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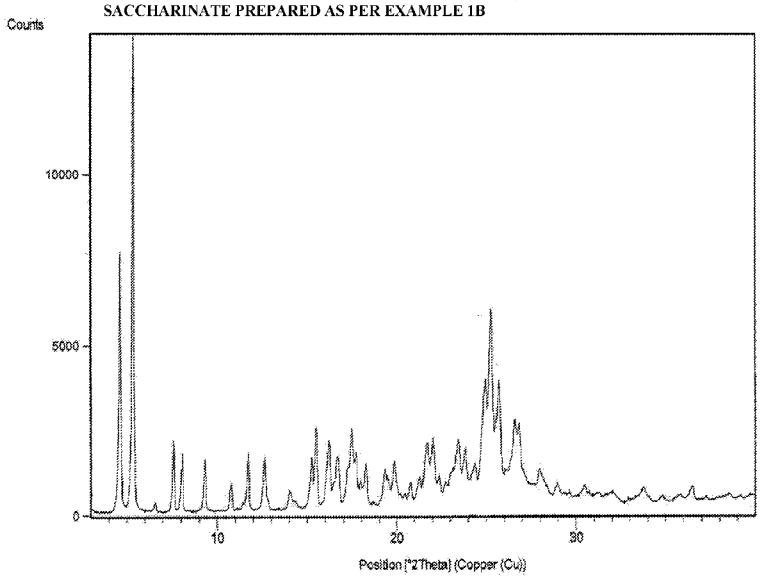
(54) **Title**: ERLOTINIB SALTS

FIGURE 1: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF ERLOTINIB SACCHARINATE PREPARED AS PER EXAMPLE 1B



(57) **Abstract**: The present invention provides erlotinib saccharinate and erlotinib maleate or hydrates thereof, their crystalline forms, processes for their preparation, and pharmaceutical compositions thereof.

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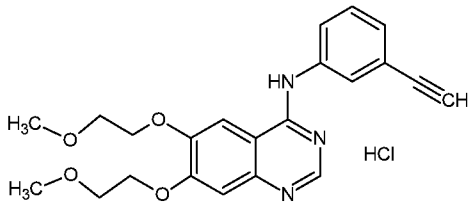
ERLOTINIB SALTS

Field of the Invention

The present invention provides erlotinib saccharinate and erlotinib maleate or hydrates thereof, their crystalline forms, processes for their preparation, and pharmaceutical compositions thereof.

Background of the Invention

Erlotinib hydrochloride of Formula A is known chemically as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine hydrochloride.



Formula A

U.S. Patent No. RE41,065, a reissue of U.S. Patent No. 5,747,498, provides a process for the preparation of erlotinib hydrochloride.

U.S. Patent No. 6,706,721 provides a process for the preparation of erlotinib mesylate.

PCT Publication No. WO 2008/122776 provides processes for the preparation of erlotinib hydrochloride, sulphate, tosylate, and oxalate.

PCT Publication No. WO 2011/068403 provides processes for the preparation of erlotinib ethanesulfonate, isethionate, bromide, malonate, L-lactate, and succinate.

PCT Publication No. WO 2012/008711 provides a process for the preparation of erlotinib dichloroacetate.

Korean Patent Registration No. KR 10-1132937 provides a process for the preparation of erlotinib napsylate.

Several processes have been reported for the preparation of erlotinib or pharmaceutically acceptable salts thereof, for example, U.S. Patent Nos. 6,476,040 and US 8,318,932; U.S. Publication No. 2013/0137867; PCT Publication Nos. WO 01/34574, WO 2004/072049, WO 2007/060691, WO 2007/138612, WO 2007/138613, WO 2008/000418,

WO 2008/012105, WO 2008/049645, WO 2008/102369, WO 2008/122776, WO 2009/002538, WO 2009/007984, WO 2009/024989, WO 2009/025873, WO 2009/025876, WO 2010/040212, WO 2010/057430, WO 2010/005924, WO 2010/109443, WO 2011/058525, WO 2011/076813, WO 2011/147102, WO 2012/028861, and WO 2012/150606.

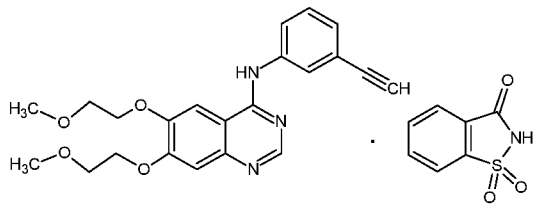
In the pharmaceutical industry there is a constant need to identify the critical physicochemical parameters such as novel salts and novel polymorphic forms that affect the drug's performance, stability, etc., which may play a key role in determining a drug's market acceptance and success.

Since erlotinib and its salts constitute an important therapeutic agent, additional salts of erlotinib are of value to pharmaceutical science. Thus, there is a need to develop novel salts of erlotinib having improved solubility, stability, excellent storage and handling stabilities, bioavailability, and that are less susceptible to degradation at lower temperatures.

Accordingly, the present inventors have prepared the erlotinib saccharinate and erlotinib maleate and hydrates thereof. The salts of the present invention are easy to prepare and isolate in solid form, particularly in crystalline forms. Further, they can be prepared by an efficient, economical, and reproducible process, which is particularly suited to large scale preparation.

Summary of the Invention

A first aspect of the present invention provides erlotinib saccharinate of Formula I.



Formula I

A second aspect of the present invention provides a crystalline form of erlotinib saccharinate.

A third aspect of the present invention provides erlotinib maleate or hydrates thereof.

A fourth aspect of the present invention provides a crystalline form of erlotinib maleate monohydrate.

A fifth aspect of the present invention provides a process for the preparation of erlotinib saccharinate or erlotinib maleate or hydrates thereof, comprising;

a) treating erlotinib free base with saccharin or maleic acid, optionally in the presence of a solvent; and

b) isolating erlotinib saccharinate, or erlotinib maleate or hydrates thereof.

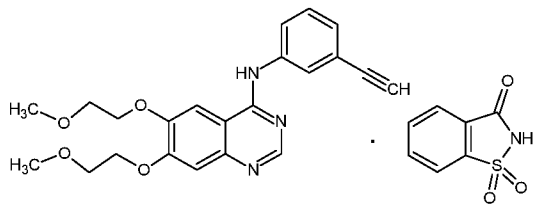
A sixth aspect of the present invention provides the use of erlotinib saccharinate or erlotinib maleate or hydrates thereof for the preparation of erlotinib or other salts, solvates, or polymorphs thereof.

A seventh aspect of the present invention provides a pharmaceutical composition comprising erlotinib saccharinate or erlotinib maleate or hydrates thereof, and a pharmaceutically acceptable carrier.

An eighth aspect of the present invention provides a method of treating non-small cell lung cancer in combination with gemcitabine for first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, comprising administering to a patient in need thereof a therapeutically effective amount of erlotinib saccharinate, or erlotinib maleate or hydrates thereof, and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

A first aspect of the present invention provides erlotinib saccharinate of Formula I.



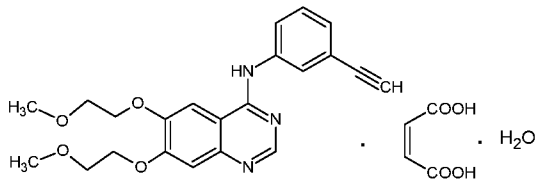
Formula I

A second aspect of the present invention provides a crystalline form of erlotinib saccharinate. The crystalline form of erlotinib saccharinate of the present invention may be characterized by an X-Ray Powder Diffractogram (XRPD) pattern substantially the same as depicted in Figure 1, exhibiting interplanar spacing (d) values at about 18.98, 16.39, 3.56, 3.52, and 3.46 (Å), and further exhibiting interplanar spacing (d) values at

about 11.62, 5.70, 5.45, 5.07, 4.03, 3.35, and 3.32 (Å). The crystalline form of erlotinib saccharinate has an XRPD pattern with characteristic peak values (2θ) at about 4.65, 5.38, 24.93, 25.27, and 25.72 ± 0.2°, and additional characteristic peak values (2θ) at about 7.60, 15.52, 16.24, 17.47, 22.00, 26.55, and 26.81 ± 0.2°. The crystalline form of erlotinib saccharinate of the present invention may be characterized by Differential Scanning Calorimetry (DSC) as depicted in Figure 2, with a characteristic endothermic peak value at about 174.90°C in the DSC thermogram. The crystalline form of erlotinib saccharinate of the present invention may be characterized by Thermogravimetric Analysis (TGA) as depicted in Figure 3 and Fourier-Transform Infra-red (FTIR) as depicted in Figure 4.

A third aspect of the present invention provides erlotinib maleate or hydrates thereof.

In one embodiment of this aspect, the present invention provides erlotinib maleate monohydrate of Formula II.



Formula II

A fourth aspect of the present invention provides a crystalline form of erlotinib maleate monohydrate. The crystalline form of erlotinib maleate monohydrate of the present invention may be characterized by an XRPD pattern substantially the same as depicted in Figure 5, exhibiting interplanar spacing (d) values at about 12.62, 6.40, 4.79, 4.57, and 4.21 (Å), and further exhibiting interplanar spacing (d) values at about 10.65, 4.99, 4.65, 4.29, 4.10, 3.61, and 2.84 (Å). The crystalline form of erlotinib maleate monohydrate has an XRPD pattern with characteristic peak values (2θ) at about 7.00, 13.82, 18.48, 19.38, and 21.08 ± 0.2°, and additional characteristic peak values (2θ) at about 8.30, 17.75, 19.04, 20.67, 21.66, 24.60, and 31.41 ± 0.2°. The crystalline form of erlotinib maleate monohydrate of the present invention may be characterized by DSC as depicted in Figure 6, with characteristic endothermic peak values at about 98.04°C and 171.69°C in the DSC thermogram. The crystalline form of erlotinib maleate monohydrate of the present invention may be characterized by TGA as depicted in Figure 7 and FTIR as depicted in Figure 8.

A fifth aspect of the present invention provides a process for the preparation of erlotinib saccharinate, or erlotinib maleate or hydrates thereof, comprising:

a) treating erlotinib free base with saccharin or maleic acid, optionally in the presence of a solvent; and

b) isolating erlotinib saccharinate, or erlotinib maleate or hydrates thereof.

The erlotinib free base may be prepared by any of the methods known in the art, including that described in U.S. Patent No. RE41,065.

Step a) of treating erlotinib free base with saccharin or maleic acid may include adding, dissolving, slurrying, stirring, or combinations thereof.

Erlotinib is treated with saccharin or maleic acid at a temperature of about 25°C to about 80°C for a time period sufficient to complete the reaction, preferably for about 5 minutes to about 24 hours, optionally followed by stirring the reaction mass at about 0°C to about 8°C, preferably at about 0°C to about 5°C for a period of about 2 minutes to about 2 hours, preferably for about 5 minutes to about 10 minutes.

Erlotinib prepared by any of the methods known in the art, before treatment with saccharin or maleic acid, is optionally purified to remove foreign particulate matter. Alternatively, it may be treated with activated charcoal to remove coloring and other related impurities in a suitable solvent.

The term "solvent" includes any solvent or solvent mixture, including water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, or mixtures thereof.

Examples of esters include ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate. Examples of alkanols include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanol solvents include methanol, ethanol, *n*-propanol, isopropanol and *n*-butanol, *sec*-butanol, isobutanol, and *tert*-butanol, preferably methanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. Examples of ketones include acetone, methyl ethyl ketone, and the like. Examples of ethers include diethyl ether, tetrahydrofuran, and the like. Examples of polar aprotic solvent include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile and *N*-methylpyrrolidone.

Step b) of isolating erlotinib saccharinate, or erlotinib maleate or hydrates thereof may be accomplished by filtration, decantation, solvent precipitation, trituration, evaporation, concentration, centrifugation, distillation, or combinations thereof, optionally followed by drying with appropriate methods, such as suck drying, drying under reduced pressure, vacuum tray drying, air drying, or combinations thereof.

A sixth aspect of the present invention provides the use of erlotinib saccharinate or erlotinib maleate or hydrates thereof for the preparation of erlotinib or other salts, solvates, or polymorphs thereof.

Erlotinib saccharinate or erlotinib maleate or hydrates thereof may be used for the preparation of erlotinib by contacting the erlotinib saccharinate or erlotinib maleate or hydrates thereof with a base. The base is selected from the group comprising of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals, ammonia, alkyl amines, hydrazine, and the like. Examples of hydroxides, carbonates, and bicarbonates of alkali and alkaline earth metals may include lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate or potassium bicarbonate. Examples of alkyl amines may include diethyl amine, triethyl amine or methyl diethylamine. Erlotinib thus obtained may be converted to other salts, solvates, or polymorphs thereof.

A seventh aspect of the present invention provides a pharmaceutical composition comprising erlotinib saccharinate, or erlotinib maleate or hydrates thereof, and a pharmaceutically acceptable carrier.

An eighth aspect of the present invention provides a method of treating non-small cell lung cancer in combination with gemcitabine for first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, comprising administering to a patient in need thereof a therapeutically effective amount of erlotinib saccharinate, or erlotinib maleate or hydrates thereof, and a pharmaceutically acceptable carrier.

Brief Description of the Drawings

Figure 1 and Figure 1a depict the XRPD of erlotinib saccharinate and the associated values, respectively, prepared as per Example 1B.

Figure 2 depicts the DSC thermogram of erlotinib saccharinate prepared as per Example 1B.

Figure 3 depicts the TGA thermogram of erlotinib saccharinate prepared as per Example 1B.

Figure 4 depicts the FTIR spectrum of erlotinib saccharinate prepared as per Example 1B.

Figure 5 and Figure 5a depict the XRPD of erlotinib maleate monohydrate and the associated values, respectively, prepared as per Example 2B.

Figure 6 depicts the DSC thermogram of erlotinib maleate monohydrate prepared as per Example 2B.

Figure 7 depicts the TGA thermogram of erlotinib maleate monohydrate prepared as per Example 2B.

Figure 8 depicts the FTIR spectrum of erlotinib maleate monohydrate prepared as per Example 2B.

The XRPD of the samples were determined by using Instrument: PANalytical®; Model: X'Pert PRO; Detector: X'celerator®; Scan Range: 3-40; Step size: 0.02; Range: 3-40 degree 2 theta; CuKα radiation at 45kV.

The DSC of the samples were determined by using Perkin Elmer®, Diamond DSC. Data collection parameters: Scanning rate: 10°C/min; Temperature: 30°C to 300°C.

The TGA of the samples were determined by using TA instrument, TGA Q500. Data collection parameters: Scanning rate: 10°C/min; Temperature: 30°C to 300°C.

The FTIR of the samples were determined by using Instrument: Perkin Elmer®; Model: Spectrum one; SCAN: 16scans; Resolution: 4.0 cm^{-1}; potassium bromide pellet method.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1A: Process for the preparation of erlotinib saccharinate

Methanol (1 mL) was added to a mixture of erlotinib free base (0.4 g) and saccharin (0.366 g) and slurried for 18 hours at 50°C. The solvent was evaporated at 25°C to 30°C and the solid obtained was dried at 55°C in a vacuum tray drier for 6 hours to obtain the title compound.

Yield: 0.706 g

Example 1B: Process for the preparation of erlotinib saccharinate

A mixture of erlotinib free base (0.8 g) and saccharin (0.366 g) was dissolved in methanol (40 mL) at 60°C to obtain a clear solution. The solution was kept aside at 25°C to 30°C. After four hours, the reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 0.923 g

Example 1C: Process for the preparation of erlotinib saccharinate

Erlotinib free base (3.0 g) was dissolved in methanol (60 mL) at 60°C to obtain a solution, followed by the addition of saccharin solution (saccharin (1.398 g) dissolved in methanol (75 mL) at 60°C). To the reaction mixture, methanol (165 mL) was added and the clear solution obtained was kept aside at 25°C to 30°C. After four hours, the reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 3.261 g

Example 1D: Process for the preparation of erlotinib saccharinate

Erlotinib free base (2.0 g) was dissolved in methanol (35 mL) at 65°C to obtain a solution, followed by the addition of saccharin solution (saccharin (0.932 g) dissolved in methanol (25 mL) at 65°C). The reaction mixture was stirred at 65°C for 5 minutes and cooled to 25°C to 30°C. The reaction mixture was further cooled to 0°C to 5°C and stirred for 10 minutes. The reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 2.578 g

Example 2A: Process for the preparation of erlotinib maleate monohydrate

Methanol (1 mL) was added to a mixture of erlotinib free base (0.4 g) and maleic acid (0.232 g) and then slurried for 18 hours at 50°C. The solvent was evaporated at 25°C to 30°C and the solid obtained was dried at 55°C in a vacuum tray drier for 6 hours to obtain the title compound.

Yield: 0.602 g

Example 2B: Process for the preparation of erlotinib maleate monohydrate

A mixture of erlotinib free base (0.8 g) and maleic acid (0.232 g) was dissolved in methanol (50 mL) at 60°C to obtain a clear solution. The solution was kept aside at 25°C to 30°C. After four hours, the reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 1.023 g

Example 2C: Process for the preparation of erlotinib maleate monohydrate

Erlotinib free base (3.0 g) was dissolved in methanol (60 mL) at 60°C to obtain a solution, followed by the addition of maleic acid solution (maleic acid (0.886 g) dissolved in methanol (75 mL) at 60°C). To the reaction mixture, methanol (30 mL) was added and the clear solution obtained was kept aside at 25°C to 30°C. After four hours, the reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 3.15 g

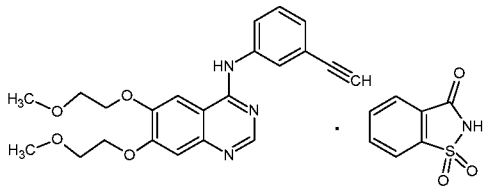
Example 2D: Process for the preparation of erlotinib maleate monohydrate

Erlotinib free base (2.0 g) was dissolved in methanol (35 mL) at 65°C to obtain a solution, followed by the addition of maleic acid solution (maleic acid (0.590 g) dissolved in methanol (20 mL) at 65°C). The reaction mixture was stirred at 65°C for 5 minutes and cooled to room temperature. The reaction mixture was further cooled to 0°C to 5°C and stirred for 5 minutes. The reaction mixture was filtered and the solid was dried under vacuum at 60°C for 6 hours to obtain the title compound.

Yield: 2.333 g

CLAIMS:

1. Erlotinib saccharinate of Formula I.



Formula I

2. The erlotinib saccharinate of claim 1, in a crystalline form.

3. The erlotinib saccharinate of claim 2, wherein the crystalline form is characterized by an XRPD pattern substantially the same as depicted in Figure 1.

4. The erlotinib saccharinate of claim 2, characterized by an XRPD pattern having interplanar spacing (d) values at 18.98, 16.39, 3.56, 3.52, and 3.46 (Å).

5. The erlotinib saccharinate of claim 4, further characterized by interplanar spacing (d) values at 11.62, 5.70, 5.45, 5.07, 4.03, 3.35, and 3.32 (Å).

6. The erlotinib saccharinate of claim 2, characterized by an XRPD pattern having characteristic peak values (2θ) at 4.65, 5.38, 24.93, 25.27, and 25.72 ± 0.2°.

7. The erlotinib saccharinate of claim 6, further characterized by characteristic peak values (2θ) at 7.60, 15.52, 16.24, 17.47, 22.00, 26.55, and 26.81 ± 0.2°.

8. The erlotinib saccharinate of claim 2, characterized by a DSC thermogram substantially as depicted in Figure 2.

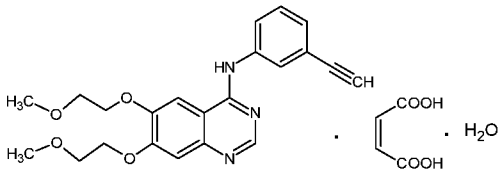
9. The erlotinib saccharinate of claim 2, characterized by an endothermic peak value at about 174.90°C in the DSC thermogram.

10. The erlotinib saccharinate of claim 2, characterized by a TGA spectrum substantially as depicted in Figure 3.

11. The erlotinib saccharinate of claim 2, characterized by an FTIR spectrum substantially as depicted in Figure 4.

12. Erlotinib maleate or hydrates thereof.

13. Erlotinib maleate monohydrate of Formula II.



Formula II

14. The erlotinib maleate monohydrate of claim 13 in a crystalline form.

15. The erlotinib maleate monohydrate of claim 14 characterized by an XRPD pattern substantially the same as depicted in Figure 5.

16. The erlotinib maleate monohydrate of claim 14 characterized by an XRPD pattern having interplanar spacing (d) values at 12.62, 6.40, 4.79, 4.57, and 4.21 (Å).

17. The erlotinib maleate monohydrate of claim 16 further characterized by interplanar spacing (d) values at 10.65, 4.99, 4.65, 4.29, 4.10, 3.61, and 2.84 (Å).

18. The erlotinib maleate monohydrate of claim 14 characterized by an XRPD pattern having characteristic peak values (2θ) at 7.00, 13.82, 18.48, 19.38, and 21.08 ± 0.2°.

19. The erlotinib maleate monohydrate of claim 18 further characterized by characteristic peak values (2θ) at 8.30, 17.75, 19.04, 20.67, 21.66, 24.60, and 31.41 ± 0.2°.

20. The erlotinib maleate monohydrate of claim 14 characterized by a DSC thermogram substantially as depicted in Figure 6.

21. The erlotinib maleate monohydrate of claim 14 characterized by endothermic peak values at about 98.04°C and 171.69°C in the DSC thermogram.

22. The erlotinib maleate monohydrate of claim 14 characterized by a TGA spectrum substantially as depicted in Figure 7.

23. The erlotinib maleate monohydrate of claim 14 characterized by an FTIR spectru substantially as depicted in Figure 8.

24. A process for the preparation of erlotinib saccharinate, or erlotinib maleate or hydrates thereof, comprising:

a) treating erlotinib free base with saccharin or maleic acid, optionally in the presence of a solvent; and

b) isolating erlotinib saccharinate, or erlotinib maleate or hydrate thereof.

25. The process according to claim 24, wherein the solvent is selected from water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents, or mixtures thereof.

26. The process according to claim 25, wherein the ester is selected from ethyl acetate, *n*-propyl acetate, isopropyl acetate, and *n*-butyl acetate.

27. The process according to claim 25, wherein the alkanol is selected from methanol, ethanol, *n*-propanol, isopropanol and *n*-butanol, *sec*-butanol, isobutanol, and *tert*-butanol.

28. The process according to claim 25, wherein the halogenated hydrocarbon is selected from dichloromethane, chloroform, and 1,2-dichloroethane.

29. The process according to claim 25, wherein the ketone is selected from acetone and methyl ethyl ketone.

30. The process according to claim 25, wherein the ether is selected from diethyl ether and tetrahydrofuran.

31. The process according to claim 25, wherein the polar aprotic solvent is selected from *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulphoxide, acetonitrile, and *N*-methylpyrrolidone.

32. The process according to claim 24, wherein treating erlotinib free base with saccharin or maleic acid is carried out at a temperature of 25°C to 80°C.

33. Erlotinib saccharinate, or erlotinib maleate or hydrates thereof for use in the preparation of erlotinib or other salts, solvates or polymorphs thereof.

34. A pharmaceutical composition comprising erlotinib saccharinate, or erlotinib maleate or hydrates thereof and a pharmaceutically acceptable carrier.

35. A method of treating non-small cell lung cancer in combination with gemcitabine for first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, which comprises administering to a patient in need thereof a therapeutically effective amount of erlotinib saccharinate, or erlotinib maleate or hydrates thereof, and a pharmaceutically acceptable carrier.

FIGURE 1: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF ERLOTINIB SACCHARINATE PREPARED AS PER EXAMPLE 1B

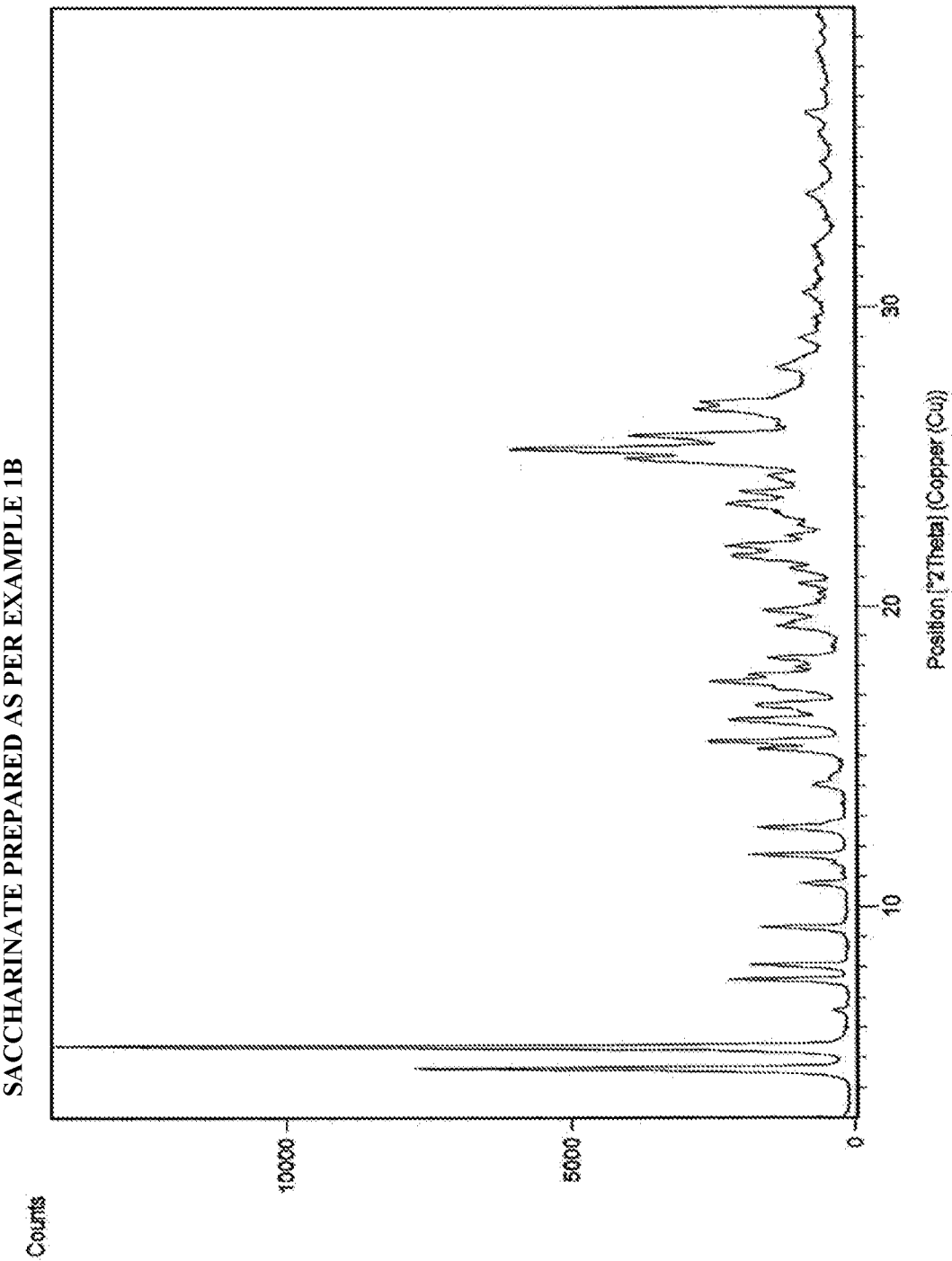


FIGURE 1a

Pos. [°2Th]	d-spacing [Å]	Rel Int. [%]	Pos. [°2Th]	d-spacing [Å]	Rel Int. [%]
4.65	18.98	54.65	22.00	4.03	14.03
5.38	16.39	100.00	22.10	4.02	10.32
6.58	13.41	2.01	22.35	3.97	6.62
7.60	11.62	15.51	22.70	3.91	4.85
8.06	10.95	12.60	23.39	3.79	13.48
9.33	9.47	10.64	23.83	3.73	12.33
10.80	8.18	4.96	24.35	3.65	8.55
11.74	7.53	12.30	24.93	3.56	27.26
12.64	6.99	11.17	25.27	3.52	41.27
14.03	6.31	3.61	25.72	3.46	25.67
15.25	5.80	10.55	26.55	3.35	18.04
15.52	5.70	17.38	26.81	3.32	17.26
16.24	5.45	14.52	27.95	3.18	7.44
16.76	5.28	8.90	28.97	3.07	4.09
17.21	5.14	8.20	30.48	2.93	3.58
17.47	5.07	17.15	31.22	2.86	1.87
17.72	5.00	11.74	32.01	2.79	1.89
18.25	4.86	9.32	33.76	2.65	2.68
19.32	4.59	8.24	34.81	2.57	0.90
19.86	4.46	9.94	35.81	2.50	1.12
20.77	4.27	5.19	36.48	2.46	2.69
21.29	4.17	6.27	38.57	2.33	0.88
21.70	4.09	13.44			

FIGURE 2: DIFFERENTIAL SCANNING CALORIMETRY (DSC) THERMOGRAM OF ERLOTINIB SACCHARINATE PREPARED AS PER EXAMPLE 1B

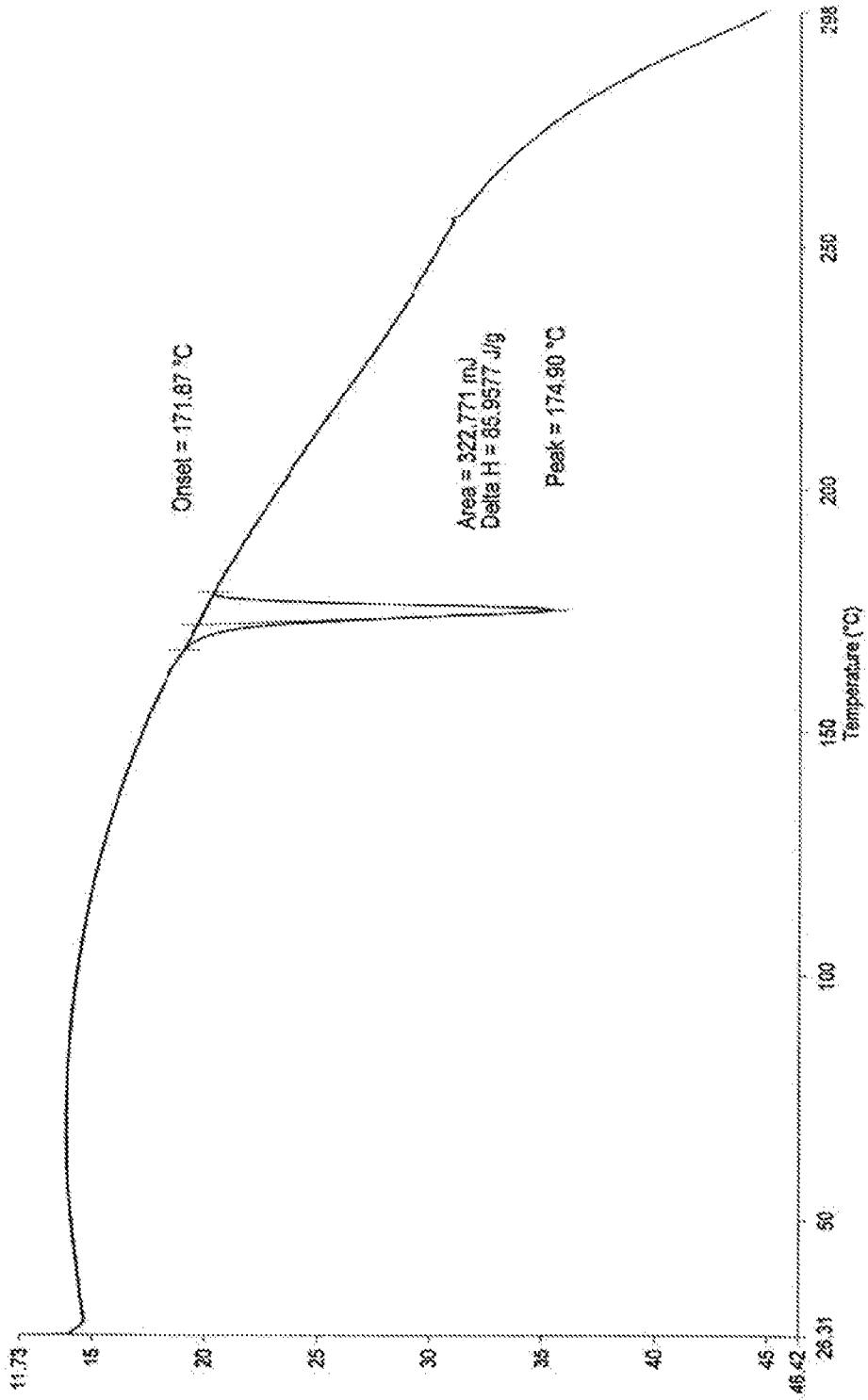


FIGURE 3: THERMOGRAVIMETRIC ANALYSIS (TGA) THERMOGRAM OF ERLOTINIB SACCHARINATE PREPARED AS PER EXAMPLE 1B

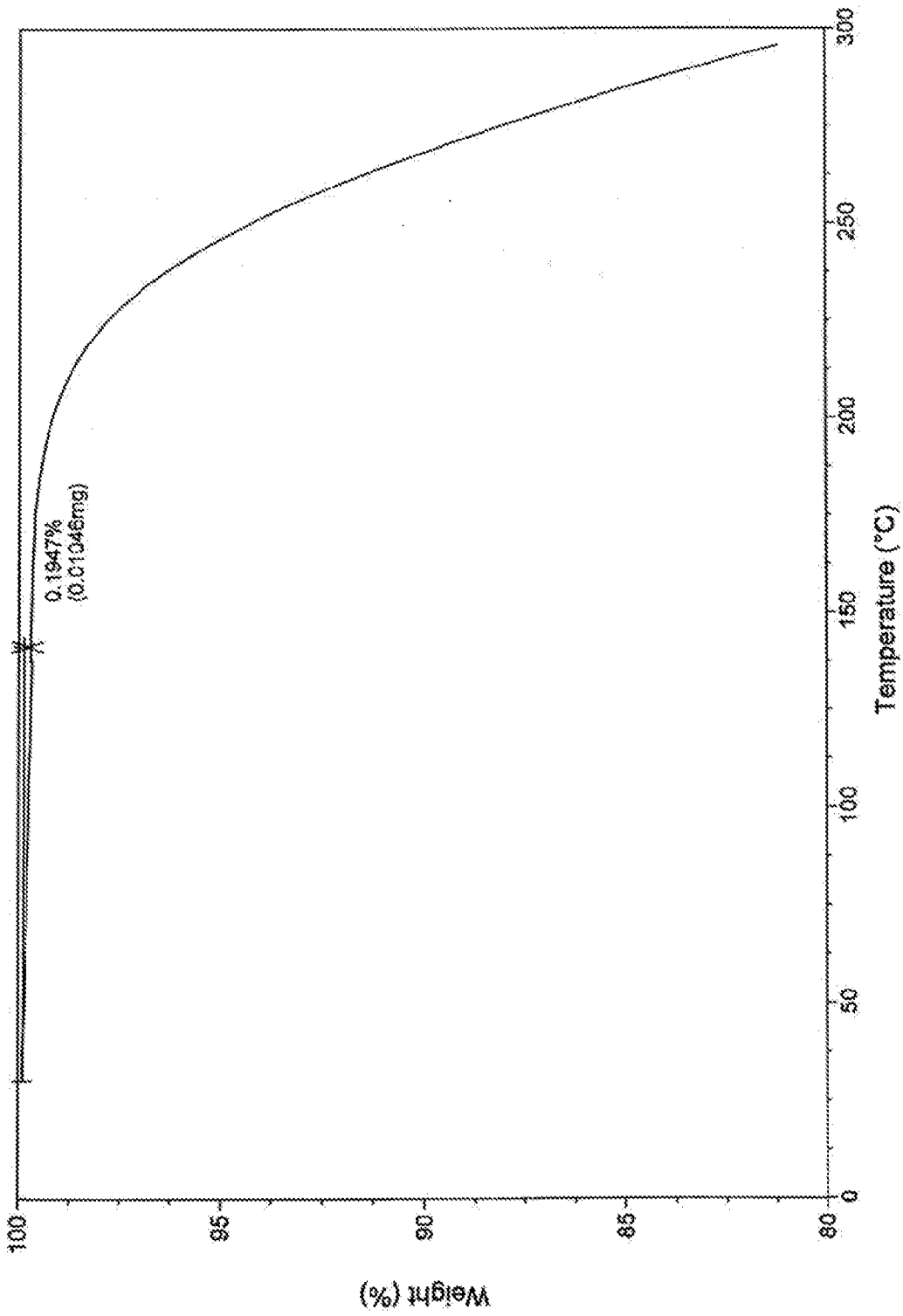


FIGURE 4: FOURIER-TRANSFORM INFRA-RED (FTIR) SPECTRUM OF ERLOTINIB SACCHARINATE PREPARED AS PER EXAMPLE 1B

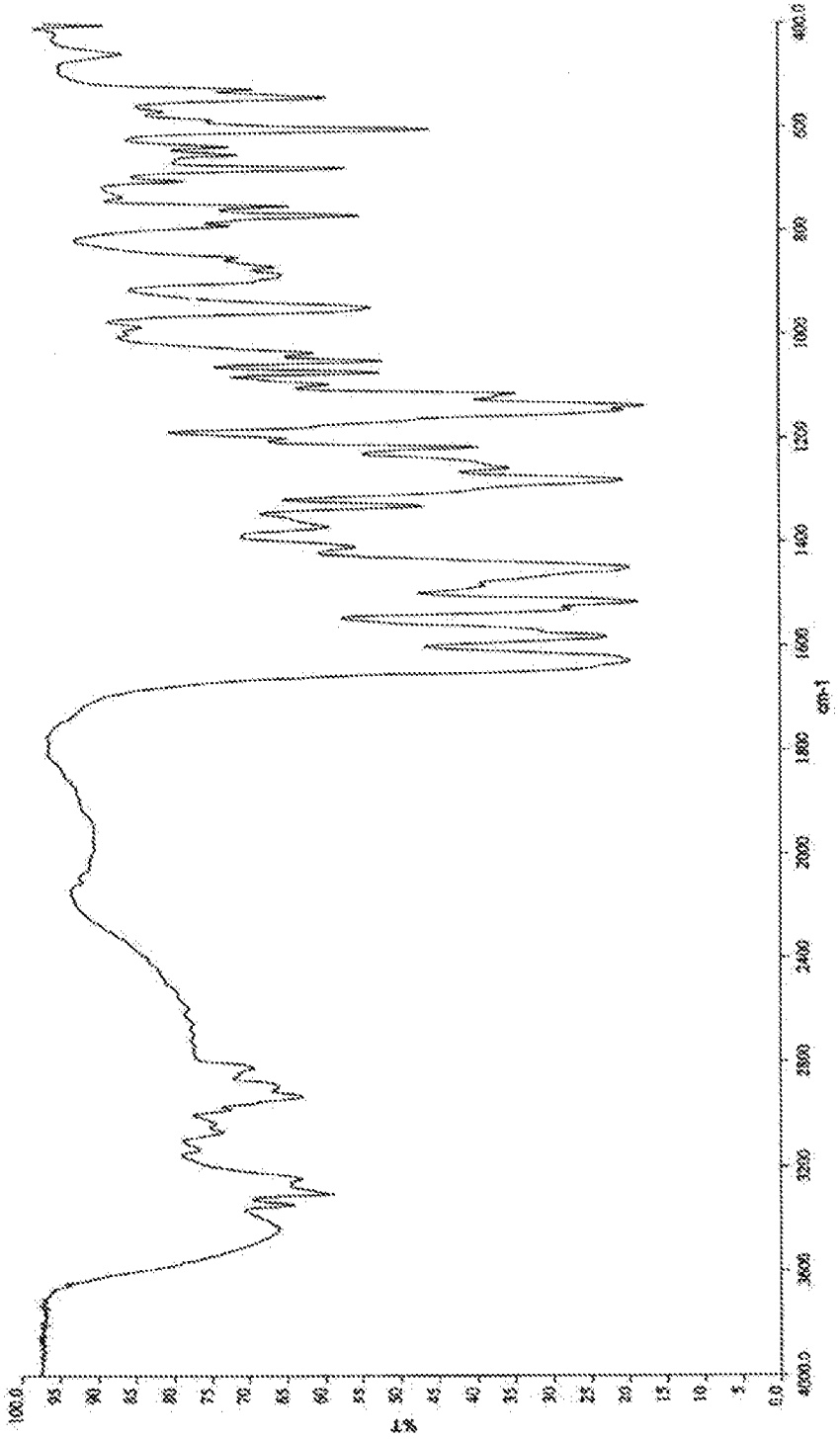


FIGURE 5: X-RAY POWDER DIFFRACTOGRAM (XRPD) OF ERLOTINIB MALEATE MONOHYDRATE PREPARED AS PER EXAMPLE 2B

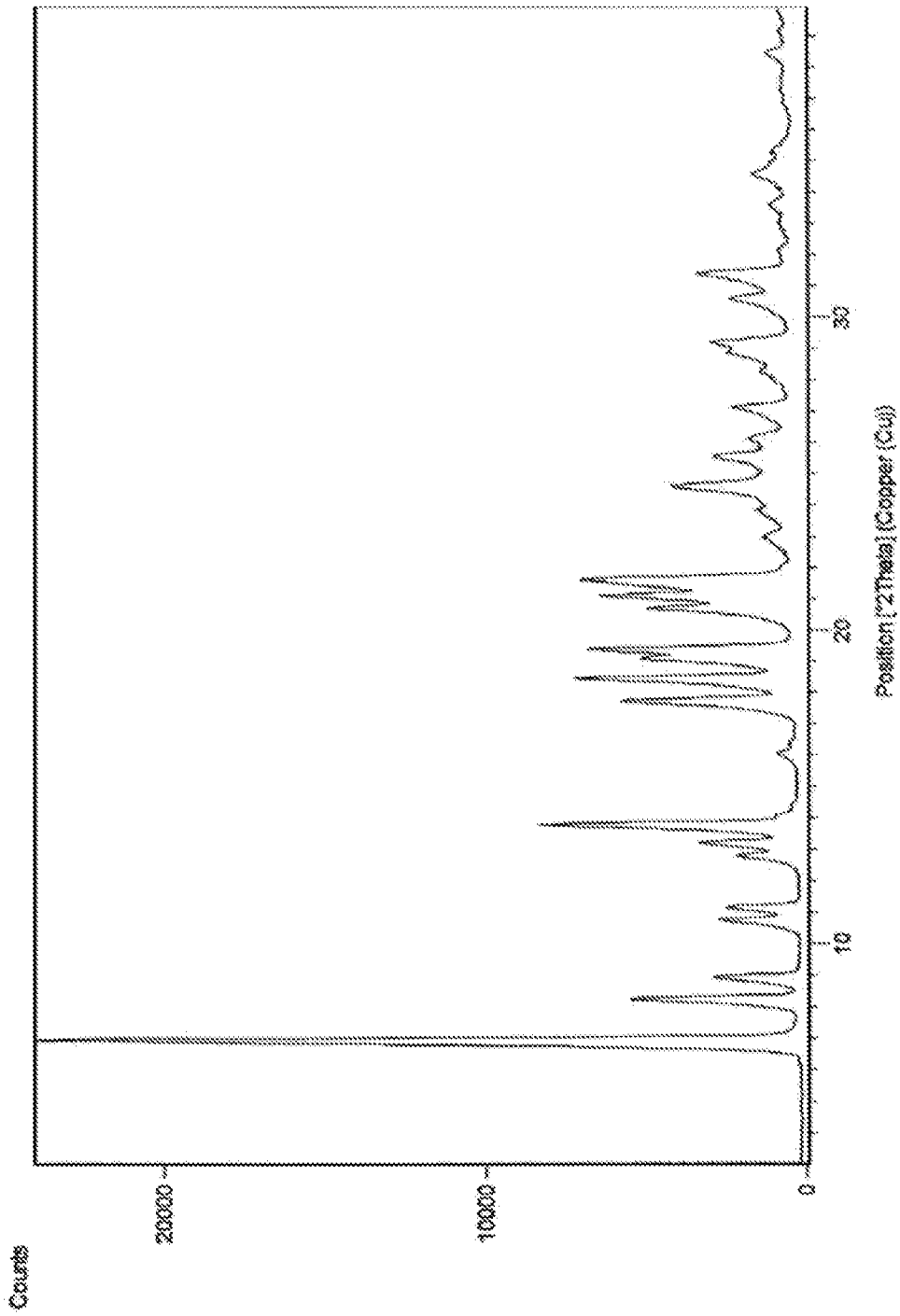


FIGURE 5a

Pos. [°2Th]	d-spacing [Å]	Rel Int. [%]	Pos. [°2Th]	d-spacing [Å]	Rel Int. [%]
7.00	12.62	100.00	22.97	3.87	5.75
8.30	10.65	21.74	23.80	3.73	6.77
8.98	9.84	11.68	24.60	3.61	19.91
10.77	8.20	12.33	25.51	3.49	13.52
11.19	7.90	9.84	26.19	3.40	7.08
12.81	6.91	9.53	27.08	3.29	10.42
13.24	6.68	14.84	28.27	3.15	6.06
13.82	6.40	38.17	28.83	3.09	10.93
14.11	6.27	3.80	29.21	3.05	13.21
16.08	5.51	3.61	30.60	2.92	10.45
16.42	5.39	2.00	31.41	2.84	15.35
17.75	4.99	26.56	32.17	2.78	3.18
18.48	4.79	33.31	33.63	2.66	4.37
19.04	4.65	23.37	34.58	2.59	7.19
19.38	4.57	32.70	35.29	2.54	4.15
20.67	4.29	23.70	37.44	2.40	2.78
21.08	4.21	30.95	38.49	2.33	4.97
21.66	4.10	28.54	39.14	2.30	3.20

FIGURE 6: DIFFERENTIAL SCANNING CALORIMETRY (DSC) THERMOGRAM OF ERLOTINIB MALEATE MONOHYDRATE PREPARED AS PER EXAMPLE 2B

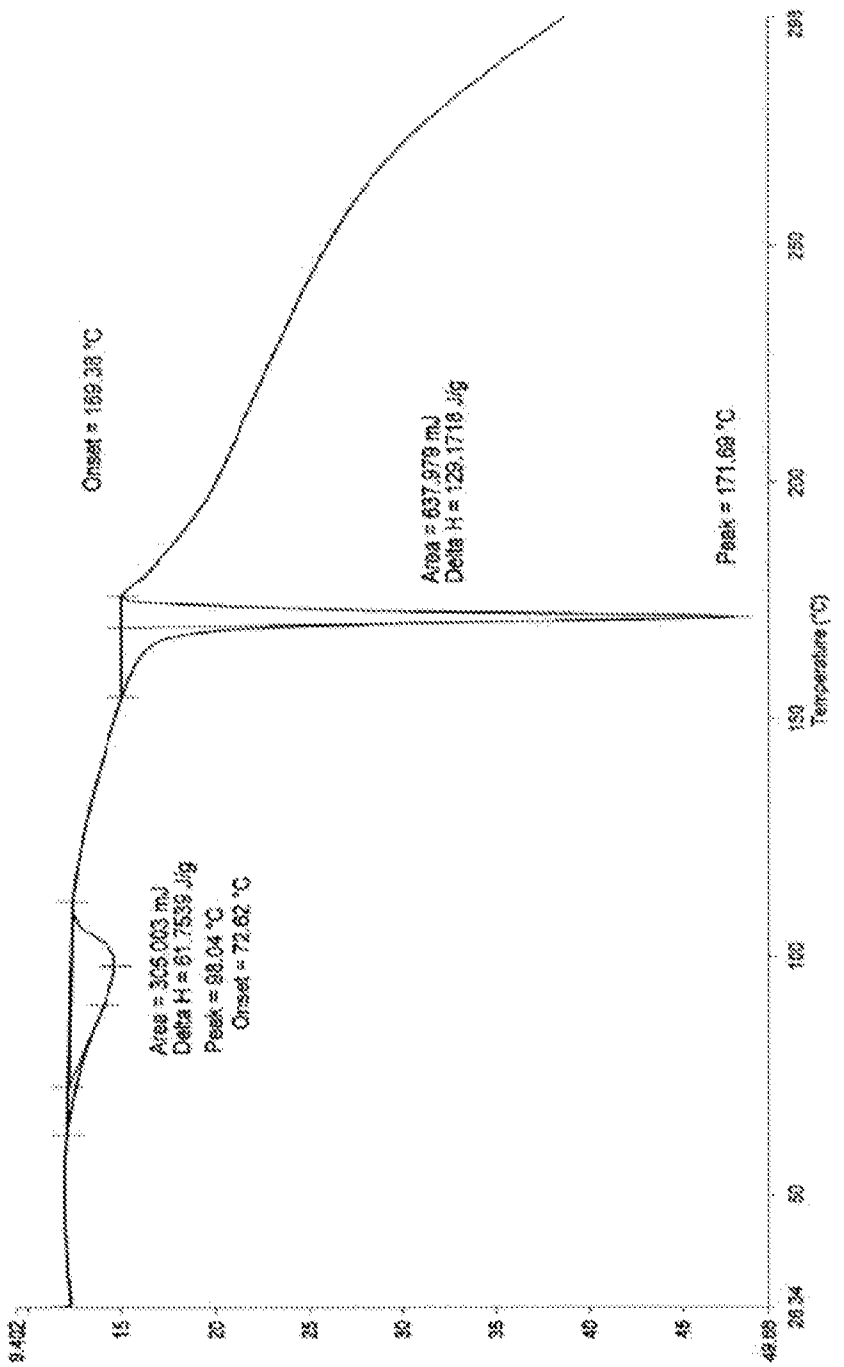
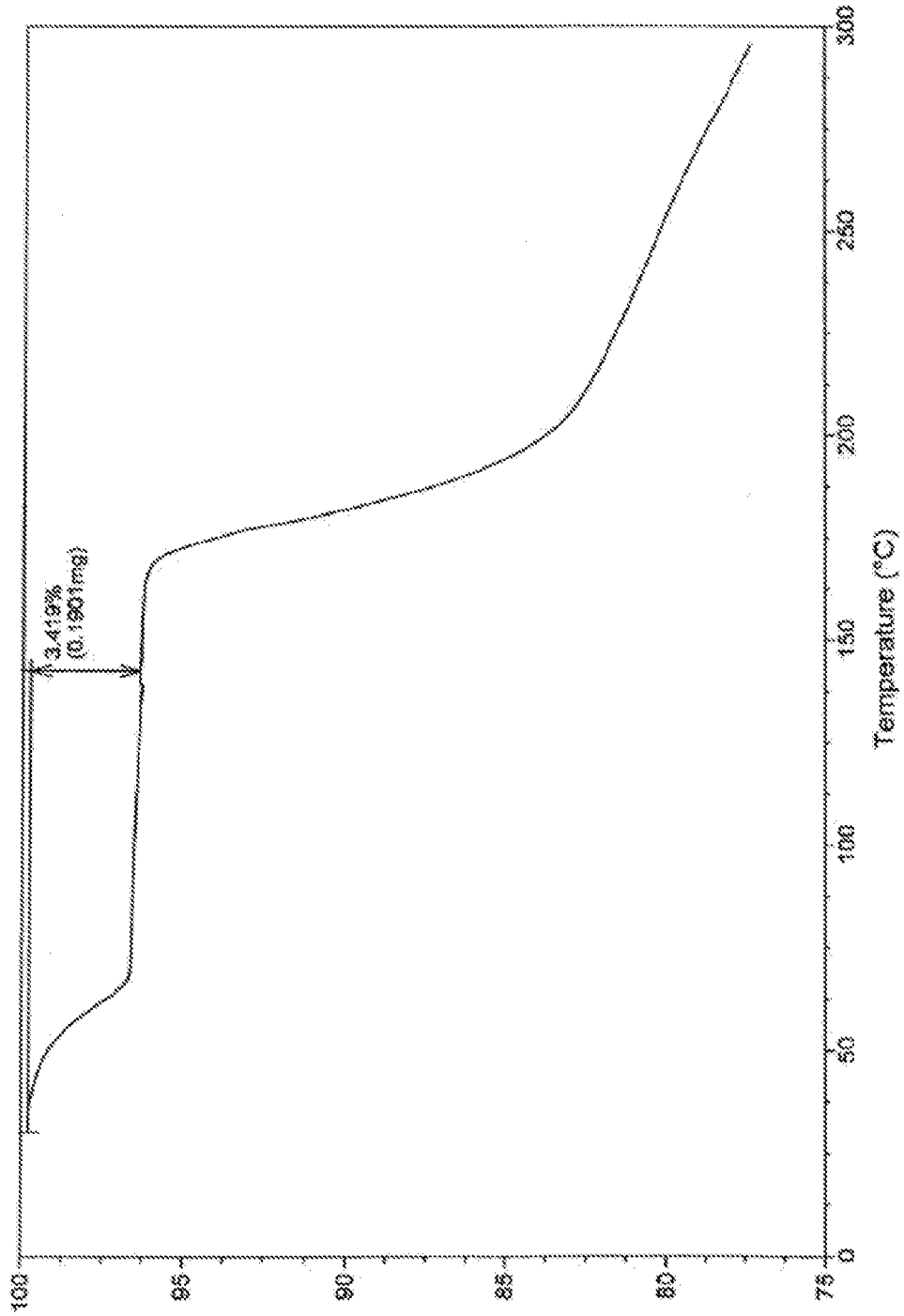


FIGURE 7: THERMOGRAVIMETRIC ANALYSIS (TGA) THERMOGRAM OF ERLOTINIB MALEATE MONOHYDRATE PREPARED AS PER EXAMPLE 2B



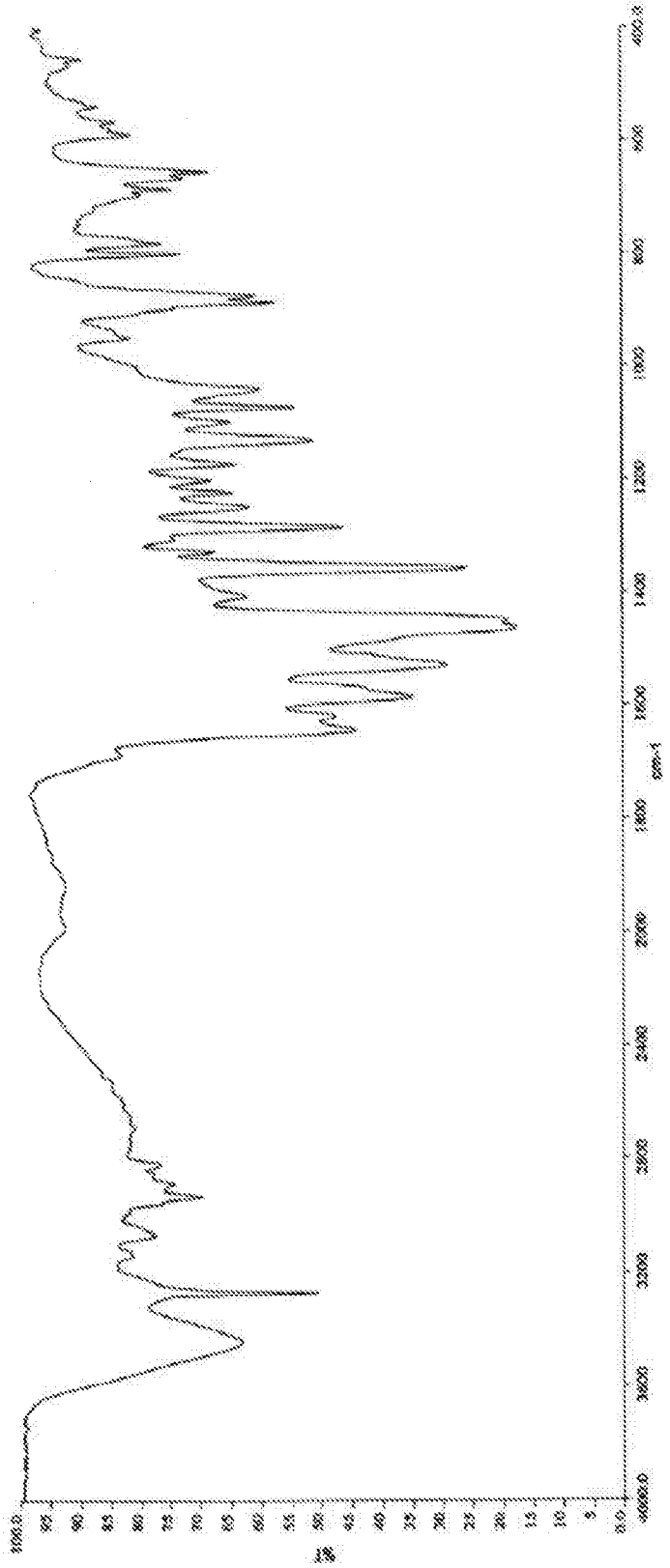


FIGURE 8: FOURIER-TRANSFORM INFRA-RED (FTIR) SPECTRUM OF ERLOTINIB MALEATE MONOHYDRATE PREPARED AS PER EXAMPLE 2B

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/058683

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/94 A61K31/517 A61P35/00
ADD.

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)
C07D A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/012105 A1 (SYNTHON BV [NL]; WESTHEIM RAYMOND JOZEF HUBERTU [NL]) 31 January 2008 (2008-01-31) cited in the application	12-14, 24-34
Y	abstract paragraphs [0046], [0047] claims 1-21	1-11, 15-23

X	WO 2012/028861 A1 (GENERICS UK LTD [GB]; MYLAN INDIA PRIVATE LTD [IN]; GORE VINAYAK GOVIN) 8 March 2012 (2012-03-08) cited in the application	12-14, 24-34
Y	abstract page 27, line 20 - page 28, line 16 examples 1-3 claims 1-62	1-11, 15-23

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[X] 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
2 May 2014	09/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Guillaume

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 348 020 A1 (ESTEVE QUIMICA SA [ES]) 27 July 2011 (2011-07-27) cited in the application	12-14, 24-34
Y	abstract paragraphs [0024] - [0026] claims 1-14	1-11, 15-23

X	WO 2010/109443 A1 (RANBAXY LAB LTD [IN]; MURUGESAN BALAGURU [IN]; VEMPALI ANANDAM [IN]; S) 30 September 2010 (2010-09-30) cited in the application	12-14, 24-34
Y	abstract page 10, lines 18-23 claims 1-34	1-11, 15-23

X	WO 2011/068403 A2 (ULTIMORPHIX TECHNOLOGIES B V [NL]; DOVA EVANTHIA [NL]; KULKARNI SAMIR) 9 June 2011 (2011-06-09) cited in the application	24-34
Y	abstract examples 1-20 claims 1-30 figures 1A-19A	1-23

Y	RAHUL BANERJEE ET AL: "Saccharin Salts of Active Pharmaceutical Ingredients, Their Crystal Structures, and Increased Water Solubilities", CRYSTAL GROWTH & DESIGN, vol. 5, no. 6, November 2005 (2005-11), pages 2299-2309, XP55115407, ISSN: 1528-7483, DOI: 10.1021/cg050125l abstract * scheme 1 *; page 2300 page 2307 - page 2308	1-11

Y	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, January 1998 (1998-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 abstract page 165, last paragraph - page 166, paragraph 1 pages 177-180, paragraph 3.1.	1-23

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/058683

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2013/054147 A2 (EGIS GYOGYSZERGYAR NYILVANOSAN MUKODO [HU]) 18 April 2013 (2013-04-18)	12-34
Y,P	abstract examples 1-10 claims 1-28 figures 1-9	1-11

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PCT/IB2014/058683

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. [X] Claims Nos.: 35
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 35 is directed towards a method of treatment of the human body by therapy and falls therefore under the provision of Rules 39.1(iv) and 67.1(iv) PCT.

2. [ ] Claims 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. [ ] Claims 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:

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

2. [ ] As all searchable claims could be searched without effort justifying an 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 claims 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 claims 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/058683

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2010109443 A1	30-09-2010
WO 2011068403 A2	09-06-2011	NONE	
WO 2013054147 A2	18-04-2013	NONE	