

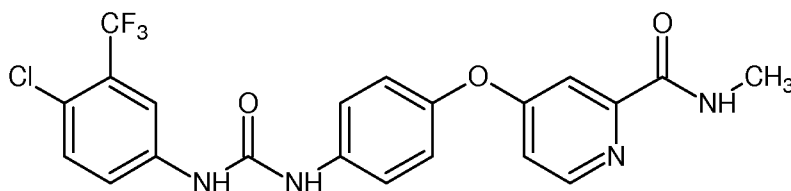
SORAFENIB ETHYLSULFONATE SALT, PROCESS FOR PREPARATION AND USE

Field of the Invention

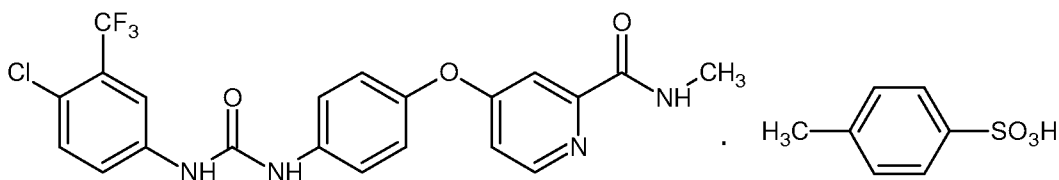
The present invention provides for compositions of sorafenib ethane sulphonate,
5 and a process for its preparation.

Background of the Invention

Sorafenib is an inhibitor of the enzyme raf kinase known from WO 00/42012. It is chemically described as 4-(4-{3-[4-Chloro-3-(trifluoromethyl) phenyl]ureido}phenoxy)-N²-methylpyridine-2-carboxamide, having a structure as represented by Formula I.

**Formula I**

Sorafenib is marketed in the United States as a tosylate salt as shown in Formula II under the brand name Nexavar[®].

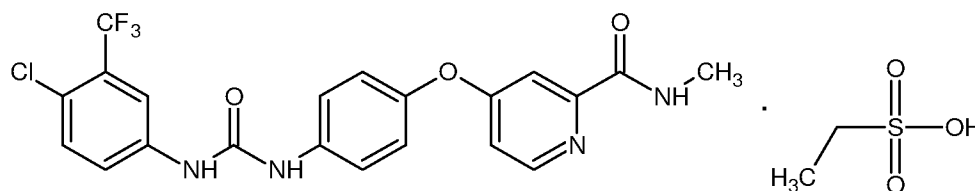
**Formula II**

Several acid addition salts of sorafenib are disclosed in WO 00/42012. Sorafenib ethane sulphonate salt of the present invention is not disclosed in the literature.

Summary of the Invention

In one general aspect, the present invention provides for sorafenib ethane
20 sulphonate of Formula III,

2

**Formula III**

solvates, hydrates and polymorphs thereof.

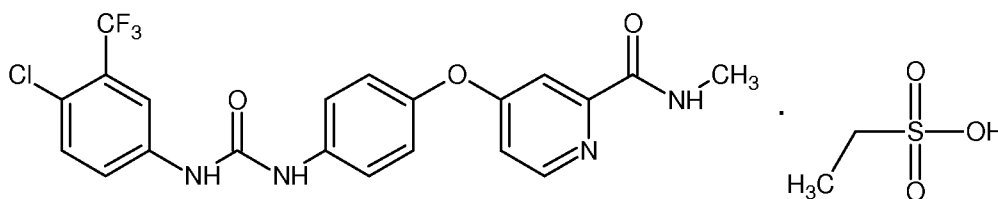
Embodiments of this aspect may include one or more of the following features.

- 5 For example, the sorafenib ethane sulphonate of Formula III may be characterized by X-ray diffraction peaks at d-spacing at about 10.84, 5.59, 5.22, 3.80, and 3.75 Å. The sorafenib ethane sulphonate of Formula III may be further characterized by X-ray diffraction peaks at d-spacing at about 5.41, 4.33, 3.47, 3.12, and 3.05 Å. The sorafenib ethane sulphonate of Formula III may also be characterized by a DSC thermogram having
- 10 endotherm at about 208.10°C.

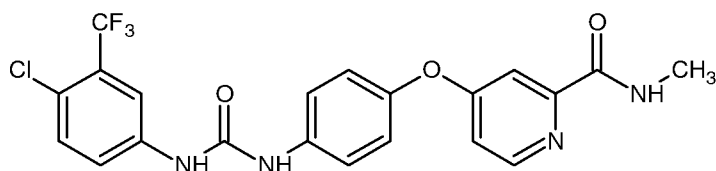
The sorafenib ethane sulphonate of Formula III may also be characterized by the X-ray diffraction pattern as depicted in Figure-1, by the DSC as depicted in Figure-2, the TGA as depicted in Figure-3, and/or the IR spectrum as depicted in Figure-4.

- 15 The sorafenib ethane sulphonate of Formula III may have a purity greater than 99% HPLC.

In another general aspect, the present invention provides for a process for the preparation of sorafenib ethane sulphonate of Formula III.

**Formula III**

- 20 The process includes contacting sorafenib free base of Formula I,

**Formula I**

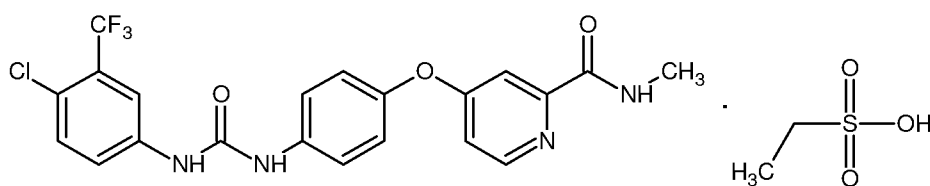
with ethane sulphonic acid.

- 5 Embodiments of this aspect may include one or more of the following features. For example, the process utilizes isolated sorafenib free base of Formula I or the sorafenib free base of Formula I, which is obtained as a solution directly from a reaction in which sorafenib free base is formed.

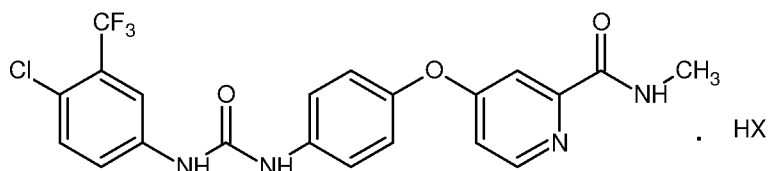
10 The sorafenib free base of Formula I is contacted with ethane sulphonic acid in a suitable solvent selected from water, polar organic solvents, dipolar aprotic organic solvents, and mixtures thereof. The polar organic solvent is selected from organic solvents containing at least one hydroxyl group, cyclic ethers, alkyl acetates and mixtures thereof. The organic solvent containing at least one hydroxyl group is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, n-pentanol, glycerol
15 or ethylene glycol. The dipolar aprotic organic solvent is selected from the group comprising of ketones, amides, nitriles, sulphoxides, or mixtures thereof.

The sorafenib free base is contacted with ethane sulphonic acid at about 0°C to the reflux temperature of the suitable solvent.

- 20 In another general aspect, the present invention provides for the use of sorafenib ethane sulphonate of Formula III,

**Formula III**

for the preparation of sorafenib acid addition salts of Formula IV.



Formula IV

The process includes contacting sorafenib ethane sulphonate with an acid of
5 Formula HX.

In yet another general aspect, the present invention provides for a pharmaceutical composition which includes sorafenib ethane sulphonate of Formula III and one or more pharmaceutically acceptable excipients.

Brief Description of the Drawings

- 10 Figure 1: X-ray Diffraction pattern (XRD) of sorafenib ethane sulphonate.
Figure 2: Differential Scanning Thermogram (DSC) of sorafenib ethane sulphonate.
Figure 3: Thermo Gravimetric analysis (TGA) of sorafenib ethane sulphonate.
Figure 4: Infra Red Spectrum (IR) of sorafenib ethane sulphonate.

Detailed Description of the Invention

In one embodiment, the present invention provides for sorafenib ethane sulphonate of Formula III as characterized by XRD peaks at about 8.15 (d-spacing at 10.84 Å), 15.83 (5.59 Å), 16.97 (5.22 Å), 23.40 (3.80 Å), and 23.66 (3.75 Å) $\pm 0.2^\circ 2\theta$.

In another embodiment, the present invention provides for sorafenib ethane
20 sulphonate of Formula III as further characterized by XRD peaks at about 16.36 (5.41 Å), 20.49 (4.33 Å), 25.63 (3.47 Å), 28.56 (3.12 Å), and 29.23 (3.05 Å) $\pm 0.2^\circ 2\theta$.

Sorafenib ethane sulphonate of Formula III may also be characterized by DSC thermogram having endotherms at about 208.10°C. It may also be characterized by XRD spectrum, DSC thermogram, TGA and IR spectra as depicted in Figures 1, 2, 3 and 4,
25 respectively. Table 1 provides the d-spacing in Å and the corresponding 2θ values.

Table 1: XRD Peaks of Sorafenib Ethane Sulphonate

Position (°2θ)	d-spacing (Å)	Relative Intensity (%)
8.15	10.84	47.21
8.44	10.48	22.55
10.14	8.73	26.93
11.67	7.58	6.60
12.19	7.26	17.22
12.37	7.15	15.67
13.67	6.48	21.66
14.20	6.24	29.39
14.64	6.05	19.95
15.83	5.59	53.63
16.36	5.41	44.79
16.97	5.22	56.44
17.37	5.11	22.84
18.38	4.83	29.38
18.63	4.76	15.21
18.84	4.71	24.12
19.09	4.65	6.80
19.35	4.59	7.08
19.96	4.45	33.92
20.35	4.36	29.92
20.49	4.33	39.85
21.38	4.15	14.45
21.65	4.11	14.47
22.35	3.98	13.36
22.56	3.94	16.01
23.15	3.84	31.98
23.40	3.80	100.00
23.66	3.75	92.08
24.14	3.69	8.49
24.66	3.61	11.56
24.89	3.58	12.41
25.63	3.47	36.67
25.85	3.45	14.31
26.39	3.38	18.65
27.23	3.27	11.94
28.56	3.12	45.78
29.23	3.05	38.90
30.05	2.97	8.51
30.69	2.91	17.11
31.05	2.88	8.92
31.74	2.82	15.05
31.98	2.80	11.18

Position (°2θ)	d-spacing (Å)	Relative Intensity (%)
32.71	2.74	7.77
33.44	2.68	3.54
34.40	2.61	6.71
34.87	2.57	5.85
36.07	2.49	10.18
37.19	2.42	7.02
38.64	2.33	7.74

The sorafenib free base of Formula I which is used for the preparation of sorafenib ethane sulphonate of Formula III, may be obtained by any of the methods known in the literature, such as those described in PCT applications WO 00/42012; WO 2006/034796; 5 WO 2006/034797; WO 2009/034308; WO 2009/054004; WO 2009/106825; and WO 2009/092070, which are herein incorporated by reference.

In general, the sorafenib free base of Formula I may be prepared by the reaction of 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline with 4-chloro-3-(trifluoromethyl)phenyl isocyanate. The starting sorafenib free base of Formula I may be obtained as a solution 10 directly from a reaction in which sorafenib free base is formed and used as such without isolation.

The term “contacting” may include dissolving, slurrying, stirring, or a combination thereof.

The reaction of the sorafenib free base of Formula I with ethane sulphonic acid 15 may be carried out by directly contacting sorafenib free base with ethane sulphonic acid. The reaction may also be carried out in the presence of a suitable solvent. A solution of ethane sulphonic acid in a suitable solvent may also be used. Preferably, ethane sulphonic acid may be added to a reaction mixture containing sorafenib free base and a suitable solvent.

20 The suitable solvent may be selected from water, polar organic solvents, dipolar aprotic organic solvents, and mixtures thereof.

The polar organic solvents may be selected from organic solvents containing at least one hydroxyl group, cyclic ethers, alkyl acetates, and mixtures thereof. Examples of organic solvents containing at least one hydroxyl group may include methanol, ethanol, n-

propanol, isopropanol, n-butanol, sec-butanol, isobutanol, n-pentanol, glycerol or ethylene glycol. Examples of cyclic ethers may include tetrahydrofuran or 1, 4-dioxane. Examples of alkyl acetates may include methyl acetate, ethyl acetate, propyl acetate, or butyl acetate.

5 The dipolar aprotic organic solvents may be selected from the group comprising of ketones, amides, nitriles, sulphoxides, or mixtures thereof. Examples of ketones may include acetone, methyl ethyl ketone, or methyl isobutyl ketone. Examples of amides may include N, N-dimethylformamide, or N, N-dimethylacetamide. Examples of nitriles may include acetonitrile, or propionitrile. Examples of sulphoxides may include dimethyl sulfoxide, or diethyl sulphoxide.

10 In the preferred embodiments of the present invention, the reaction of sorafenib free base with ethane sulphonic acid may be carried out in polar organic solvents selected from organic solvents containing at least one hydroxyl group, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol, n-pentanol, glycerol, or ethylene glycol.

15 Ethane sulphonic acid may be added slowly to the reaction mixture containing sorafenib free base and the suitable solvent.

In the preferred embodiment of the present invention ethane sulphonic acid may be added to the reaction mixture containing sorafenib free base and the suitable solvent over a period of about 20 minutes, preferably, about 10 minutes.

20 The reaction of sorafenib free base with ethane sulphonic acid may be carried out at a temperature of about 0°C to the reflux temperature of the suitable solvent, preferably, at about 15°C to about 80°C, most preferably, at about 15°C to about 35°C.

The solution may be stirred for about 30 minutes to about 8 hours, preferably, for about 4 hours.

25 The reaction mixture containing sorafenib free base, ethane sulphonic acid and solvent(s) may be treated with a decolorizing agent such as activated charcoal before precipitation.

Generally, an ethane sulphonate salt of sorafenib precipitates out of the reaction mixture. The precipitation may be spontaneous depending upon the solvent used and the

reaction conditions. The precipitation may also be facilitated by seeding or by reducing the temperature.

Isolation of the ethane sulphonate salt of sorafenib may be accomplished by concentration, precipitation, cooling, filtration or centrifugation, or a combination thereof, followed by drying under reduced pressure. The sorafenib ethane sulphonate may be further purified by recrystallization for better purity.

The process of the present invention provides sorafenib ethane sulphonate of high purity.

The sorafenib ethane sulphonate of Formula III may be converted into a sorafenib free base of Formula I of high purity by hydrolysis in a neutral medium or in the presence of a base. The base may be selected from 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 diethyl amine.

The processes of the present invention provides sorafenib free base of high purity.

The conversion of the sorafenib ethane sulphonate of Formula III to sorafenib acid addition salts of Formula IV may be carried out by directly contacting sorafenib with an acid of Formula HX.

The acid of Formula HX may be selected from the group comprising hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *para*-toluene sulphonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid or mandelic acid.

The conversion of the sorafenib ethane sulphonate of Formula III to the sorafenib acid addition salts of Formula IV may also be carried out by a process comprising conversion of sorafenib ethane sulphonate to sorafenib free base in the first step followed by the reaction of sorafenib free base with the acid of Formula HX.

In a preferred embodiment of the present invention, sorafenib ethane sulphonate may be converted to sorafenib tosylate by heating a reaction mixture containing sorafenib ethane sulphonate, ethyl acetate and water to a temperature of about 70°C; slowly adding a solution of *para*-toluene sulphonic acid monohydrate in ethyl acetate-water mixture to the
5 above reaction mixture over a period of about 30 minutes; cooling the reaction mixture to about 32°C; stirring overnight; further cooling to about 0°C to about 5°C; and stirring for about 3 hours. Sorafenib tosylate may be obtained from the above reaction mixture by slowly raising the temperature to about 32°C, and filtering and drying under reduced pressure. Drying may be carried out at about 55°C for about 5 hours.

10 Solvates, hydrates and polymorphs of sorafenib ethane sulphonate of Formula III are also included within the scope of the present invention. Polymorphs of sorafenib ethane sulphonate may include both amorphous and crystalline forms.

The amorphous form may be obtained by conventional methods such as spray drying, lyophilization and evaporation of the solvent under reduced pressure.

15 Sorafenib ethane sulphonate is usually administered as part of a pharmaceutical composition. Accordingly, in a further aspect, there is provided a pharmaceutical composition that comprises ethane sulphonate salt of sorafenib and one or more pharmaceutically acceptable carriers, diluents or excipients and optionally other therapeutic ingredients. Pharmaceutical compositions comprising the sorafenib ethane
20 sulphonate of Formula III may be administered orally, topically, parenterally, by inhalation or spray, rectally or in the form of injectables. Injectables include intravenous, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques.

In the foregoing section, embodiments are described by way of examples to
25 illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of the examples would be evident to persons ordinarily skilled in the art, which are within the scope of the present invention.

Methods

The XRD pattern was recorded using Panalytical Expert PRO with Xcelerator as
30 detector, 3-40 as scan range, 0.02 as step size and 3-40° 2θ as range.

DSC and TGA were recorded using Mettler Toledo DSC 821e and TA instrument-Q 500, respectively.

HPLC was performed using a Zorbax SB AQ, 250 mm x 4.6 mm, 5 μ m column having the following parameters:

- 5 Flow rate: 1.0 mL/ minute
- Detector: UV at 260 nm
- Injection volume: 10 μ L
- Column oven Temperature: 30°C
- Run time: 50 minutes
- 10 Buffer: Orthophosphoric acid in water
- Mobile Phase: Buffer and Methanol

EXAMPLES

Example 1: Preparation of Sorafenib Ethane Sulphonate

- 15 Ethanol (20 mL) was added to a reaction vessel containing sorafenib free base (4.0 g). Ethane sulphonic acid (1.62 mL) was added drop wise to the above reaction mixture. The reaction mixture was stirred at about 25°C to 35°C for about 4 hours. The solid was filtered, washed with ethanol (2 x 10 mL) and dried under reduced pressure at about 60°C for about 5 hours to obtain sorafenib ethane sulphonate.

Yield: 91%

- 20 HPLC Purity: 99.46%

Example 2: Preparation of Sorafenib Tosylate

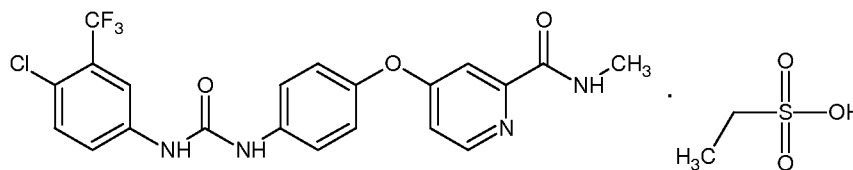
- 25 A reaction mixture containing sorafenib ethane sulphonate (5.0 g), ethyl acetate (50 mL) and water (1 mL) was heated to about 70°C. A solution of *para*-toluene sulphonic acid monohydrate (3.3 g) in ethyl acetate: water:: 1.0 mL: 0.2 mL was slowly added over a period of about 30 minutes to the above reaction mixture. The reaction mixture was cooled to about 32°C and stirred overnight. The reaction mixture was further cooled to about 0°C to about 5°C and stirred for about 3 hours. Temperature of the

reaction mixture was slowly raised to about 32°C. The solid material was filtered and dried under reduced pressure at about 55°C for about 5 hours to obtain sorafenib tosylate.

Yield: 36.1%

We claim:

- 1 1. Sorafenib ethane sulphonate of Formula III



Formula III

4 solvates, hydrates and polymorphs thereof.

- 1 2. The sorafenib ethane sulphonate of claim 1 characterized by X-ray diffraction
2 peaks at d-spacing at about 10.84, 5.59, 5.22, 3.80, and 3.75 Å.

- 1 3. The sorafenib ethane sulphonate of claim 1 further characterized by X-ray
2 diffraction peaks at d-spacing at about 5.41, 4.33, 3.47, 3.12, and 3.05 Å.

- 1 4. The sorafenib ethane sulphonate of claim 1, characterized by DSC thermogram
2 having endotherm at about 208.10°C.

- 1 5. The sorafenib ethane sulphonate of claim 1, characterized by X-ray diffraction
2 pattern as depicted in Figure 1.

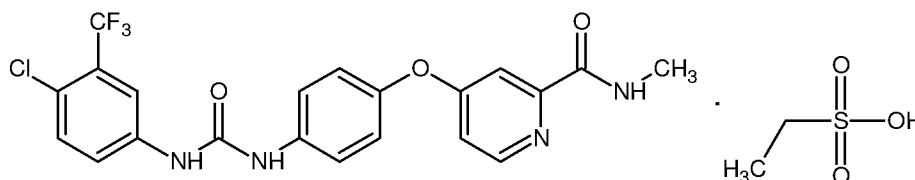
- 1 6. The sorafenib ethane sulphonate of claim 1, characterized by DSC as depicted in
2 Figure 2.

- 1 7. The sorafenib ethane sulphonate of claim 1, characterized by TGA as depicted in
2 Figure 3.

- 1 8. The sorafenib ethane sulphonate of claim 1, characterized by IR spectrum as
2 depicted in Figure 4.

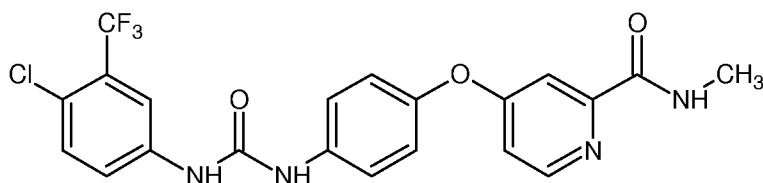
- 1 9. The sorafenib ethane sulphonate of claim 1, having greater than 99% HPLC purity.

- 1 10. A process for the preparation of sorafenib ethane sulphonate of Formula III,



Formula III

4 the process comprising contacting sorafenib free base of Formula I



6 **Formula I**

7 with ethane sulphonic acid.

1 11. The process according to claim 10, wherein the process utilizes isolated sorafenib
2 free base of Formula I or the sorafenib free base of Formula I, which is obtained as
3 a solution directly from a reaction in which sorafenib free base is formed, is used
4 without isolation.

1 12. The process according to claim 10, wherein the sorafenib free base of Formula I is
2 contacted with ethane sulphonic acid in a suitable solvent selected from water,
3 polar organic solvents, dipolar aprotic organic solvents, and mixtures thereof.

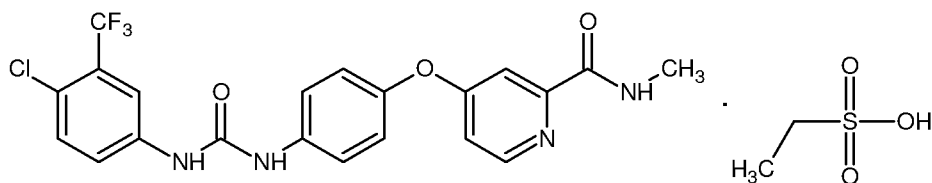
1 13. The process according to claim 12, wherein the polar organic solvent is selected
2 from organic solvents containing at least one hydroxyl group, cyclic ethers, alkyl
3 acetates and mixtures thereof.

1 14. The process according to claim 13, wherein the organic solvent containing at least
2 one hydroxyl group is selected from methanol, ethanol, n-propanol, isopropanol, n-
3 butanol, sec-butanol, isobutanol, n-pentanol, glycerol or ethylene glycol.

1 15. The process according to claim 12, the dipolar aprotic organic solvent is selected
2 from the group comprising of ketones, amides, nitriles, sulphoxides, or mixtures
3 thereof.

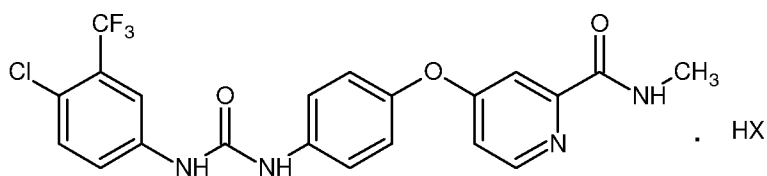
1 16. The process according to claim 10, wherein the sorafenib free base is contacted
2 with ethane sulphonic acid at about 0°C to the reflux temperature of the suitable
3 solvent.

- 1 17. Use of sorafenib ethane sulphonate of Formula III



3 **Formula III**

- 4 for the preparation of sorafenib acid addition salts of Formula IV,



6 **Formula IV**

- 7 the process comprising contacting sorafenib ethane sulphonate with an acid of
- 8 Formula HX.

- 1 18. A pharmaceutical composition comprising sorafenib ethane sulphonate of Formula
- 2 III and one or more pharmaceutically acceptable excipients.

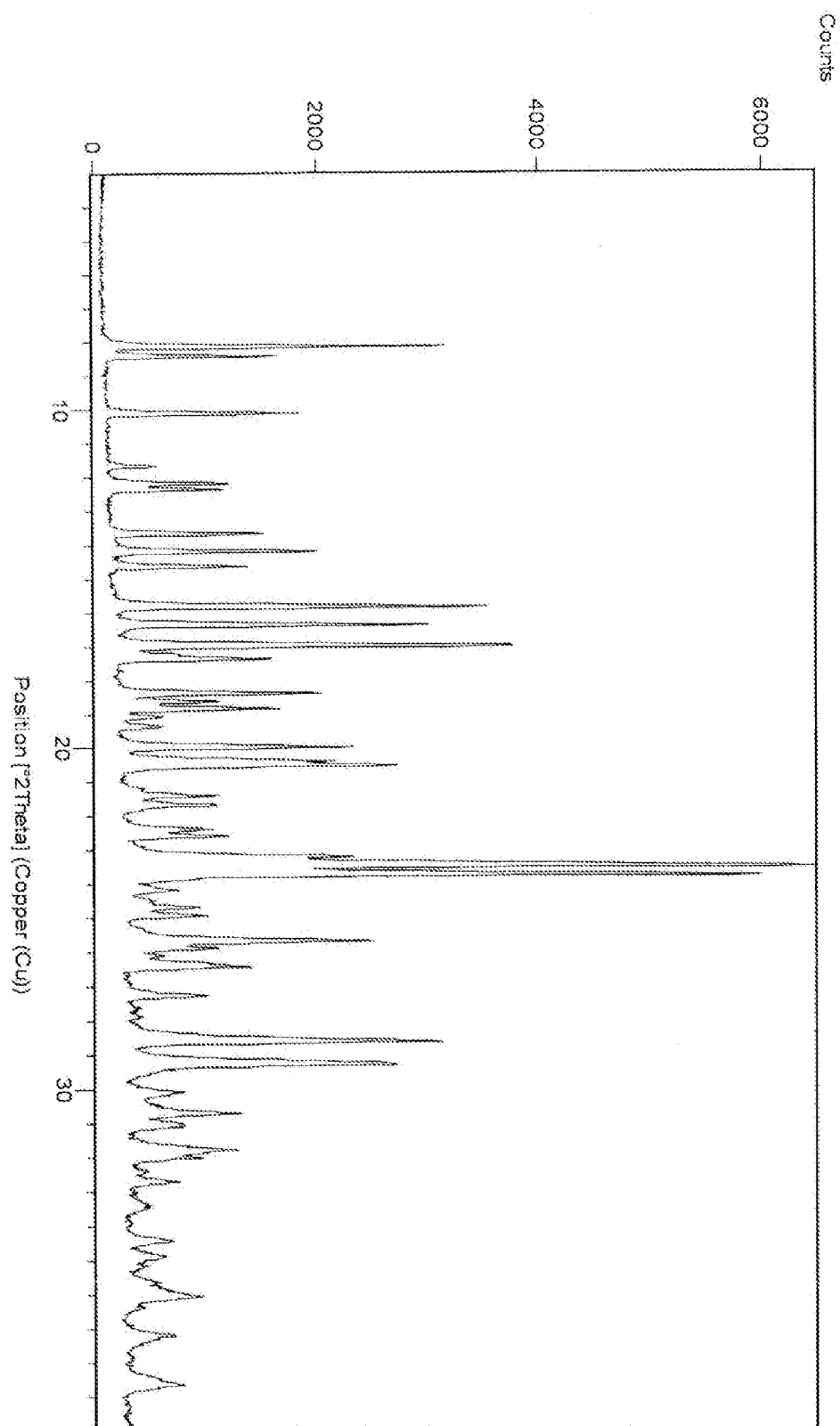


FIGURE 1

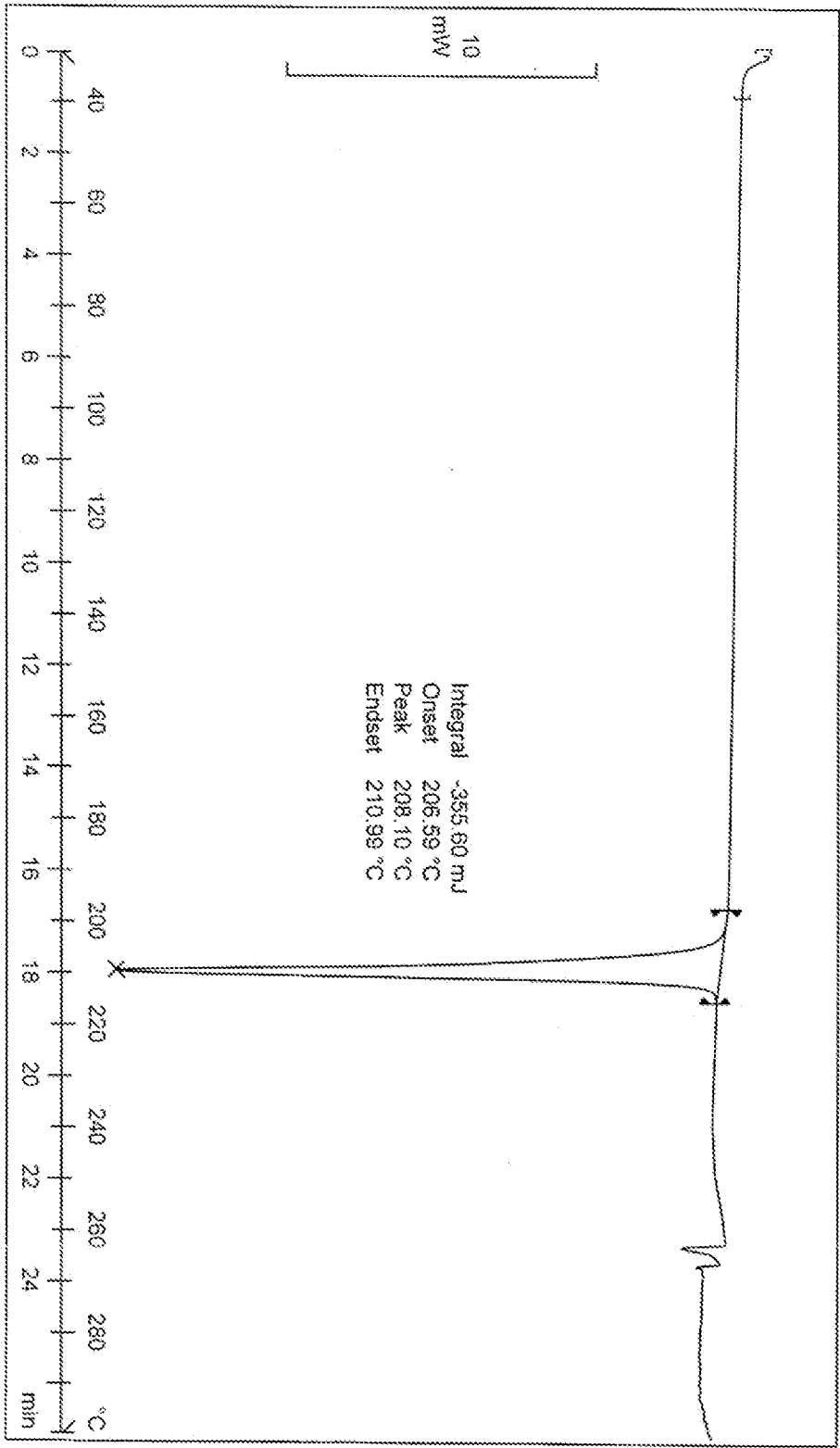


FIGURE 2

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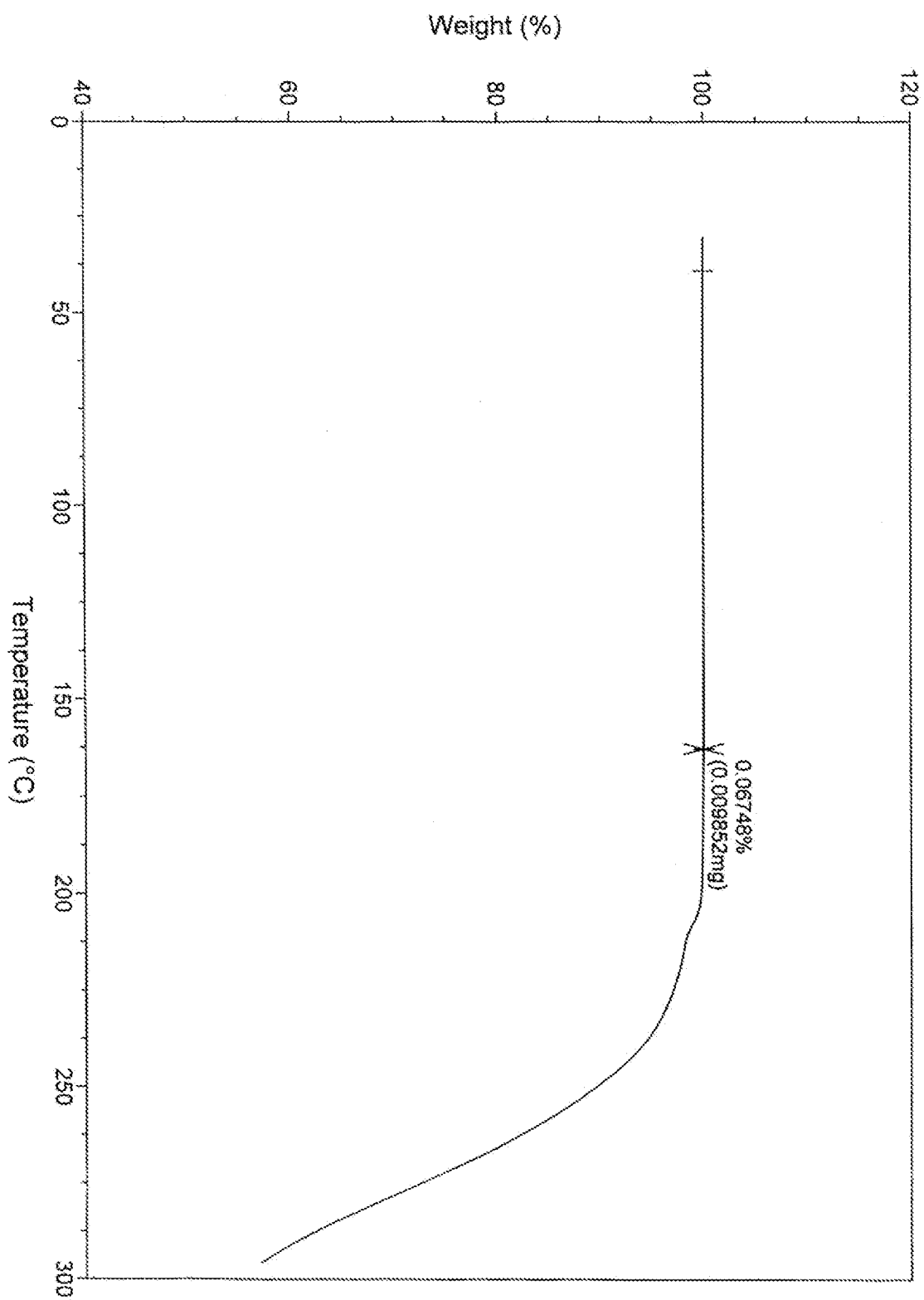


FIGURE 3

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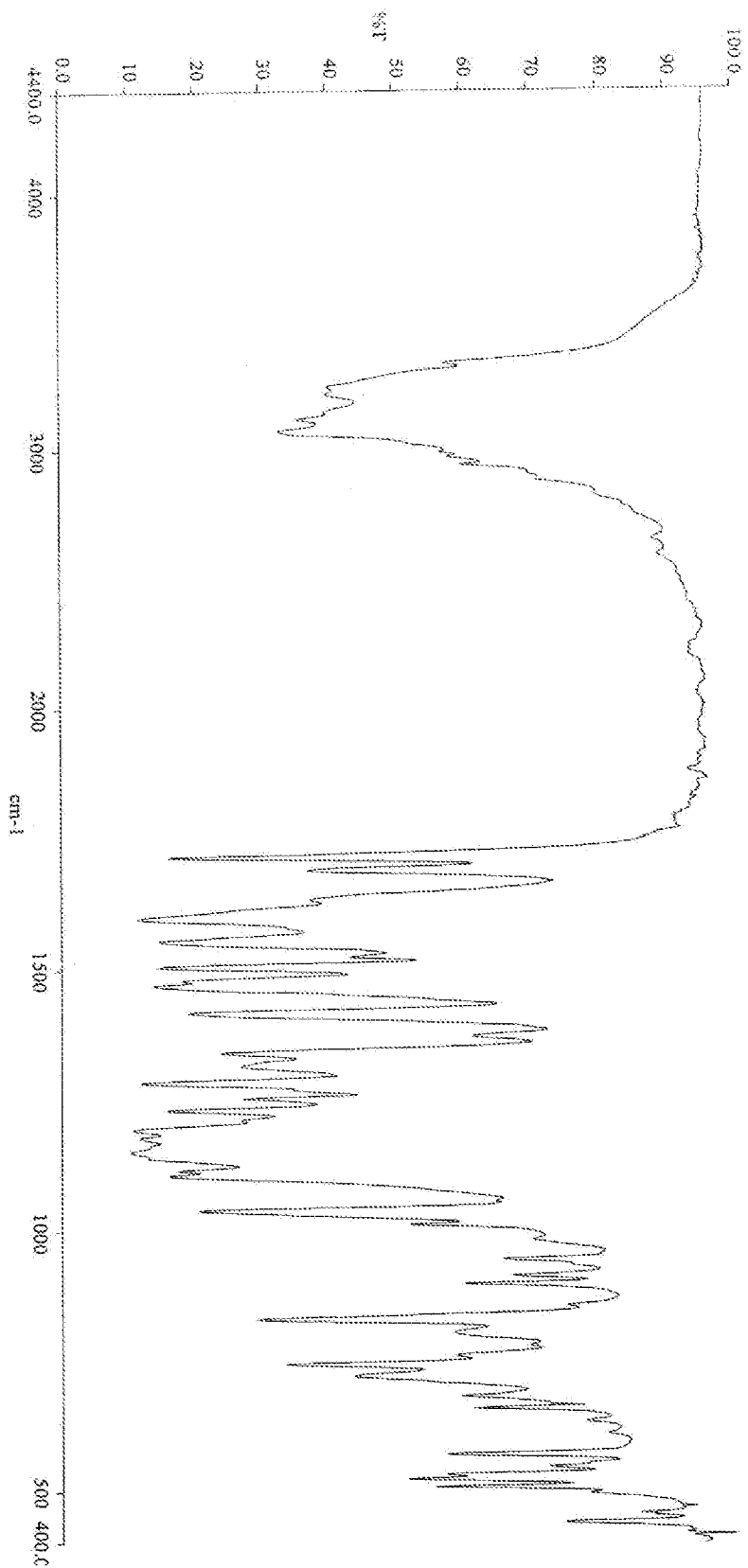


FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/055151

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/81 A61K31/44 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 A61P

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CN 101 584 661 A (UNIV BEIJING [CN]) 25 November 2009 (2009-11-25) the whole document	1-18
X	& DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 30 September 2009 (2009-09-30), Wang, Xueqing: "Sorafenib self-microemulsifying drug delivery system for oral medication or intravenous injection, and the preparation method and application thereof", XP002619295, retrieved from STN Database accession no. 2009:1482361 Compound with CAS registry number 1199618-55-7 (Sorafenib ethylsulfonate salt) ----- -/-	1-18



Further documents are listed in the continuation of Box C.



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 document 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
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"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
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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 docu-
ments, 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

31 January 2011

Date of mailing of the international search report

07/02/2011

Name and mailing address of the ISA/

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Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/055151

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/068383 A1 (BAYER HEALTHCARE AG [DE]; WEBER OLAF [DE]; RIEDL BERND [DE]) 21 June 2007 (2007-06-21)	1-9, 18
Y	Sorafenib, compound "Z1"; page 12, line 1 - line 6 Representative salts of the compounds of the invention include: ethansulfonate; page 16, line 11 - line 16 Use of Sorafenib or salt for the manufacture of medicament: claims 8, 1 Pharmaceutical compositions: claims 36-38 -----	10-17
Y	WO 2006/034796 A1 (BAYER HEALTHCARE AG [DE]; LOEGERS MICHAEL [DE]; GEHRING REINHOLD [DE];) 6 April 2006 (2006-04-06) Sorafenib Tosylate salt: claim 1 Process to make Sorafenib Tosylate salt by mixing free base and tosylic acid (method 5a - 5c); page 19 - page 21; claim 1 -----	10-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2010/055151

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 101584661	A	25-11-2009	NONE
WO 2007068383	A1	21-06-2007	CA 2633417 A1 21-06-2007 EP 1962829 A1 03-09-2008 JP 2009524585 T 02-07-2009
WO 2006034796	A1	06-04-2006	AR 053973 A1 30-05-2007 AU 2005289099 A1 06-04-2006 BR PI0515944 A 12-08-2008 CA 2581835 A1 06-04-2006 CN 101052619 A 10-10-2007 EC SP077357 A 26-04-2007 EP 1797037 A1 20-06-2007 GT 200500269 A 11-05-2006 JP 2008514657 T 08-05-2008 KR 20070058676 A 08-06-2007 NZ 554119 A 30-07-2010 PE 15842009 A1 28-10-2009 PE 15852009 A1 31-10-2009 PE 15862009 A1 31-10-2009 PE 15872009 A1 05-11-2009 PE 08252006 A1 20-10-2006 SG 155997 A1 29-10-2009 SV 2006002243 A 13-10-2006 US 2008262236 A1 23-10-2008 UY 29143 A1 28-04-2006 ZA 200702511 A 30-07-2008