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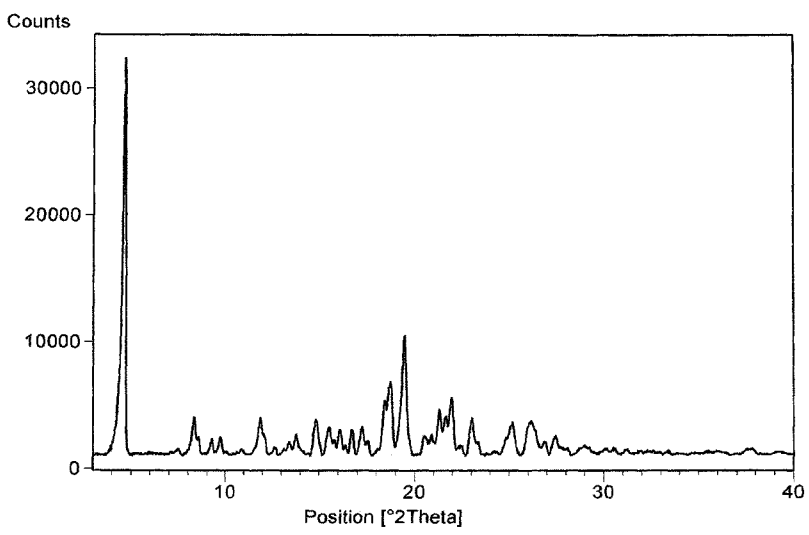
(54) **Title**: POLYMORPHIC FORMS OF LAPATINIB DITOSYLATE AND PROCESSES FOR THEIR PREPARATION

Fig. 1



(57) **Abstract**: There is provided a crystalline form of Lapatinib, termed APO-I, and methods for making APO-I. There is also provided a crystalline solvate form of Lapatinib, termed APO-II, and methods for making APO-II.

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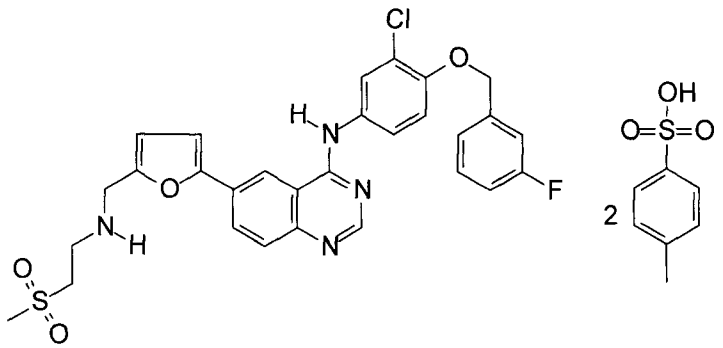
POLYMORPHIC FORMS OF LAPATINIB DITOSYLATE AND PROCESSES FOR THEIR PREPARATION

TECHNICAL FIELD

The present invention relates to polymorphic forms of Lapatinib ditosylate and processes for their preparation.

BACKGROUND

Lapatinib ditosylate (**1**) is a kinase inhibitor and is indicated in combination with: (1) capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab and (2) letrozole for the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated. It is marketed in USA as Tykerb®. Chemically, Lapatinib ditosylate is *N*-(3-chloro-4-{[(3-fluorophenyl)methyl]oxy}phenyl)-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate).



Lapatinib Ditosylate (1)

US 6,713,485 relates to substituted heteroaromatic compounds, methods for their preparation, pharmaceutical compositions containing them and their use in medicine. Specifically, US 6,713,485 relates to quinazoline derivatives useful in treating disorders mediated by protein tyrosine kinase activity, in particular erbB-2 and/or EGFR activity.

US 7,157,466 describes ditosylate salts of 4-quinazolineamines as well as methods of using the same in the treatment of disorders characterized by aberrant erbB family PTK activity.

WO 2008/154469 describes salts of 4-quinazolineamines as well as methods of using the same in the treatment of disorders characterized by aberrant erbB family PTK activity.

WO 2009/079541 describes crystalline forms of anhydrate ditosylate salts of 4-quinazolineamines as well as methods of using the same in the treatment of disorders characterized by aberrant erbB family PTK activity.

WO 2009/079547 describes crystalline forms of 4-quinazolineamines as well as methods of using the same in the treatment of disorders characterized by aberrant erbB family PTK activity.

US 2009/0281315 provides polymorphs of Lapatinib ditosylate, processes for preparing them, and pharmaceutical compositions comprising one or more of these polymorphs.

US 2009/0306106 provides crystalline forms of Lapatinib base, Form X and Form Y, and amorphous Lapatinib base, pharmaceutical compositions comprising the crystalline forms of Lapatinib base, and/or the amorphous Lapatinib base, and processes for their preparation.

SUMMARY

The present invention relates, at least in part, to crystalline forms of Lapatinib ditosylate, namely polymorphic forms of Lapatinib ditosylate termed herein APO-I and APO-II. Processes for preparing these forms are also provided.

In illustrative embodiments of the present invention, there is provided APO-I polymorphic form of Lapatinib ditosylate.

In illustrative embodiments of the present invention, there is provided an APO-I polymorphic form of Lapatinib ditosylate described herein having a powder X-ray diffraction pattern comprising peaks, in terms of degrees 2-theta, at approximately 4.6, 18.8, 19.5, 21.3, 22.0 and 23.0.

In illustrative embodiments of the present invention, there is provided an APO-I polymorphic form of Lapatinib ditosylate described herein wherein the powder X-ray diffraction pattern further comprising peaks, in terms of

degrees 2-theta, at approximately 8.3, 9.3, 11.8, 13.8, 14.9, 16.8, 17.3, 25.2 and 26.2.

In illustrative embodiments of the present invention, there is provided an APO-I polymorphic form of Lapatinib ditosylate described herein having a DSC thermogram comprising two endothermic peaks with peak onset temperatures of approximately 169.5°C and 247.9°C and peak maximums of approximately 179.5°C and 250.5°C

In illustrative embodiments of the present invention, there is provided an APO-I polymorphic form of Lapatinib ditosylate described herein having a PXRD diffractogram substantially similar to a PXRD diffractogram as depicted in Figure 1.

In illustrative embodiments of the present invention, there is provided an APO-I polymorphic form of Lapatinib ditosylate described herein having a DSC thermogram substantially similar to a DSC thermogram as depicted in Figure 2.

In illustrative embodiments of the present invention, there is provided APO-II polymorphic form of Lapatinib ditosylate.

In illustrative embodiments of the present invention, there is provided an APO-II polymorphic form of Lapatinib ditosylate described herein having a powder X-ray diffraction pattern comprising peaks, in terms of degrees 2-theta, at approximately 4.4, 8.3, 13.1, 19.3, 20.9 and 21.4.

In illustrative embodiments of the present invention, there is provided an APO-II polymorphic form of Lapatinib ditosylate described herein wherein the powder X-ray diffraction pattern further comprising peaks, in terms of degrees 2-theta, at approximately 9.6, 10.5, 14.0, 15.0 16.9, 18.2, 25.3, and 26.6.

In illustrative embodiments of the present invention, there is provided an APO-II polymorphic form of Lapatinib ditosylate described herein having a DSC thermogram comprising three endothermic peaks with peak onset temperatures of approximately 98.5°C, 167.7°C and 247.0°C and peak maximums of approximately 119.5°C, 177.8°C and 249.4°C

In illustrative embodiments of the present invention, there is provided an APO-II polymorphic form of Lapatinib ditosylate described herein having a

PXRD diffractogram substantially similar to a PXRD diffractogram as depicted in Figure 3.

In illustrative embodiments of the present invention, there is provided an APO-II polymorphic form of Lapatinib ditosylate described herein having a DSC thermogram substantially similar to a DSC thermogram as depicted in Figure 4.

In illustrative embodiments of the present invention, there is provided a polymorphic form of Lapatinib ditosylate described herein in a pharmaceutical formulation.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-I comprising: drying APO-II at atmospheric pressure.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-I comprising drying APO-II *in vacuo*.

In illustrative embodiments of the present invention, there is provided a process described herein wherein the drying occurs at a temperature of from about 0°C to about 60°C.

In illustrative embodiments of the present invention, there is provided a process described herein wherein the drying occurs at a temperature of from about 20°C to about 50°C.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-II comprising: I. mixing Lapatinib ditosylate with isopropanol thereby forming a first mixture; II. heating the first mixture to a first temperature; III. maintaining the first mixture at the first temperature; IV. cooling the first mixture to a second temperature; V. maintaining the first mixture at the second temperature thereby forming a first precipitate; and VI. recovering the first precipitate thereby isolating APO-II.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-II comprising: I. mixing Lapatinib ditosylate with isopropanol thereby forming a second mixture; II. heating the second mixture to a third temperature; III. heating the second mixture to a fourth temperature; IV. maintaining the second mixture at the fourth temperature; V. cooling the second mixture to a fifth temperature; VI. maintaining the second mixture at

the fifth temperature thereby forming a second precipitate; VII. recovering the second precipitate thereby isolating APO-II.

In illustrative embodiments of the present invention, there is provided a process described herein further comprising adding solid APO-II, APO-I, or a mixture thereof to the second mixture prior to heating the second mixture to the fourth temperature and after heating the second mixture to the third temperature.

In illustrative embodiments of the present invention, there is provided a process described herein wherein the Lapatinib ditosylate is selected from the group consisting of amorphous Lapatinib ditosylate, Lapatinib ditosylate monohydrate and mixtures thereof.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-II comprising: I. mixing Lapatinib base with isopropanol thereby forming a third mixture; II. heating the third mixture to a sixth temperature; III. adding to the third mixture *p*-toluenesulfonic acid followed by isopropanol thereby forming a fourth mixture; IV. heating the fourth mixture to a seventh temperature; V. maintaining the fourth mixture at the seventh temperature; VI. cooling the fourth mixture to an eighth temperature; VII. maintaining the fourth mixture at the eighth temperature thereby forming a third precipitate; VIII. recovering the third precipitate thereby isolating APO-II.

In illustrative embodiments of the present invention, there is provided a process for preparing APO-II comprising: I. mixing Lapatinib base with isopropanol thereby forming a third mixture; II. heating the third mixture to a sixth temperature; III. adding to the third mixture an isopropanol solution of *p*-toluenesulfonic acid thereby forming a fourth mixture; IV. heating the fourth mixture to a seventh temperature; V. maintaining the fourth mixture at the seventh temperature; VI. cooling the fourth mixture to an eighth temperature; VII. maintaining the fourth mixture at the eighth temperature thereby forming a third precipitate; VIII. recovering the third precipitate thereby isolating APO-II.

In illustrative embodiments of the present invention, there is provided a process described herein further comprising adding solid APO-II, APO-I or a mixture thereof to the third mixture prior to adding *p*-toluenesulfonic acid and after heating the third mixture to the sixth temperature.

Other aspects and features of the present invention will become apparent to those ordinarily skilled in the art upon review of the following description of specific embodiments of the invention in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Drawings which illustrate embodiments of the invention are:

Figure 1: is a powder X-ray diffraction (PXRD) diffractogram of APO-I.

Figure 2: is a differential scanning calorimetry (DSC) thermogram of APO-I.

Figure 3: is a powder X-ray diffraction (PXRD) diffractogram of APO-II.

Figure 4: is a differential scanning calorimetry (DSC) thermogram of APO-II.

DETAILED DESCRIPTION

When used in reference to a diffractogram, a spectrum and/or data presented in a graph, the term "substantially similar" means that the subject diffractogram, spectrum and/or data presented in a graph encompasses all diffractograms, spectra and/or data presented in graphs that vary within acceptable boundaries of experimentation that are known to a person of skill in the art. Such boundaries of experimentation will vary depending on the type of the subject diffractogram; spectrum and/or data presented in a graph, and are known to and understood by a person of skill in the art.

When used in reference to a peak in a powder X-ray diffraction (PXRD) diffractogram, the term "approximately" means that the peak may vary by ± 0.2 degrees 2θ of the subject value.

When used in reference to a peak in a differential scanning calorimetry (DSC) thermogram, the term "approximately" means that the peak may vary by ± 1 degree of the subject value.

As used herein when referring to a diffractogram, spectrum and/or to data presented in a graph, the term "peak" refers to a feature that one skilled in the art would recognize as not attributing to background noise.

Depending on the nature of the methodology applied and the scale selected to display results obtained from an X-ray diffraction analysis, an intensity of a peak obtained may vary quite dramatically. For example, it is

possible to obtain a relative peak intensity of 0.01% when analyzing one sample of a substance, but another sample of the same substance may show a much different relative intensity for a peak at the same position. This may be due, in part, to the preferred orientation of the sample and its deviation from the ideal random sample orientation, sample preparation and the methodology applied. Such variations are known and understood by a person of skill in the art.

In an illustrative embodiment, the present invention comprises a crystalline form of Lapatinib ditosylate which is a polymorphic form referred to herein as APO-I. A typical DSC thermogram for APO-I comprises two endothermic peaks with peak onset temperatures of approximately 169.5°C and 247.9°C and peak maximums of approximately 179.5°C and 250.5°C. An illustrative DSC thermogram of APO-I is given in Figure 2.

Illustrative peaks, expressed in angle 2-theta, appearing in a typical PXRD for APO-I include 4.6 ± 0.2, 8.3 ± 0.2, 9.3 ± 0.2, 11.8 ± 0.2, 13.8 ± 0.2, 14.9 ± 0.2, 16.8 ± 0.2, 17.3 ± 0.2, 18.8 ± 0.2, 19.5 ± 0.2, 21.3 ± 0.2, 22.0 ± 0.2, 23.0 ± 0.2, 25.2 ± 0.2, and 26.2 ± 0.2. Illustrative relative peak intensities of the aforementioned peaks appearing in a typical PXRD for APO-I, expressed in terms of percent, are illustrated below in Table 1.

Table 1: Relative Peak Intensities for APO-I

Angle 2-theta	Relative Intensity %
4.6	100.0
8.3	9.3
9.3	3.5
11.8	9.2
13.8	6.0
14.9	9.6
16.8	7.0
17.3	7.8
18.8	22.8
19.5	33.2
21.3	20.8

Table 1: Relative Peak Intensities for APO-I	
Angle 2-theta	**Relative Intensity %**
22.0	23.2
23.0	13.7
25.2	10.3
26.2	11.7

An illustrative PXRD diffractogram of APO-I is given in Figure 1.

In an illustrative embodiment, the present invention comprises a crystalline isopropanol solvate form of Lapatinib ditosylate which is a polymorphic form referred to herein as APO-II. A typical DSC thermogram for APO-II comprises three endothermic peaks with peak onset temperatures of approximately 98.5°C, 167.7°C and 247.0°C and peak maximums of approximately 119.5°C, 177.8°C and 249.4°C. An illustrative DSC thermogram of APO-II is given in Figure 4.

Illustrative peaks, expressed in angle 2-theta, appearing in a typical PXRD for APO-I include 4.4 ± 0.2, 8.3 ± 0.2, 9.6 ± 0.2, 10.5 ± 0.2, 13.1 ± 0.2, 14.0 ± 0.2, 15.0 ± 0.2, 16.9 ± 0.2, 18.2 ± 0.2, 19.3 ± 0.2, 20.9 ± 0.2, 21.4 ± 0.2, 25.3 ± 0.2, and 26.6 ± 0.2. Illustrative relative peak intensities of the aforementioned peaks appearing in a typical PXRD for APO-II, expressed in terms of percent, are illustrated below in Table 2.

Table 2: Relative Peak Intensities for APO-II	
Angle 2-theta	**Relative Intensity %**
4.4	100.0
8.3	10.3
9.6	3.5
10.5	3.1
13.1	7.2
14.0	3.3
15.0	2.7
16.9	4.6

Table 2: Relative Peak Intensities for APO-II	
Angle 2-theta	**Relative Intensity %**
18.2	6.2
19.3	12.8
20.9	21.5
21.4	15.0
25.3	7.6
26.6	7.2

An illustrative PXRD diffractogram of APO-II is given in Figure 3.

In another illustrative embodiment, the present invention provides a process of preparing APO-II comprising:

a. mixing Lapatinib ditosylate with isopropanol thereby forming a first mixture;
b. heating the first mixture to a first temperature;
c. maintaining the first mixture at the first temperature;
d. cooling the first mixture to a second temperature;
e. maintaining the first mixture at the second temperature thereby forming a first precipitate; and
f. recovering the first precipitate thereby isolating APO-II.

The Lapatinib ditosylate for mixing with isopropanol may be in any form or a mixture of forms, for example and without limitation, amorphous Lapatinib ditosylate and/or Lapatinib ditosylate monohydrate.

A volume of isopropanol used to mix with the Lapatinib ditosylate may be from about 5 volumes to about 20 volumes. The volume may be from about 6 volumes to about 10 volumes.

The first temperature may be in a range of from about 60°C to about 82°C. The first temperature may be approximately refluxing temperature. The first mixture is maintained at the first temperature for a first period of time from about 0.5 hours to about 18 hours. Often the first period of time is from about 2 hours to about 8 hours. Often the first period of time is from about 4 hours to about 5 hours.

The second temperature may be in a range of from about 0°C to about 40°C. The second temperature may be in a range of from about 20°C to about 30°C. The first mixture is maintained at the second temperature for a second period of time from about 0.5 hours to about 18 hours. Often the second period of time is from about 2 hours to about 5 hours.

Recovering the first precipitate may be carried out by any known method such as filtration, centrifugation, and/or decantation.

In another illustrative embodiment, the present invention provides another process of preparing APO-II comprising:

g. mixing Lapatinib ditosylate with isopropanol thereby forming a second mixture;
h. heating the second mixture to a third temperature;
i. optionally adding solid APO-II, APO-I or both to the second mixture;
j. heating the second mixture to a fourth temperature;
k. maintaining the second mixture at the fourth temperature;
l. cooling the second mixture to a fifth temperature;
m. maintaining the second mixture at the fifth temperature thereby forming a second precipitate; and
n. recovering the second precipitate thereby isolating APO-II.

The Lapatinib ditosylate for mixing with isopropanol may be in any form or a mixture of forms, for example and without limitation, amorphous Lapatinib ditosylate and/or Lapatinib ditosylate monohydrate.

A volume of isopropanol used to mix with the Lapatinib ditosylate may be from about 5 volumes to about 20 volumes. The volume may be from about 6 volumes to about 10 volumes.

The third temperature may be in a range of from about 55°C to about 75°C. The third temperature may be in a range of from about 60°C to about 65°C.

If added, an amount of APO-II, APO-I or both used in step i may be from about 0.01 w/w percent to about 50 w/w percent relative to the amount of

Lapatinib ditosylate added in step g. Hence, the second mixture may or may not contain one or both of added APO-I and/or APO-II

The fourth temperature may be in a range of from about 60°C to about 82°C. The fourth temperature may be approximately refluxing temperature. The second mixture is maintained at the fourth temperature for a third period of time from about 0.5 hours to about 18 hours. The third period of time may be from about 2 hours to about 8 hours. Often the third period of time is about 4 hours to about 5 hours.

The fifth temperature may be in a range of from about 0°C to about 40°C. The fifth temperature may be from about 20°C to about 30°C. The second mixture is maintained at the fifth temperature for a fourth period of time from about 0.5 hours to about 18 hours. Often the fourth period of time is from about 2 hours to about 5 hours.

Recovering the second precipitate may be carried out by any known method such as filtration, centrifugation, and/or decantation.

In another illustrative embodiment, the present invention provides another process of preparing APO-II comprising:

o. mixing Lapatinib base with isopropanol thereby forming a third mixture;

p. heating the third mixture to a sixth temperature;

q. optionally adding solid APO-II , APO-I or both to the third mixture;

r. adding to the third mixture *p*-toluenesulfonic acid followed by isopropanol or adding an isopropanol solution of *p*-toluenesulfonic acid thereby forming a fourth mixture;

s. heating the fourth mixture to a seventh temperature;

t. maintaining the fourth mixture at the seventh temperature;

u. cooling the fourth mixture to an eighth temperature;

v. maintaining the fourth mixture at the eighth temperature thereby forming a third precipitate; and

w. recovering the third precipitate thereby isolating APO-II.

A volume of isopropanol used to mix with the Lapatinib base may be from about 5 volumes to about 20 volumes. The volume may be from about 6 volumes to about 10 volumes.

The sixth temperature may be in a range of from about 55°C to about 75°C. The sixth temperature may be in a range of from about 65°C to about 75°C.

If added, an amount of APO-II, APO-I or both used in step q may be from about 0.01 w/w percent to about 50 w/w percent relative to the amount of Lapatinib added in step o. Hence, the third mixture may or may not contain one or both of added APO-I and/or APO-II. Similarly, depending on whether or not one or both of APO-I and/or APO-II was added to the third mixture, the composition of the fourth mixture will vary accordingly.

An amount of *p*-toluenesulfonic acid (whether in an isopropanol solution or not) added to the third mixture is about 2.0 equivalents to about 2.2 equivalents.

The seventh temperature may be in a range of from about 60°C to about 82°C. The seventh temperature may be approximately refluxing temperature. The fourth mixture is maintained at the seventh temperature for a fifth period of time from about 0.5 hours to about 18 hours. Often the fifth period of time is from about 2 hours to about 8 hours. Often the fifth period of time is from about 4 hours to about 5 hours.

The eighth temperature may be in a range of from about 0°C to about 40°C. The eighth temperature may be from about 20°C to about 30°C. The fourth mixture is maintained at the eighth temperature for a sixth period of time from about 0.5 hours to about 18 hours. Often the sixth period of time is from about 2 hours to about 5 hours.

Recovering the third precipitate may be carried out by any known method such as filtration, centrifugation, and/or decantation.

Following the above steps a-f and/or g-n and/or o-w, polymorphic Form APO-II Lapatinib ditosylate may be produced.

In another illustrative embodiment, the present invention provides a process of preparing APO-I comprising drying APO-II at atmospheric pressure or *in vacuo*. The drying may occur at a temperature in a range of from about

0°C to about 60°C. The drying temperature may be in the range of from about 20°C to about 50°C. Often the drying temperature may be in a range of from about 45°C to about 50°C.

The following examples are illustrative of some of the embodiments of the invention described herein. These examples do not limit the spirit or scope of the invention in anyway.

Examples:

Powder X-Ray Diffraction (PXRD) Analysis: The data were acquired on a PANanalytical X-Pert Pro MPD diffractometer with fixed divergence slits and an X-Celerator RTMS detector. The diffractometer was configured in Bragg-Brentano geometry; data was collected over a 2 theta range of 3 to 40 using CuKα radiation at a power of 40 mA and 45 kV. CuKβ radiation was removed using a divergent beam nickel filter. A step size of 0.017 degrees was used. A step time of 50 seconds was used. Samples were rotated at 1 Hz to reduce preferred orientation effects. The samples were prepared by the back-loading technique.

Differential Scanning Calorimetry (DSC) Analysis: The DSC thermograms were collected on a Mettler-Toledo 821e instrument. Samples (1 to 3 mg) were weighed into a 40 µL aluminum pan and were crimped closed with an aluminum lid. The samples were analyzed under a flow of nitrogen (ca. 55 mL/min) at a scan rate of 10°C/minute, from 0 to 280°C.

Example 1:

Preparation of isopropanol solvate of Lapatinib ditosylate (APO-II) and APO-I form of Lapatinib ditosylate:

Lapatinib ditosylate monohydrate (15 g) was slurried in isopropyl alcohol (90 mL) at 80-82°C for about 4 h. The mixture was cooled down slowly to 20-25°C and stirred at that temperature for about 16 h, filtered, washed with isopropyl alcohol (38 mL) and suction dried to provide Lapatinib ditosylate isopropanol solvate (APO-II). The APO-II product obtained was subjected to PXRD analysis and the results are shown in Figure 3. DSC

analysis was also performed and the results obtained were substantially similar to those shown in Figure 4.

Lapatinib ditosylate isopropanol solvate from above was dried *in vacuo* at 45-50°C for 82 hours to provide 13.7 g of Lapatinib ditosylate of crystalline form APO-I. The APO-I product obtained was subjected to PXRD analysis as well as DSC analysis and the results are shown in Figures 1 and 2, respectively.

Example 2:

Preparation of isopropanol solvate of Lapatinib ditosylate (APO-II) and APO-I form of Lapatinib ditosylate using seeding:

A mixture of Lapatinib ditosylate monohydrate (10 g) and isopropyl alcohol (60 mL) was heated to 60-65°C, seeded with crystals of Lapatinib ditosylate form APO-I (0.8 g) and the suspension heated to 80-82°C and slurried for about 4 h. The mixture was cooled down slowly to 25-30°C, filtered, washed with isopropyl alcohol (25 mL) and suction dried to provide Lapatinib ditosylate isopropanol solvate (APO-II). The APO-II product obtained was subjected to PXRD analysis as well as DSC analysis. The results of the PXRD analysis and the DSC analysis were substantially similar to those shown in Figures 3 and 4.

Lapatinib ditosylate isopropanol solvate from above was dried *in vacuo* at 45-50°C for 1 day to provide 10.2 g of Lapatinib ditosylate crystalline form APO-I. The APO-I product obtained was subjected to PXRD analysis as well as DSC analysis. The results of the PXRD analysis were substantially similar to those shown in Figure 1.

Example 3:

Preparation of isopropanol solvate of Lapatinib ditosylate (APO-II) and APO-I form of Lapatinib ditosylate from Lapatinib base:

A mixture of Lapatinib base (2 g) and isopropyl alcohol (18 mL) were heated to 70-75°C. Seeds of Lapatinib ditosylate form APO-I (0.1 g) were added, followed by *p*-toluenesulfonic acid monohydrate (1.37 g, 2.1 eq.), and rinsed with isopropanol (2 mL). The suspension was heated to 80-82°C for

about 4 h. The mixture was cooled down slowly to 25-30°C, filtered, washed with isopropanol (5 mL) and suction dried to provide Lapatinib ditosylate isopropanol solvate (APO-II). The APO-II product obtained was subjected to PXRD analysis. The results of the PXRD analysis were substantially similar to those shown in Figure 3.

Lapatinib ditosylate isopropanol solvate from above was dried *in vacuo* at 45-50°C for about 1 day to provide 3.0 g of Lapatinib ditosylate form APO-I. The APO-I product formed was subjected to PXRD analysis. The results of the PXRD analysis were substantially similar to those shown in Figure 1.

Example 4:

Preparation of isopropanol solvate of Lapatinib ditosylate (APO-II):

Amorphous Lapatinib ditosylate (1 g - prepared according to methods similar to those described in example 1 of WO 2009/079541) in isopropyl alcohol (6 mL) was heated to about 75°C. Additional isopropyl alcohol (1 mL) was added and the mixture was slurried at that temperature for about 4 h. The mixture was cooled down slowly to 20-25°C and stirred at that temperature for about 18 h, filtered, washed with isopropyl alcohol and suction dried to provide Lapatinib ditosylate isopropanol solvate (APO-II). The APO-II product formed was subjected to PXRD analysis as well as DSC analysis. The results of the PXRD analysis were substantially similar to those shown in Figure 3. The results of the DSC analysis are shown in Figure 4.

Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. Furthermore, numeric ranges are provided so that the range of values is recited in addition to the individual values within the recited range being specifically recited in the absence of the range. The word "comprising" is used herein as an open-ended term, substantially equivalent

to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing.

Citation of references herein is not an admission that such references are prior art to the present invention. Furthermore, material appearing in the background section of the specification is not an admission that such material is prior art to the invention. Any priority document(s) are incorporated herein by reference as if each individual priority document were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

What is claimed is:

1. APO-I polymorphic form of Lapatinib ditosylate.

2. The APO-I polymorphic form of Lapatinib ditosylate of claim 1 having a powder X-ray diffraction pattern comprising peaks, in terms of degrees 2-theta, at approximately 4.6, 18.8, 19.5, 21.3, 22.0 and 23.0.

3. The APO-I polymorphic form of Lapatinib ditosylate of claim 2 wherein the powder X-ray diffraction pattern further comprising peaks, in terms of degrees 2-theta, at approximately 8.3, 9.3, 11.8, 13.8, 14.9, 16.8, 17.3, 25.2 and 26.2.

4. The APO-I polymorphic form of Lapatinib ditosylate of claim 3 having a DSC thermogram comprising two endothermic peaks with peak onset temperatures of approximately 169.5°C and 247.9°C and peak maximums of approximately 179.5°C and 250.5°C

5. The APO-I polymorphic form of Lapatinib ditosylate of claim 1 having a PXRD diffractogram substantially similar to a PXRD diffractogram as depicted in Figure 1.

6. The APO-I polymorphic form of Lapatinib ditosylate of claim 3 having a DSC thermogram substantially similar to a DSC thermogram as depicted in Figure 2.

7. APO-II polymorphic form of Lapatinib ditosylate.

8. The APO-II polymorphic form of Lapatinib ditosylate of claim 7 having a powder X-ray diffraction pattern comprising peaks, in terms of degrees 2-theta, at approximately 4.4, 8.3, 13.1, 19.3, 20.9 and 21.4.

9. The APO-II polymorphic form of Lapatinib ditosylate of claim 8 wherein the powder X-ray diffraction pattern further comprising peaks, in terms of degrees 2-theta, at approximately 9.6, 10.5, 14.0, 15.0 16.9, 18.2, 25.3, and 26.6.

10. The APO-II polymorphic form of Lapatinib ditosylate of claim 9 having a DSC thermogram comprising three endothermic peaks with peak onset temperatures of approximately 98.5°C, 167.7°C and 247.0°C and peak maximums of approximately 119.5°C, 177.8°C and 249.4°C

11. The APO-II polymorphic form of Lapatinib ditosylate of claim 7 having a PXRD diffractogram substantially similar to a PXRD diffractogram as depicted in Figure 3.

12. The APO-II polymorphic form of Lapatinib ditosylate of claim 9 having a DSC thermogram substantially similar to a DSC thermogram as depicted in Figure 4.

13. The polymorphic form of any one of claims 1 to 12 in a pharmaceutical formulation.

14. A process for preparing APO-I comprising: drying APO-II at atmospheric pressure.

15. A process for preparing APO-I comprising drying APO-II *in vacuo*.

16. The process of claim 14 or 15 wherein the drying occurs at a temperature of from about 0°C to about 60°C.

17. The process of claim 14 or 15 wherein the drying occurs at a temperature of from about 20°C to about 50°C.

18. A process for preparing APO-II comprising:

I. mixing Lapatinib ditosylate with isopropanol thereby forming a first mixture;
II. heating the first mixture to a first temperature;
III. maintaining the first mixture at the first temperature;
IV. cooling the first mixture to a second temperature;
V. maintaining the first mixture at the second temperature thereby forming a first precipitate; and
VI. recovering the first precipitate thereby isolating APO-II.

19. A process for preparing APO-II comprising:
I. mixing Lapatinib ditosylate with isopropanol thereby forming a second mixture;
II. heating the second mixture to a third temperature;
III. heating the second mixture to a fourth temperature;
IV. maintaining the second mixture at the fourth temperature;
V. cooling the second mixture to a fifth temperature;
VI. maintaining the second mixture at the fifth temperature thereby forming a second precipitate;
VII. recovering the second precipitate thereby isolating APO-II.

20. The process of claim 19 further comprising adding solid APO-II, APO-I, or a mixture thereof to the second mixture prior to heating the second mixture to the fourth temperature and after heating the second mixture to the third temperature.

21. The process of any one of claims 18 to 20 wherein the Lapatinib ditosylate is selected from the group consisting of amorphous Lapatinib ditosylate, Lapatinib ditosylate monohydrate and mixtures thereof.

22. A process for preparing APO-II comprising:
I. mixing Lapatinib base with isopropanol thereby forming a third mixture;
II. heating the third mixture to a sixth temperature;

III. adding to the third mixture *p*-toluenesulfonic acid followed by isopropanol thereby forming a fourth mixture;
IV. heating the fourth mixture to a seventh temperature;
V. maintaining the fourth mixture at the seventh temperature;
VI. cooling the fourth mixture to an eighth temperature;
VII. maintaining the fourth mixture at the eighth temperature thereby forming a third precipitate;
VIII. recovering the third precipitate thereby isolating APO-II.

23. A process for preparing APO-II comprising:
I. mixing Lapatinib base with isopropanol thereby forming a third mixture;
II. heating the third mixture to a sixth temperature;
III. adding to the third mixture an isopropanol solution of *p*-toluenesulfonic acid thereby forming a fourth mixture;
IV. heating the fourth mixture to a seventh temperature;
V. maintaining the fourth mixture at the seventh temperature;
VI. cooling the fourth mixture to an eighth temperature;
VII. maintaining the fourth mixture at the eighth temperature thereby forming a third precipitate;
VIII. recovering the third precipitate thereby isolating APO-II.

24. The process of claim 22 or 23 further comprising adding solid APO-II, APO-I or a mixture thereof to the third mixture prior to adding *p*-toluenesulfonic acid and after heating the third mixture to the sixth temperature.

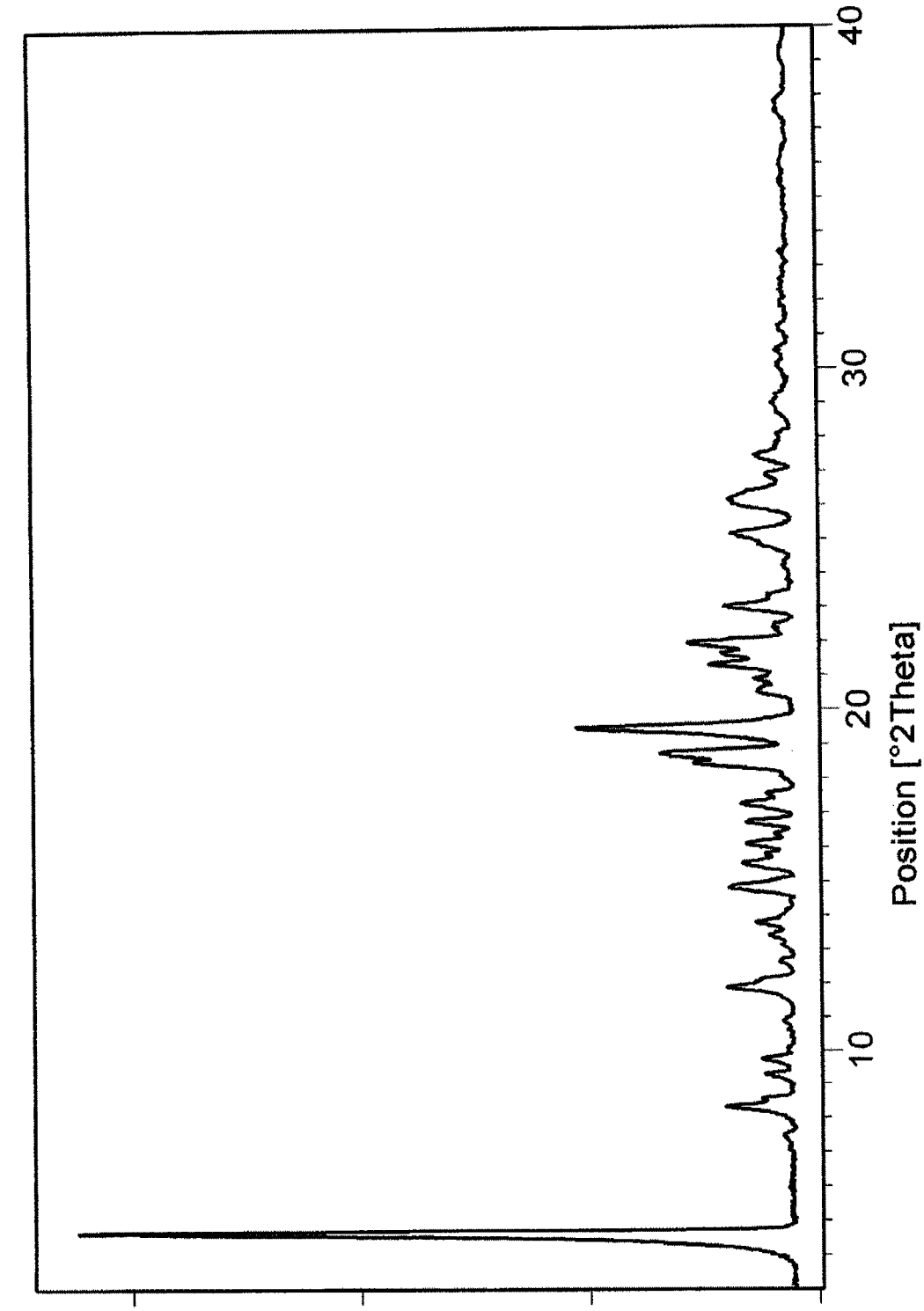


Fig. 1

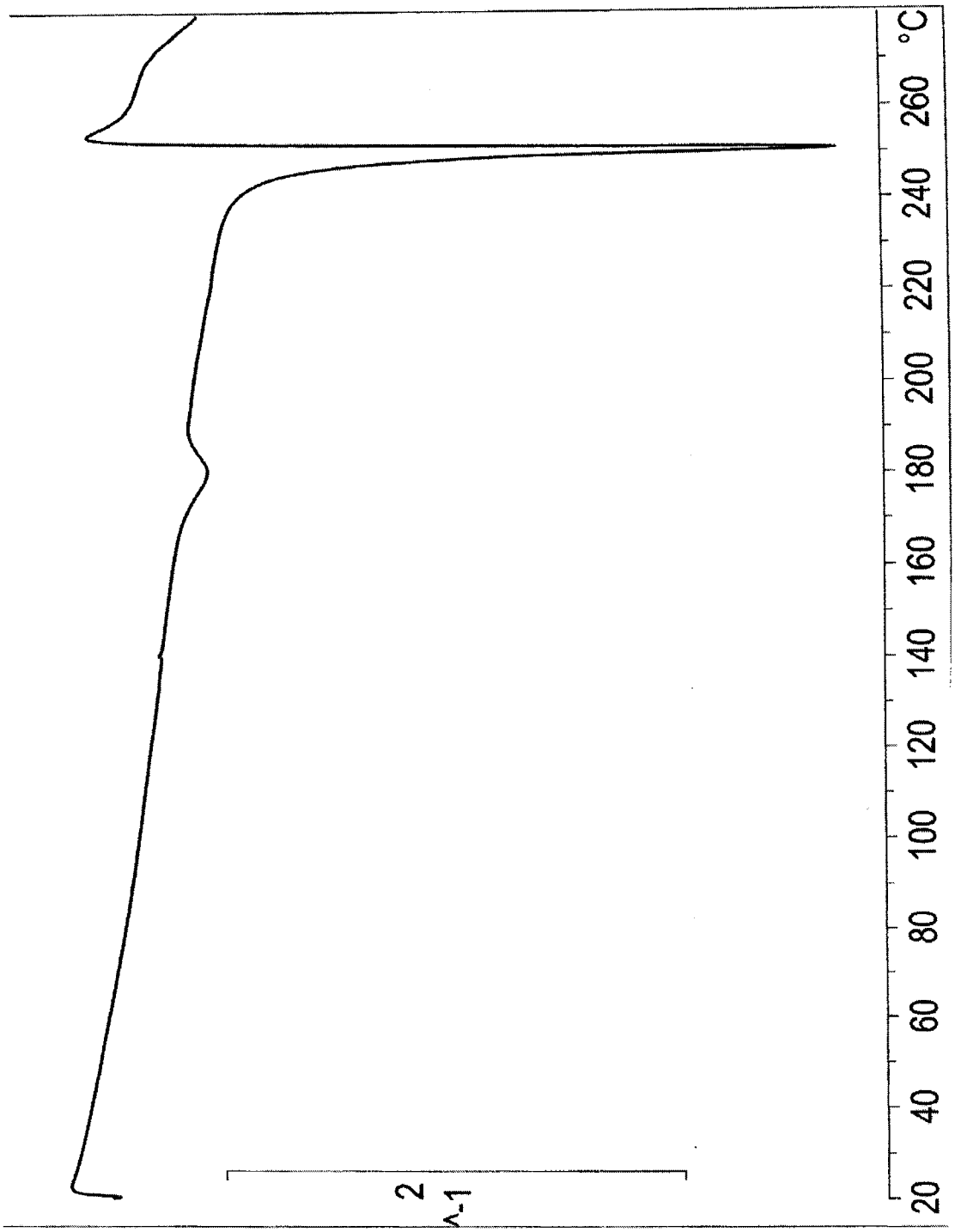


Fig. 2

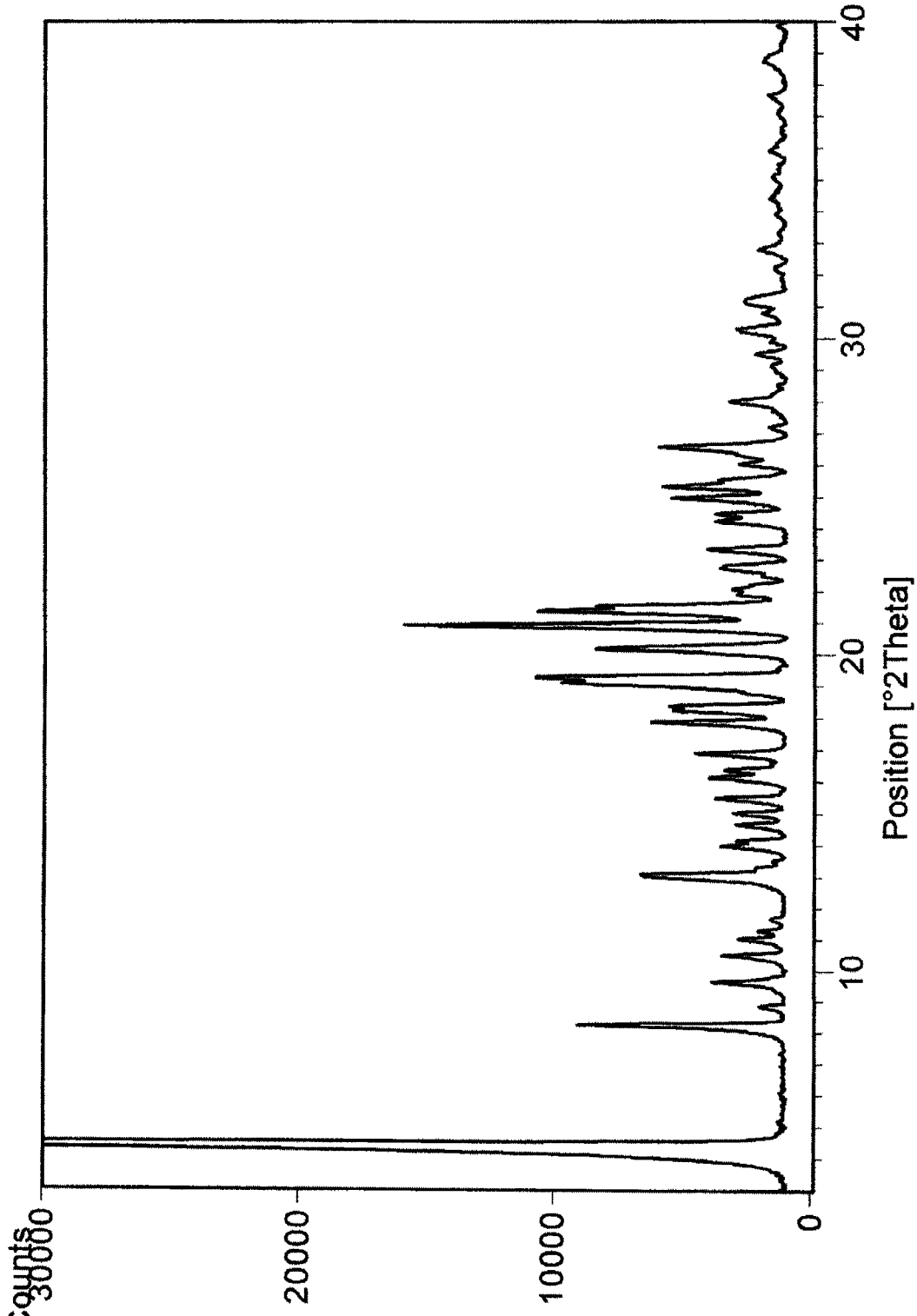


Fig. 3

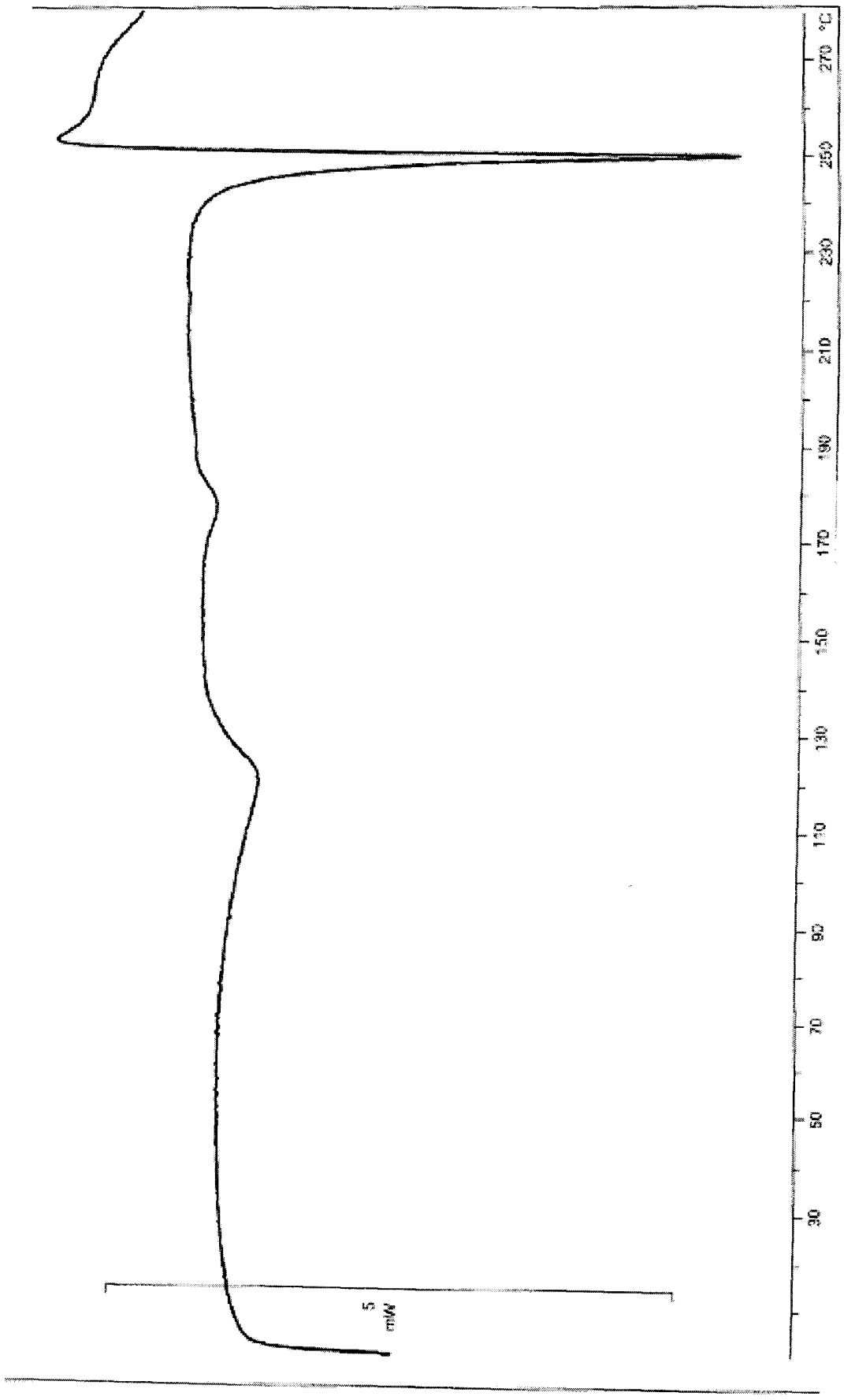


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/000439

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 405/04*** (2006.01) , ***C07C 309/30*** (2006.01) , ***C30B 7/08*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***C07D 405*** (2006.01), ***C07C 309*** (2006.01) , ***C30B 7/08*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN; Canadian Patent Database*, TotalPatent*

*Keywords: lapatinib, quinazolin!amin!, PXRD, XRPD, X!ray, diffract!

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/137714 (METSGER et al.) 12 November 2009 (12-11-2009) see the whole document and in particular examples 14 and 24; paragraphs [00154], [00155], [00188] and [00189]; and claims 68 and 79 (family member US 2009/0281315 cited by the applicant)	1-24
P, X	IP.com Journal (2011), 11(3B), 4 (No. IPCOM000204533D), (ANON.) 02 Mars 2011 (02-03-2011) see preparation of Form B	1, 2, 5, 7, 8, 11, 13
A	WO 2009/079541 (CRAIG et al.) 25 June 2009 (25-06-2009) (cited by the applicant)	1-24
A	WO 2009/079547 (CRAIG et al.) 25 June 2009 (25-06-2009) (cited by the applicant)	1-24
A	US 7157466 (MCCLURE et al.) 27 January 2002 (27-01-2002) (cited by the applicant)	1-24
P, A	US 2011/0071169 (HUANG et al.) 24 Mars 2011 (24-03-2011)	1-24

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2011 (21-07-2011)	18 August 2011 (18-08-2011)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Assia Semra (819) 994-1728

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/000439

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [ ] Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :

2. [ ] Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. [ ] Claim Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

See Extra Sheet.

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Box No. III (continuation)

The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1-6, 13 (part) and 14-17 are directed to a crystalline polymorphic form of lapatinib ditosylate (APO-I) , pharmaceutical composition thereof as well as to processes for preparing said polymorphic form of lapatinib ditosylate.

Group B - Claims 7-12, 13 (part) and 18-24 are directed to a crystalline isopropanol solvate polymorphic form of lapatinib ditosylate (APO-II) , pharmaceutical composition thereof as well as processes for preparing said polymorphic form of lapatinib ditosylate.

The claims must be limited to one inventive concept as set out in Rule 13 of the PCT.

The claims of the above Groups do not fulfill the requirement of unity of invention referred to in Rule 13.1 because the only special technical feature linking these claims is lapatinib ditosylate which is already known.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2009137714A2	12 November 2009 (12-11-2009)	US2009281315A1	12 November 2009 (12-11-2009)
		US2009306106A1	10 December 2009 (10-12-2009)
		WO2009137714A3	18 March 2010 (18-03-2010)
		WO2009140144A1	19 November 2009 (19-11-2009)
WO2009079541A1	25 June 2009 (25-06-2009)	None	
WO2009079547A1	25 June 2009 (25-06-2009)	None	
US7157466B2	02 January 2007 (02-01-2007)	AR031248A1	17 September 2003 (17-09-2003)
		AT353891T	15 March 2007 (15-03-2007)
		AU7307101A	14 January 2002 (14-01-2002)
		AU2001273071B2	08 September 2005 (08-09-2005)
		AU2010274106A1	17 February 2011 (17-02-2011)
		BR0111947A	06 May 2003 (06-05-2003)
		CA2413134A1	10 January 2002 (10-01-2002)
		CA2413134C	11 May 2010 (11-05-2010)
		CN1440403A	03 September 2003 (03-09-2003)
		CN1211382C	20 July 2005 (20-07-2005)
		CN1636992A	13 July 2005 (13-07-2005)
		CN1305872C	21 March 2007 (21-03-2007)
		CZ20024223A3	14 May 2003 (14-05-2003)
		CZ299561B6	03 September 2008 (03-09-2008)
		CZ300945B6	23 September 2009 (23-09-2009)
		DE60126611D1	29 March 2007 (29-03-2007)
		DE60126611T2	22 November 2007 (22-11-2007)
		DK1294715T3	04 June 2007 (04-06-2007)
		EP1294715A1	26 March 2003 (26-03-2003)
		EP1294715B1	14 February 2007 (14-02-2007)
		EP1792902A1	06 June 2007 (06-06-2007)
		ES2280382T3	16 September 2007 (16-09-2007)
		HK1051041A1	10 August 2007 (10-08-2007)
		HU0303022A2	29 December 2003 (29-12-2003)
		HU0303022A3	30 March 2009 (30-03-2009)
		IL153111A	08 July 2008 (08-07-2008)
		IL153111D0	24 June 2003 (24-06-2003)
		IL184115D0	31 October 2007 (31-10-2007)
		JP2004502687A	29 January 2004 (29-01-2004)
		JP4102185B2	18 June 2008 (18-06-2008)
		JP2008050363A	06 March 2008 (06-03-2008)
		KR20070100936A	12 October 2007 (12-10-2007)
		KR100850393B1	04 August 2008 (04-08-2008)
		MXPA02012681A	25 April 2003 (25-04-2003)
		NO20026196D0	23 December 2002 (23-12-2002)
		NO20026196A	24 February 2003 (24-02-2003)
		NO324637B1	26 November 2007 (26-11-2007)
		NO20063572A	24 February 2003 (24-02-2003)
		NZ522989A	24 June 2005 (24-06-2005)
		NZ538778A	29 September 2006 (29-09-2006)
		PL203943B1	30 November 2009 (30-11-2009)
		PL365637A1	10 January 2005 (10-01-2005)
		PL204958B1	26 February 2010 (26-02-2010)
		PT1294715E	31 May 2007 (31-05-2007)
		US2003220354A1	27 November 2003 (27-11-2003)
		US2008058519A1	06 March 2008 (06-03-2008)
		WO0202552A1	10 January 2002 (10-01-2002)
		ZA200209819A	31 May 2006 (31-05-2006)
US2011071169A1	24 March 2011 (24-03-2011)	None	