid dosage forms Compound (I) is admixed with at least one pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alginates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Pharmaceutically acceptable adjuvants known in the pharmaceutical formulation art may also be used in the pharmaceutical compositions of this disclosure. These include, but are not limited to, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. If desired, a pharmaceutical composition of this disclosure may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pII buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, and butylated hydroxytoluene.

Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the active compound(s), or a crystalline form of the active compound(s), with, for example, suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

Because the active compound(s), or a crystalline form of the active compound(s), is maintained during their preparation, solid dosage forms are preferred for the pharmaceutical composition of this disclosure. Solid dosage forms for oral administration, which includes capsules, tablets, pills, powders, and granules, are particularly preferred. In such solid dosage forms, the active compound(s) mixed with at least one inert, pharmaceutically acceptable excipient (also known as a pharmaceutically acceptable carrier). Administration of the active compound(s), or a crystalline form of the active compound(s), in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of

solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. One preferable route of administration is oral administration, using a convenient dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

General Preparation Methods of Crystalline Forms

Crystalline forms may be prepared by a variety of methods including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms of a solvent mixture include, but are not limited to, for example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding of a supersaturated solvent mixture of the compound and/or salt thereof; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S. R. Byrn, R. R. Pfeiffer, and J. G. Stowell, 2nd Edition, SSCI, West Lafayette, Ind. (1999).

In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the Compound (I) in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

In one method that can be used in preparing crystals, Compound (I), Compound (II) and/or Compound (III) can be suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product. Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in Programmed Cooling Batch Crystallizers," J. W. Mullin and J. Nyvlt, Chemical Engineering Science, 1971, 26, 3690377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size may be generated by sieving, milling, or micronizing large crystals, or by microcrystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

A cooled crystallization mixture may be filtered under vacuum and the isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, differential scanning calorimetry (DSC); x-ray powder diffraction (XRPD); and thermogravimetric analysis (TGA) to assure the crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt. % isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt. % isolated yield. Optionally, the product may be delumped by being comilled or passed through mesh screen.

The features and advantages of this disclosure may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of this disclosure that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof. The disclosure is further illustrated by the following examples, which are not to be construed as limiting the disclosure in scope or spirit to the specific procedures described in them.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference. All measurements are subject to experimental error and are within the spirit of the invention.

As used herein, "amorphous" refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

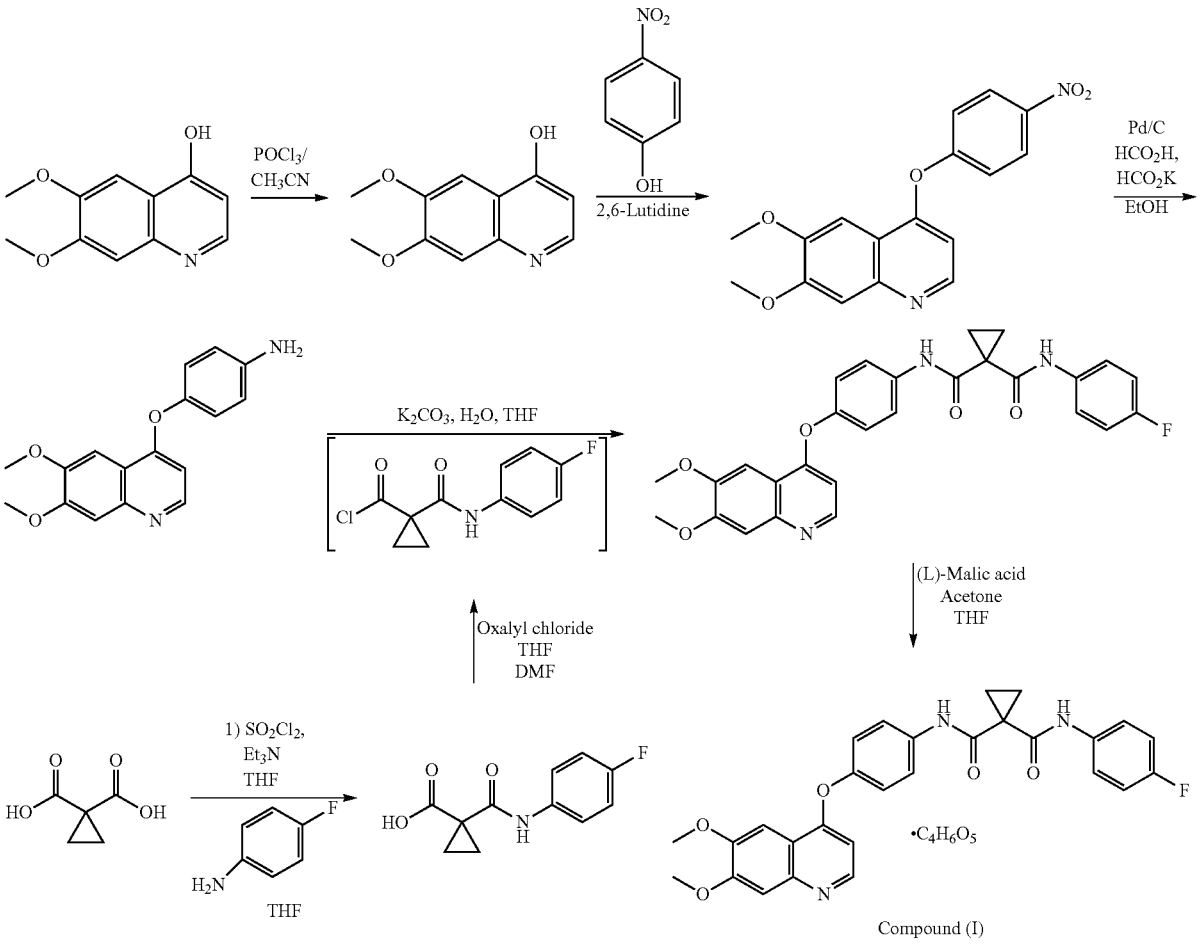
As used herein, the term "substantially pure" means the crystalline form of Compound (I) referred to contains at least about 90 wt. % based on the weight of such crystalline form. The term "at least about 90 wt. %," while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, about 91, about 92, about 93, about 94, about 95, about 96, about 97, about 98, about 99 and about 100% wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectroscopy, and/or infrared spectroscopy.

PREPARATIVE EXAMPLES

Example 1: Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof (Compound (I))

The synthetic route used for the preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and the (L)-malate salt thereof is depicted in Scheme 1:

SCHEME 1



The process shown in Scheme 1 is described in more detail below.

1.1 Preparation of 4-Chloro-6,7-dimethoxy-quinoline

A reactor was charged sequentially with 6,7-dimethoxy-quinoline-4-ol (1 L, 10.0 kg) and acetonitrile (64.0 L). The resulting mixture was heated to approximately 65° C. and phosphorus oxychloride ($POCl_3$, 50.0 kg) was added. After the addition of $POCl_3$, the temperature of the reaction mixture was raised to approximately 80° C. The reaction was deemed complete (approximately 9.0 hours) when <2% of the starting material remained (in process high-performance liquid chromatography [HPLC] analysis). The reaction mixture was cooled to approximately 10° C. and then quenched into a chilled solution of dichloromethane (DCM, 238.0 kg), 30% NH_4OH (135.0 kg), and ice (440.0 kg). The resulting mixture was warmed to approximately 14° C., and phases were separated. The organic phase was washed with water (40.0 kg) and concentrated by vacuum distillation with the removal of solvent (approximately 190.0 kg). Methyl-t-butyl ether (MTBE, 50.0 kg) was added to the batch, and the mixture was cooled to approximately 10° C., during which time the product crystallized out. The solids were recovered by centrifugation, washed with n-heptane (20.0 kg), and dried at approximately 40° C. to afford the title compound (8.0 kg).

1.2 Preparation of 6,7-Dimethyl-4-(4-nitro-phenoxy)-quinoline

A reactor was sequentially charged with 4-chloro-6,7-dimethoxy-quinoline (8.0 kg), 4 nitrophenol (7.0 kg), 4 dimethylaminopyridine (0.9 kg), and 2,6 lutidine (40.0 kg). The reactor contents were heated to approximately 147° C. When the reaction was complete (<5% starting material remaining as determined by in process HPLC analysis, approximately 20 hours), the reactor contents were allowed to cool to approximately 25° C. Methanol (26.0 kg) was added, followed by potassium carbonate (3.0 kg) dissolved in water (50.0 kg). The reactor contents were stirred for approximately 2 hours. The resulting solid precipitate was filtered, washed with water (67.0 kg), and dried at 25° C. for approximately 12 hours to afford the title compound (4.0 kg).

1.3 Preparation of 4-(6,7-Dimethoxy-quinoline-4-yloxy)-phenylamine

A solution containing potassium formate (5.0 kg), formic acid (3.0 kg), and water (16.0 kg) was added to a mixture of

6,7-dimethoxy-4-(4-nitro-phenoxy)-quinoline (4.0 kg), 10% palladium on carbon (50% water wet, 0.4 kg) in tetrahydrofuran (40.0 kg) that had been heated to approximately 60° C. The addition was carried out such that the temperature of the reaction mixture remained approximately 60° C. When the reaction was deemed complete as determined using in-process HPLC analysis (<2% starting material remaining, typically 15 hours), the reactor contents were filtered. The filtrate was concentrated by vacuum distillation at approximately 35° C. to half of its original volume, which resulted in the precipitation of the product. The product was recovered by filtration, washed with water (12.0 kg), and dried under vacuum at approximately 50° C. to afford the title compound (3.0 kg; 97% AUC).

1.4 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid

Triethylamine (8.0 kg) was added to a cooled (approximately 4° C.) solution of commercially available cyclopropane-1,1-dicarboxylic acid (2 1, 10.0 kg) in THF (63.0 kg) at a rate such that the batch temperature did not exceed 10° C. The solution was stirred for approximately 30 minutes, and then thionyl chloride (9.0 kg) was added, keeping the batch temperature below 10° C. When the addition was complete, a solution of 4-fluoroaniline (9.0 kg) in THF (25.0 kg) was added at a rate such that the batch temperature did not exceed 10° C. The mixture was stirred for approximately 4 hours and then diluted with isopropyl acetate (87.0 kg). This solution was washed sequentially with aqueous sodium hydroxide (2.0 kg dissolved in 50.0 L of water), water (40.0 L), and aqueous sodium chloride (10.0 kg dissolved in 40.0 L of water). The organic solution was concentrated by vacuum distillation followed by the addition of heptane, which resulted in the precipitation of solid. The solid was recovered by centrifugation and then dried at approximately 35° C. under vacuum to afford the title compound. (10.0 kg).

1.5 Preparation of 1-(4-Fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride

Oxalyl chloride (1.0 kg) was added to a solution of 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarboxylic acid (2.0 kg) in a mixture of THF (11 kg) and N, N-dimethylformamide (DMF; 0.02 kg) at a rate such that the batch temperature did not exceed 30° C. This solution was used in the next step without further processing.

1.6 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

The solution from the previous step containing 1-(4-fluoro-phenylcarbamoyl)-cyclopropanecarbonyl chloride was added to a mixture of 4-(6,7-dimethoxy-quinoline-4-yloxy)-phenylamine (3.0 kg) and potassium carbonate (4.0 kg) in THF (27.0 kg) and water (13.0 kg) at a rate such that the batch temperature did not exceed 30° C. When the reaction was complete (in typically 10 minutes), water (74.0 kg) was added. The mixture was stirred at 15-30° C. for approximately 10 hours, which resulted in the precipitation of the product. The product was recovered by filtration, washed with a premade solution of THF (11.0 kg) and water (24.0 kg), and dried at approximately 65° C. under vacuum for approximately 12 hours to afford the title compound (free base, 5.0 kg). ^{1}H NMR (400 MHz, d_6-DMSO): δ 10.2 (s, 1H), 10.05 (s, 1H), 8.4 (s, 1H), 7.8 (m, 2H), 7.65 (m, 2H), 7.5 (s, 1H), 7.35 (s, 1H), 7.25 (m, 2H), 7.15 (m, 2H), 6.4 (s, 1H), 4.0 (d, 6H), 1.5 (s, 4H). LCMS: M+H=502.

1.7 Preparation of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L) malate salt (Compound (I))

A solution of (L)-malic acid (2.0 kg) in water (2.0 kg) was added to a solution of Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinoline-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide free base (15, 5.0 kg) in ethanol, maintaining a batch temperature of approximately 25° C. Carbon (0.5 kg) and thiol silica (0.1 kg) were then added, and the resulting mixture was heated to approximately 78° C., at which point water (6.0 kg) was added. The reaction mixture was then filtered, followed by the addition of isopropanol (38.0 kg), and was allowed to cool to approximately 25° C. The product was recovered by filtration and washed with isopropanol (20.0 kg) and dried at approximately 65° C. to afford Compound (I) (5.0 kg).

Example 2: Preparation of Crystalline Compound (I), Form N-1

A solution was prepared by adding tetrahydrofuran (12 mL/g-bulk-LR (limiting reagent); 1.20 L) and N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (100 g; 1.00 equiv; 100.00 g) and (L)-malic acid (1.2 equiv (molar); 32.08 g) to a 1 L reactor. Water (0.5317 mL/g-bulk-LR; 53.17 mL) was added and the solution was heated to 60° C. and maintained at that temperature for one hour until the solids were fully dissolved. The solution was passed through a Polish Filter.

At 60° C., acetonitrile (12 mL/g-bulk-LR; 1.20 L) was added over a period of 8 hours. The solution was held at 60° C. for 10 hours. The solution was then cooled to 20° C. and held for 1 hour. The solids were filtered and washed with acetonitrile (12 mL/g-bulk-LR; 1.20 L). The solids were dried at 60° C. (25 mm IIg) for 6 hours to afford Compound (I), Form N-1 (108 g; 0.85 equiv; 108.00 g; 85.22% yield) as a white crystalline solid.

Example 3: Alternate Preparation of Crystalline Compound (I), Form N-1

A solution was prepared with 190 mL tetrahydrofuran (110 mL), methyl isobutyl ketone, and 29 mL water. Next, 20 mL of this solution were transferred into an amber bottle, and then saturated by adding N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (L)-malate until a thick slurry formed, and aging for at least 2 h with stirring at room temperature. The solids were removed by filtration through a Buchner funnel, rendering a clear saturated solution.

Separately, a powder blend was made with known amounts of two batches of Compound (I): (1) 300 mg of batch 1, which contained approximately 41% Compound (I), Form N-1 and 59% Compound (I), Form N-2 by Raman spectroscopy analysis, and (2) 200 mg of batch 2, which had a XPRD pattern similar to Compound (I), Form N-2.

The Compound (I), Form N-1 and Compound (I), Form N-2 powder blend was added into the saturated solution, and the slurry was aged under magnetic stirring at room temperature for 25 days. The slurry was then sampled and

filtered through a Buchner funnel to obtain 162 mg of wet cake. The wet cake was dried in a vacuum oven at 45° C. to afford 128 mg of crystalline Compound (I) in the N-1 form.

Example 4: Preparation of Crystalline Compound (I), Form N-2

4.1 Preparation of Crystalline Compound (I), Form N-2 Seed Crystals

A solution was prepared by combining 20 ml of acetone and 300 mg of freebase N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide in a 25 ml screw capped vial. Next, 0.758 ml of a 0.79M (L)-malic acid stock solution was added to the vial with magnetic stirring. The solution was then left stirring for 24 hr at ambient temperature. The sample was then suction filtered with 0.45 μm PTFE filter cartridge and dried in vacuo at ambient temperature overnight.

4.2 Preparation of Crystalline Compound (I), Form N-2

To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (48 g; 1.00 equiv; 48.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (L)-malic acid (1.2 equiv (molar); 15.40 g) was dissolved into methyl isobutyl ketone (10 mL/g-bulk-LR; 480.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 48.00 mL). Next, 50 mL of the (L)-malic acid solution was added to the first solution at 50° C. Seed crystals were added (1% 480 mg) and the malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% tetrahydrofuran/methyl isobutyl ketone (10V, 480 ml.). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (I) (55.7 g; 0.92 equiv; 55.70 g; 91.56% yield) as an off-white crystalline solid.

Example 5: Preparation of Crystalline Compound (III), Form N-1

A one ml aliquot (DL)-malic acid salt of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, slurried in tetrahydrofuran (THF), was heated to 60° C. on a hot-plate in a half-dram vial. Next, tetrahydrofuran was added drop-wise until an almost clear solution was obtained. The vial was capped, removed from the hot plate and equilibrated at ambient temperature without agitation. Crystallization was apparent after several hours and the solution was allowed to stand overnight to allow completion. Several droplets of the resulting slurry were placed on a glass slide for microscopic analysis. The crystalline material consisted of many elongated plates ranging up to 60 microns in the longest dimension.

Alternate Preparation of Crystalline Compound (III), Form N-1

To a reactor were added N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (15 g; 1.00 equiv; 15.00 g) and tetrahydrofuran (16.5 mL/g-bulk-LR; 792.00 mL). The water content was adjusted to 1 wt % water. The solution was heated to 60° C. Once dissolved, the solution was passed through a polish filter to provide the first solution.

In a separate reactor, (DL)-malic acid (1.2 equiv (molar); 4.53 g) was dissolved into methyl isobutyl ketone (8 mL/g-bulk-LR; 120.00 mL) and tetrahydrofuran (1 mL/g-bulk-LR; 15.00 mL). Next, 20 mL of the solution was added to the first solution at 50° C. The malic acid solution was added at 50° C. dropwise via an addition funnel (1.3 ml/min (3 h)). The slurry was held at 50° C. for 18 h and then was cooled to 25° C. over 30 min. The solids were filtered, and washed with 20% THF/MIBK (0V, 150 mL). The solids were dried under vacuum at 60° C. for 5 h to afford Compound (III) (15.52 g; 86.68% yield) as an off-white solid.

Example 6: Preparation of Amorphous Compound (I)

A solution was prepared with 5 g of N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (L)-malate and 250 mL of a 1:1 (v:v) mixture of methanol and dichloromethane. The hazy solution was filtered through a 0.45 micron filter to yield a clear, yellowish solution. The solution was pumped through the spray dryer nozzle at a rate of 12.9 cc/min, and was atomized by nitrogen gas fed at a rate of 10.911 min. The temperature at the inlet of the cyclone was set to 65° C. to dry the wet droplets. Dry amorphous powder (1.5 g) was collected (yield=30%).

CHARACTERIZATION EXAMPLES

I. NMR Spectra in Dimethyl Sulfoxide Solution

I.1 Compound (I), Form N-1

^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m. 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, 1H, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

^{13}C NMR (d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.2 Compound (I), Form N-2

^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2H), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

^{13}C NMR (d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17, 122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

I.3 Compound (III), Form N-1

^{1}H NMR (400 MHz, d_6-DMSO): δ 1.48 (s, 1H), 2.42-2.48 (m, 1H), 2.60-2.65 (m, 1H), 3.93-3.96 (m, 6H), 4.25-4.30 (dd, 1H, J=5, 8 Hz), 6.44 (d, J=5 Hz, 1H), 7.12-7.19 (m, 2H), 7.22-7.26 (m, 2H), 7.40 (s, 1H), 7.51 (s, 1H), 7.63-7.68 (m, 2H), 7.76-7.80 (m, 2 II), 8.46-8.49 (m, 1H), 10.08 (s, 1H), 10.21 (s, 1H).

^{13}C NMR (d_6-DMSO): 15.36, 31.55, 55.64, 55.67, 66.91, 99.03, 102.95, 107.66, 114.89, 115.07, 115.11, 121.17,

122.11, 122.32, 122.39, 135.15, 136.41, 146.25, 148.7, 149.28, 149.38, 152.54, 157.03, 159.42, 160.02, 168.07, 171.83, 174.68.

Characterization of Solid State Forms of N-(4-{[6,7-bis (methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate

II. Powder X-Ray Diffraction (XRPD) Studies

X-Ray Powder Diffraction (XRPD) patterns were collected on a Bruker AXS C2 GADDS diffractometer equipped with an automated XYZ stage, laser video microscope for auto-sample positioning and a HiStar 2-dimensional area detector. The radiation source used was copper (Cu Kα=1.5406 Å), wherein the voltage was set at 40 kV and the current was set at 40 mA, X-ray optics consists of a single Göbel multilayer mirror coupled with a pinhole collimator of 0.3 mm. The beam divergence, i.e. the effective size of the X-ray beam on the sample, was approximately 4 mm. A θ-θ continuous scan mode was employed with a sample-detector distance of 20 cm which gives an effective 2θ range of 3.2°-29.8°. Samples run under ambient conditions (from about 18° C. to about 25° C.) were prepared as flat plate specimens using powder as received without grinding. Approximately 1-2 mg of the sample was lightly pressed on a glass slide to obtain a flat surface. Typically the sample would be exposed to the X-ray beam for 120 seconds. Beam divergence (i.e., effective size of X-ray spot, gives a value of approximately 4 mm. Alternatively, the powder samples were placed in sealed glass capillaries of 1 mm or less in diameter; the capillary was rotated during data collection at a sample-detector distance of 15 cm. Data were collected for 3≤2θ≤35° with a sample exposure time of at least 2000 seconds. The resulting two-dimensional diffraction arcs were integrated to create a traditional 1-dimensional XRPD pattern with a step size of 0.02 °2θ in the range of 3 to 35 °2θ±0.2 °2θ. The software used for data collection was GADDS for WNT 4.1.16 and the data were analyzed and presented using Diffrac Plus EVA v 9.0.0.2 or v 13.0.0.2.

II.1 Compound (I), Form N-1

FIG. **1** shows the experimental XRPD pattern of crystalline Compound (I), Form N-1 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 19.4, 21.5, 22.8, 25.1, and 27.6 (±0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-1. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

II.2 Compound (I), Form N-2

FIG. **8** shows the experimental XRPD pattern of crystalline Compound (I), Form N-2 acquired at room temperature (about 25° C.). A list of the peaks are shown in Table 2, above. The 2θ values at 20.9 and 21.9 (±0.2 °2θ) are useful for characterizing crystalline Compound (I), Form N-2. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

II.3 Compound (III), Form N-1

FIG. **15** shows the experimental and the simulated XRPD pattern of crystalline Compound (III), Form N-1, acquired at 25° C. using a spinning capillary sample. A list of the peaks are shown in Table 2, above. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-2.

II.4 Amorphous Compound (I)

FIG. **22** shows the experimental XRPD pattern of amorphous Compound (I) acquired at room temperature (about 25° C.). The spectra is characterized a broad peak and the absence of sharp peaks, which is consistent with an amorphous material.

III. Single Crystal X-Ray Study for Compound (III), Form N-1

Data were collected on a Bruker-Nonius CAD4 serial diffractometer. Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle reflections. Intensities were measured using Cu Kα radiation (λ=1.5418 Å) at a constant temperature with the θ-2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data were collected on a Bruker-Nonius Kappa CCD 2000 system using Cu Kα radiation (λ=1.5418 Å). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. & Minor, W. (1997) in *Macromolecular Crystallography*, eds. Carter, W. C. Jr & Sweet, R. M. (Academic, NY), Vol. 276, pp. 307-326) in the Collect program suite (Collect Data collection and processing user interface: Collect: Data collection software, R. Hooft, Nonius B. V., 1998). Alternately, single crystal data were collected on a Bruker-AXS APEX2 CCD system using Cu Kα radiation (λ=1.5418 Å). Indexing and processing of the measured intensity data were carried out with the APEX2 software package/program suite (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27). When indicated, crystals were cooled in the cold stream of an Oxford cryo system (Oxford Cryosystems Cryostream cooler J. Cosier and A. M. Glazer, J. Appl. Cryst., 1986, 19, 105) during data collection.

The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP, Structure Determination Package, Enraf-Nonius, Bohemia N.Y. 11716. Scattering factors, including f' and f'', in the SDP software were taken from the "International Tables for Crystallography", Kynoch Press, Birmingham, England, 1974; Vol IV, Tables 2.2A and 2.3.1) with minor local modifications or the crystallographic packages MAXUS (maXus solution and refinement software suite: S. Mackay, C. J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, K. Shankland. maXus: a computer program for the solution and refinement of crystal structures from diffraction data) or SHELXTL (APEX2 Data collection and processing user interface: APEX2 User Manual, v1.27).

The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\Sigma_w(|F_o|-|F_c|)^2$. R is defined as $\Sigma||F_o|-|F_c||/\Sigma|_o|$ while $R_w=[\Sigma_w(|F_o|-|_c|)^2/\Sigma_w|F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogens were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

"Hybrid" simulated powder X-ray patterns were generated as described in the literature (Yin. S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review,* 2003, 6, 2, 80). The room temperature cell parameters were obtained by performing a cell refinement using the CellRefine.xls program. Input to the program includes the 2-theta position of ca. 10 reflections, obtained from the experimental room temperature powder pattern; the corresponding Miller indices, hkl, were assigned based on the single-crystal data collected at low temperature. A new (hybrid) XRPD was calculated (by either of the software programs, Alex or LatticeView) by inserting the

molecular structure determined at low temperature into the room temperature cell obtained in the first step of the procedure. The molecules are inserted in a manner that retains the size and shape of the molecule and the position of the molecules with respect to the cell origin, but, allows intermolecular distances to expand with the cell.

A single crystal, measuring 40×30×10 microns, was selected from the slurry of crystals described in Example 5 for single crystal diffraction analysis. The selected crystal was affixed to a thin glass fiber with a small amount of a light grease, and mounted at room temperature on a Bruker ApexII single crystal diffractometer equipped with a rotating copper anode.

Crystalline Compound (III), From N-1 is characterized by unit cell parameters approximately equal to those reported in Table 4. The unit cell parameters were measured at a temperature of about 25° C.

TABLE 4

a = 14.60 Å
b = 5.20 Å
c = 39.09 Å
α = 90.0°
β = 90.4°
γ = 90.0°
Space group: $P2_1/n$
Molecules of Compound (I)/unit cell: 4
Volume = 2969 $Å^3$

Structure solution and refinement were routine in the monoclinic space group, $P2_1/n$, with four formula units in the unit cell. The structure contains cations of N-(4-{[6,7-bis(methyloxy)-quinolin-4-yl]oxy}phenyl)-N'-(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide, protonated at the quinoline nitrogen atom, and singly ionized malic acid anions, in a 1:1 ratio. Further, the crystal contained a 1:1 ratio of (L)-malic acid ions to (D)-malic acid ions. Table 5 fractional atomic coordinates for Compound (III), Form N-1 calculated at a temperature of about 25° C.

Based on the single crystal X-ray data, crystalline Compound (III), Form N-1 may be characterized by a simulated powder x-ray diffraction (XRPD) pattern substantially in accordance with the simulated pattern shown in FIG. **15** and/or by an observed XRPD pattern substantially in accordance with the experimental pattern shown in FIG. **15**.

TABLE 5

Fractional Atomic Coordinates for Compound (III), Form N-1 Calculated at a Temperature of about 25° C.

Atom	X	Y	Z
O1	0.30601	−0.52166	0.22875
O2	0.29518	0.12504	0.09391
O3	0.19041	−0.53232	0.18147
F5	−0.07307	2.12170	−0.08811
O6	0.18186	1.20500	−0.03241
O7	0.57137	0.22739	0.23473
O8	0.58700	−0.17911	0.24998
O9	0.41742	0.76377	−0.04319
N10	0.28649	0.82210	−0.01420
O11	0.87391	0.22086	0.31241
N12	0.46887	0.17029	0.17613
C13	0.29647	0.64886	0.01247
C14	0.31416	1.08187	−0.06304
C15	0.33900	−0.02207	0.14761
N16	0.20651	1.40640	−0.08267
C17	0.40079	−0.01723	0.17602
C18	0.29743	0.29956	0.06604
C19	0.00418	1.80556	−0.05680
C20	0.11925	1.73626	−0.11097
C21	0.22556	1.24019	−0.05791
C22	0.39150	−0.17467	0.20389
C23	0.22558	0.63870	0.03619
O24	0.62714	0.39565	0.29760
C25	0.34591	0.87438	−0.03961
C26	0.36467	−0.51389	0.25773
C27	0.26562	−0.20277	0.14859
C28	0.35380	0.15272	0.12054
C29	0.07365	1.60604	−0.05443
C30	0.04897	1.92890	−0.11212
C31	0.73841	0.04517	0.28641
C32	0.32089	−0.35160	0.20385
C33	0.36641	0.29052	0.04302
C34	0.42458	0.32272	0.12143
C35	0.11723	−0.54030	0.15742
C36	0.12933	1.59042	−0.08228
C37	−0.00344	1.93494	−0.08547
C38	0.36439	0.47245	0.01586
C39	0.59040	0.05797	0.25625
C40	0.25712	−0.35516	0.17574
C41	0.63543	0.13842	0.29041
C42	0.22703	0.46640	0.06306
C43	0.34559	1.01717	−0.10021
C44	0.39312	1.20834	−0.08137
C45	0.48224	0.32340	0.15059
O46	0.77400	0.04784	0.34652
C47	0.79349	0.09920	0.31966
H10	0.22646	0.91057	−0.01479
H16	0.24790	1.42164	−0.10317
H19	−0.04176	1.82973	−0.03893
H20	0.16347	1.73025	−0.13083
H22	0.43179	−0.17902	0.22447
H23	0.17093	0.73524	0.03244
H27	0.21953	−0.24212	0.12962
H29	0.07954	1.50390	−0.03492
H30	0.04671	2.05817	−0.13354
H33	0.41851	0.16255	0.04395
H34	0.43433	0.41859	0.10106
H38	0.41440	0.45648	−0.00227
H41	0.61062	0.02238	0.31086
H42	0.17752	0.45794	0.07911
H45	0.53033	0.44239	0.15049
H31a	0.76754	0.12071	0.26693
H31b	0.74726	−0.15247	0.28137
H43a	0.30237	1.06909	−0.12187
H43b	0.36868	0.85693	−0.10836
H44a	0.45563	1.18725	−0.07495
H44b	0.38932	1.39942	−0.08846
H26a	0.35958	−0.37184	0.27147
H26b	0.42813	−0.55605	0.25348
H26c	0.34954	−0.66814	0.27571
H35a	0.08189	−0.39941	0.15398
H35b	0.06671	−0.68838	0.16269
H35c	0.13276	−0.61095	0.13323
H11	0.88836	0.21926	0.28968
H12	0.50720	0.16494	0.19477
H24	0.61522	0.45898	0.27789

IV. Solid State Nuclear Magnetic Resonance (SSNMR)

All solid-state C-13 NMR measurements were made with a Bruker DSX-400, 400 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and the TPPM pulse sequence and ramp amplitude cross-polarization (RAMP-CP) with magic-angle spinning (MAS) at approximately 12 kHz (A. E. Bennett et al, *J. Chem. Phys.*, 1995, 103, 6951), (G. Metz, X. Wu and S. O. Smith, *J. Magn. Reson. A.*, 1994, 110, 219-227). Approximately 70 mg of sample, packed into a canister-design zirconia rotor was used for each experiment. Chemical shifts (δ) were referenced to external adamantane with the high frequency resonance being set to 38.56 ppm (W. L Earl and D. L VanderHart, *J. Magn. Reson.*, 1982, 48, 35-54).

IV.1 Compound (I), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-1 is shown in FIG. **2**. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

SS ^{13}C NMR Peaks: 18.1, 20.6, 26.0, 42.9, 44.5, 54.4, 55.4, 56.1, 70.4, 99.4, 100.1, 100.6, 114.4, 114.9, 115.8, 119.6, 120.1, 121.6, 123.2, 124.1, 136.4, 138.6, 140.6, 145.4, 150.1, 150.9, 156.2, 157.4, 159.4, 164.9, 167.1, 170.8, 175.7, and 182.1 ppm, ±0.2 ppm.

FIG. **3** shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows peaks at 118.6, 119.6, 120.7, 134.8, 167.1, 176.0, and 180 ppm, ±0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-1.

FIG. **4** shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-1. The spectrum shows a peak at −121.6, −120.8, and −118.0 ppm, ±0.2 ppm.

IV.2 Compound (I), Form N-2

The solid state ^{13}C NMR spectrum of crystalline Compound (I), Form N-2 is shown in FIG. **9**. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

SS ^{13}C NMR Peaks: 20.5, 21.8, 23.0, 25.9, 26.4, 38.0, 41.7, 54.7, 55.8, 56.2, 56.6, 69.7, 99.4, 100.0, 100.4, 100.8, 102.3, 114.5, 115.5, 116.7, 119.0, 120.2, 121.1, 121.2, 122.1, 122.9, 124.5, 136.0, 137.3, 138.1, 138.9, 139.5, 140.2, 144.9, 145.7, 146.1, 150.7, 156.7, 157.7, 159.6, 159.7, 165.1, 167.0, 168.0, 171.5, 177.3, 179.3, 180.0, and 180.3 ppm, ±0.2 ppm.

FIG. **10** shows the solid state ^{15}N NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at 118.5, 120.8, 135.1, 167.3, and 180.1 ppm, ±0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (I), Form N-2.

FIG. **11** shows the solid state ^{19}F NMR spectrum of crystalline Compound (I), Form N-2. The spectrum shows peaks at −121.0 and −119.1 ppm, ±0.2 ppm. Those peaks, individually or together, may be sufficient to characterize crystalline Compound (I), Form N-2.

IV.3 Compound (III), Form N-1

The solid state ^{13}C NMR spectrum of crystalline Compound (III), Form N-1 is shown in FIG. **16**. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

SS ^{13}C NMR Peaks: 20.8, 26.2, 44.8, 55.7, 70.7, 100.4, 101.0, 114.7, 115.2, 116.0, 119.7, 120.4, 121.6, 124.4, 136.9, 138.9, 141.1, 145.7, 150.3, 156.5, 157.6, 159.6, 165.2, 167.4, 171.2, 176.3, and 182.1 ppm, ±0.2 ppm.

FIG. **17** shows the solid state ^{15}N NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows peaks at 119.6, 134.7, and 175.5 ppm, ±0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize crystalline Compound (III), Form N-1.

FIG. **18** shows the solid state ^{19}F NMR spectrum of crystalline Compound (III), Form N-1. The spectrum shows a peak at −120.5 ppm, ±0.2 ppm.

IV.4 Compound (I), Amorphous

FIG. **23** shows the solid state ^{13}C NMR spectrum of amorphous Compound (I). The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

SS ^{13}C NMR Peaks (ppm): 12.2, 17.8, 20.3, 21.8, 27.2, 33.8, 41.7, 56.9, 69.9, 99.9, 102.2, 115.6, 122.2, 134.4, 137.8, 142.9, 149.1, 150.9, 157.3, 159.7, 167.0, 171.7, 173.1, 177.4, and 179.5 ppm, ±0.2 ppm.

FIG. **24** shows the solid state ^{15}N NMR spectrum of amorphous Compound (I). The spectrum shows peaks at 120.8, 131.8, 174.7, and 178.3 ppm, ±0.2 ppm. The entire list of peaks, or a subset thereof, may be sufficient to characterize amorphous Compound (I).

FIG. **25** shows the solid state ^{19}F NMR spectrum of amorphous Compound (I). The spectrum shows a peak at −118.9 ppm, ±0.2 ppm.

V. Thermal Characterization Measurements

Thermal Gravimetric Analysis (TGA)

The TGA measurements were performed in a TA Instruments™ model Q500 or 2950, employing an open pan setup. The sample (about 10-30 mg) was placed in a platinum pan previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate.

Differential Scanning Calorimetry (DSC) Analysis

DSC measurements were performed in a TA Instruments™ model Q2000, Q1000 or 2920, employing an open pan setup. The sample (about 2-6 mg) was weighed in an aluminum pan and recorded accurately recorded to a hundredth of a milligram, and transferred to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and 300° C. at 10° C./min heating rate. The plot was made with the endothermic peaks pointing down.

V.1 Compound (I), Form N-1

FIG. **5** shows the TGA thermogram for crystalline Compound (I), Form N-1, which shows a weight loss of approximately 0.4 weight % at a temperature of 170° C.

FIG. **6** shows the DSC thermogram for crystalline Compound (I), Form N-1, which showed a melting point of approximately 187° C.

V.2 Compound (I), Form N-2

FIG. **12** shows the TGA thermogram for crystalline Compound (I), Form N-2, which shows a weight loss of approximately 0.1 weight % at a temperature of 170° C.

FIG. **13** shows the DSC thermogram for crystalline Compound (I), Form N-2, which showed a melting point of approximately 186° C.

V.3 Compound (III), Form N-1

FIG. **19** shows the TGA thermogram for crystalline Compound (III), Form N-1, which shows a weight loss of approximately 0.2 weight % at a temperature of 170° C.

FIG. **20** shows the DSC thermogram for crystalline Compound (III), Form N-1, which showed a melting point of approximately 186° C.

V.2 Compound (I), Amorphous

FIG. **26** shows the DSC for crystalline Compound (I).

VI. Moisture Vapor Isotherm Measurements

Moisture sorption isotherms were collected in a VTI SGA-100 Symmetric Vapor Analyzer using approximately 10 mg of sample. The sample was dried at 60° C. until the loss rate of 0.0005 wt %/min was obtained for 10 minutes. The sample was tested at 25° C. and 3 or 4, 5, 15, 25, 35, 45, 50, 65, 75, 85, and 95% RH. Equilibration at each RH was reached when the rate of 0.0003 wt %/min for 35 minutes was achieved or a maximum of 600 minutes.

VI.1 Compound (I), Form N-1

FIG. **7** shows the moisture vapor isotherm of crystalline Compound (I), Form N-1.

VI.2 Compound (I), Form N-1

FIG. **14** shows the moisture vapor isotherm of crystalline Compound (I), Form N-2.

VI.3 Compound (III), Form N-1

FIG. **21** shows the moisture vapor isotherm of crystalline Compound (III), Form N-1.

VI.4 Compound (I), Amorphous

FIG. **27** shows the moisture vapor isotherm of amorphous Compound (I).

The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications can be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications can be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, and wherein said salt is crystalline.

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

3. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is liver cancer.

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