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(54) Title: NOVEL SALTS OF 3-(2-IMIDAZO[1,2-b]PYRIDAZIN-3-YLETHYNYL)-4-METHYL-N-[4-[(4-METHYL- 1-
PIPERAZINYLMETHYL]-3-(TRIFLUOROMETHYL)PHENYL] BENZAMIDE

(57) Abstract: A pharmaceutically acceptable salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4- methyl-1-
piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and at least one acid component, selected from the group con-
sisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-tolu-
enesulphonic acid.



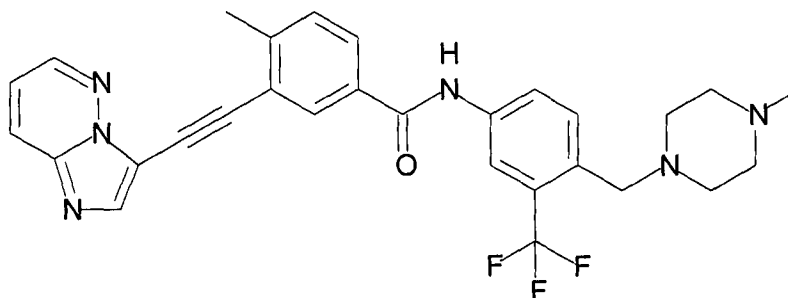
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Novel salts of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide

Background of the invention

5 1. Field of the invention

The present invention relates to a novel salts of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide of Formula I



(I)

10 and at least one acid component, processes of their preparation, and to their use in pharmaceutical compositions.

2. Background information

3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide compound which is also known as ponatinib (CAS no.: 943319-70-8) has a tyrosine kinase inhibitor activity which is effectively used for the treatment of chronic myeloid leukaemia (CML) as well as Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL).

20 The enzyme tyrosine kinase is a subclass of protein kinase and it plays an important role in the phosphate group transfer in form adenosine triphosphate (ATP) to a protein in the cell. The phosphate group is attached to the appropriate amino acid, tyrosine on the protein. Tyrosine kinases act as an "on" and "off" switch, however, can easily undergo mutation by sticking in the "on" position resulting in uncontrolled growth of the cell that leads to the development of cancer. Consequently, tyrosine kinase inhibitors are often used as effective agents for cancer treatments.

25 WO2007075869 describes protein kinase inhibitors with valuable pharmacological effect in the treatment of related diseases. One example of the compounds disclosed is ponatinib; preparation of the base and the hydrochloride salt thereof are described.

Summary of the invention

30 The object of the present invention is to provide novel pharmaceutically acceptable salts of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and at least one acid component, selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid.

The novel salts of ponatinib are as follows:

- A) the salt of ponatinib and benzoic acid;
- B) the salt of ponatinib and citric acid;
- C) the salt of ponatinib and fumaric acid;
- 5 D) the salt of ponatinib and L-tartaric acid;
- E) the salt of ponatinib and maleic acid;
- F) the salt of ponatinib and phosphoric acid;
- G) the salt of ponatinib and sulphuric acid;
- H) the salt of ponatinib and succinic acid;
- 10 I) the salt of ponatinib and *p*-toluenesulphonic acid.

The present invention further relates to pharmaceutical formulations comprising one of the novel salts of ponatinib and to the use thereof for the treatment of cancer.

- 15 An advantage of the newly prepared salts consists in their good physical and chemical characteristics, which make them suitable for preparation of a dosage form.

Brief description of the figures

The figures depict the following spectra of the various salts prepared according to the invention.

- 20 **Figure 1** is a FTIR spectra of the salt of ponatinib and benzoic acid;
- Figure 2** is a ¹H-NMR spectra the salt of ponatinib and benzoic acid;
- Figure 3** is a ssNMR spectra the salt of ponatinib and benzoic acid;
- Figure 4** is an XRPD pattern of the salt of ponatinib and benzoic acid;
- Figure 5** is a FTIR spectra of the salt of ponatinib and citric acid;
- 25 **Figure 6** is a ssNMR spectra the salt of ponatinib and citric acid;
- Figure 7** is an XRPD pattern of the salt of ponatinib and citric acid;
- Figure 8** is a FTIR spectra of the salt of ponatinib and fumaric acid;
- Figure 9** is a ¹H-NMR spectra the salt of ponatinib and fumaric acid;
- Figure 10** is a ssNMR spectra the salt of ponatinib and fumaric acid;
- 30 **Figure 11** is an XRPD pattern of the salt of ponatinib and fumaric acid;
- Figure 12** is a FTIR spectra of the salt of ponatinib and phosphoric acid;
- Figure 13** is a ssNMR spectra the salt of ponatinib and phosphoric acid;
- Figure 14** is an XRPD pattern of the salt of ponatinib and phosphoric acid;
- Figure 15** is a FTIR spectra of the salt of ponatinib and sulphuric acid;
- 35 **Figure 16** is a ssNMR spectra the salt of ponatinib and sulphuric acid;
- Figure 17** is an XRPD pattern of the salt of ponatinib and sulphuric acid;
- Figure 18** is a FTIR spectra of the salt of ponatinib and succinic acid;
- Figure 19** is a ssNMR spectra the salt of ponatinib and succinic acid;

Figure 20 is an XRPD pattern of the salt of ponatinib and succinic acid;

Figure 21 is a FTIR spectra of the salt of ponatinib and *p*-toluenesulphonic acid;

Figure 22 is a ¹H-NMR spectra the salt of ponatinib and *p*-toluenesulphonic acid;

Figure 23 is a ssNMR spectra the salt of ponatinib and *p*-toluenesulphonic acid;

5 **Figure 24** is an XRPD pattern of the salt of ponatinib and *p*-toluenesulphonic acid;

Figure 25 is a FTIR spectra of the salt of ponatinib and L-tartaric acid;

Figure 26 is a ssNMR spectra the salt of ponatinib and L-tartaric acid;

Figure 27 is an XRPD pattern of the salt of ponatinib and L-tartaric acid;

Figure 28 is a FTIR spectra of the salt of ponatinib and maleic acid;

10 **Figure 29** is a ssNMR spectra the salt of ponatinib and maleic acid;

Figure 30 is an XRPD pattern of the salt of ponatinib and maleic acid.

Detailed description of the invention

15 The aim of the present invention is to provide novel pharmaceutically acceptable salts of ponatinib with advantageous properties for pharmaceutical use regarding their physico-chemical properties (e.g. stability, solubility) and which can be produced in a reproducible manner even in industrial scale.

20 The above mentioned objects have been achieved by the novel pharmaceutically acceptable salts of ponatinib with benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid. The invention also relates to a method of preparation of these salts. It has been surprisingly found that the above-mentioned chemically and morphologically stable salts of ponatinib can be prepared and have not been described in the literature and no analytical data (X-Ray Powder Diffraction patterns, Single-Crystal X-Ray Diffraction data etc.) serving to characterize the crystalline salt has been provided.

25 The present invention thus relates to a pharmaceutically acceptable salt of ponatinib and at least one acid component selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid.

The inventive salts of ponatinib can be obtained with acceptable yields and high purity.

30 The inventive salts may exist in different solid forms with different internal structures (polymorphism), which may have different physico-chemical properties, Therefore, crystalline modifications of the inventive salt cover individual crystals and/or mixtures thereof with another crystalline modification in any ratio.

35 Substantially pure crystalline forms and substantially pure amorphous form can be prepared, as well as mixtures of different crystalline forms in any ratio or mixtures of crystalline form(s) with the amorphous form.

The inventive salt formed from ponatinib and at least one pharmaceutically acceptable acid component can be present in a crystalline form or in an amorphous form. Preferably it is in a crystalline form.

40 The inventively claimed salts may be in an anhydrous and/or a solvent-free form; or they may be in a hydrated or solvated form.

All said salts can be prepared by the reaction of ponatinib with an acid selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid in a solvent selected from the group consisting of C1-C4 alkyl alcohols and any their mixtures, preferably in methanol, ethanol and 2-propanol.

The selected solvents, preferably methanol, ethanol and 2-propanol are suitable for the preparation of the salts of ponatinib in a yield and purity which is favorable from efficient and safe production point of view of a pharmaceutically active compound.

The reaction was carried out in the range of temperature 40-60°C, preferably at temperature 50°C. The resulting salt was isolated from the reaction mixture at room temperature.

The salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide and acid component selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid can be obtained by a process comprising following steps:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C, preferably to 50°C;

b/ addition of the acid component in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C, preferably at 50°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the mixture of the step d/ overnight at the room temperature;

f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

The term "room temperature" is defined as a temperature between 15 °C and 29 °C for the purpose of this invention; preferably it is between 20-23°C.

The term „overnight" as used in this patent application is related to the duration of the given process step. The process that is to be carried out „overnight" has to be performed for at least 10 hours, preferably 12-16 hours.

The term „drying at laboratory condition" means drying at room temperature and relative humidity 20-60%.

The novel salts according to the invention can be used for preparation of ponatinib in a free form (Formula I). The novel salts according to the present invention can be used for preparation of any other pharmaceutically acceptable salt of ponatinib.

Use of any of the novel salts of ponatinib for preparation of ponatinib in its free form is also part of the invention. Use of any of the novel salts of ponatinib for conversion of any of the novel salts of ponatinib to other pharmaceutical acceptable salt thereof is also part of the invention.

5 Another aspect of the invention are novel crystalline salts of ponatinib with an acid component selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid. The salts according to this aspect of the invention are in a crystalline or a substantially crystalline state. The word „substantially” is understood as comprising at least of 95% by weight of the respective solid form.

10 The crystalline salt of ponatinib and benzoic acid according to the present invention can be characterized by an FTIR spectroscopy and solid-state NMR investigation. The crystalline salt of ponatinib and benzoic acid is characterised by a FTIR spectrum comprising characteristic peaks at 570, 678, 717, 838, 1109, 1142, 1387, 1659, 2217 and 3384 cm⁻¹ wavenumbers, shown in **Figure 1**. The solid-state NMR spectrum is shown in **Figure 3**.

15 The crystalline salt of ponatinib and benzoic acid according to the invention has the characteristic XRPD pattern as shown in **Figure 4**. The salt of ponatinib and benzoic acid has the following most characteristic powder diffraction peaks illustrated in **Table 1**, below:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.55	13.491	80.8
10.17	8.690	12.2
10.96	8.067	16.0
11.52	7.672	54.2
12.74	6.943	23.7
14.29	6.194	27.0
15.99	5.538	32.4
17.03	5.201	29.7
18.42	4.814	18.6
20.04	4.426	27.4
21.48	4.134	21.9
23.58	3.770	37.4
23.90	3.721	100.0
25.89	3.439	20.0
28.16	3.167	29.3
28.91	3.086	14.2

Table 1

The crystalline salt of ponatinib and benzoic acid was prepared with excellent purity of 97.5%.

20

The crystalline salt of ponatinib and citric acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and citric acid is characterised by a FTIR spectrum spectrum comprising characteristic peaks at 593, 793, 1052, 1121, 1160, 1316, 1593, 1733, 2212 and 2839 cm⁻¹ wavenumbers, shown in **Figure 5**. The solid-state NMR spectrum is shown **Figure 6**.

25

The crystalline salt of ponatinib and citric acid according to the invention has the a characteristic XRPD pattern as shown in **Figure 7**. The salt of ponatinib and citric acid has the following most characteristic powder diffraction peaks illustrated in **Table 2**, below:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
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4.74	18.625	76.5
5.63	15.691	100.0
7.50	11.779	54.9
9.34	9.462	31.7
9.72	9.094	30.9
11.19	7.903	23.7
12.61	7.016	51.2
14.22	6.223	31.6
14.93	5.931	17.7
16.30	5.432	28.4
16.99	5.213	33.1
17.68	5.013	15.4
19.50	4.549	10.7
21.36	4.157	12.4
22.01	4.034	11.1
25.30	3.518	20.4
26.51	3.359	12.6

Table 2

The crystalline salt of ponatinib and citric acid was prepared with excellent purity of 99.1%.

5 The crystalline salt of ponatinib and fumaric acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and fumaric acid is characterised by a FTIR spectrum comprising characteristic peaks at 609, 670, 840, 1125, 1161, 1289, 1599, 1672, 2213 and 3067 cm^{-1} wavenumbers, shown in **Figure 8**. The solid-state NMR spectrum is shown in **Figure 10**.

10 The crystalline salt of ponatinib and fumaric acid according to the invention has the characteristic XRPD pattern as shown in **Figure 11**. The salt of ponatinib and fumaric acid has the following most characteristic powder diffraction peaks illustrated in **Table 3**, below:

Pos. [$^{\circ}$ 2Th.]	d-spacing [Å]	Rel. Int. [%]
10.62	8.322	13.2
11.78	7.505	15.1
12.52	7.065	15.8
13.29	6.656	16.9
13.67	6.474	40.2
14.16	6.251	32.2
14.48	6.112	17.4
14.90	5.942	61.6
15.45	5.729	21.9
17.52	5.058	39.0
17.93	4.942	16.6
18.41	4.816	30.5
18.78	4.720	68.6
19.58	4.530	25.9
19.89	4.460	100.0
20.48	4.334	29.3
22.87	3.885	42.0
23.26	3.821	39.0
24.30	3.660	49.0

25.57	3.481	24.7
28.60	3.119	20.1
32.52	2.751	8.6

Table 3

The crystalline salt of ponatinib and fumaric acid was prepared with excellent purity of 99.1%.

5 The crystalline salt of ponatinib and phosphoric acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and phosphoric acid is characterised by a FTIR spectrum comprising characteristic peaks at 644, 803, 849, 904, 1083, 1121, 1250, 1423, 1652 and 2428 cm^{-1} wavenumbers, shown in **Figure 12**. The solid-state NMR spectrum is shown in **Figure 13**.

10 The crystalline salt of ponatinib and phosphoric acid according to the invention has the characteristic XRPD pattern as shown in **Figure 14**. The salt of ponatinib and phosphoric acid has the following most characteristic powder diffraction peaks illustrated in **Table 4**, below:

Pos. [$^{\circ}$ 2 θ .]	d-spacing [Å]	Rel. Int. [%]
8.28	10.676	45.7
11.14	7.939	29.3
12.40	7.135	100.0
13.45	6.577	17.2
13.95	6.345	22.3
14.42	6.139	43.9
14.77	5.993	62.1
15.27	5.796	56.7
16.50	5.369	52.1
17.74	4.995	36.1
19.31	4.593	32.4
21.31	4.167	17.1
22.39	3.967	47.6
23.00	3.864	43.3
24.09	3.692	22.8
25.03	3.555	36.4
25.40	3.504	30.8
25.92	3.435	30.7
26.76	3.329	35.4

Table 4

The crystalline salt of ponatinib and phosphoric acid was prepared with excellent purity of 99.4%.

15

The crystalline salt of ponatinib and sulphuric acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and sulphuric acid is characterised by a FTIR spectrum comprising characteristic peaks at 577, 745, 796, 1107, 1167, 1421, 1542, 1667, 2475 and 3018 cm^{-1} wavenumbers, shown in **Figure 15**.

20 The solid-state NMR spectrum is shown in **Figure 16**.

The crystalline salt of ponatinib and sulphuric acid according to the invention has the characteristic XRPD pattern as shown in **Figure 17**. The salt of ponatinib and sulphuric acid has the following most characteristic powder diffraction peaks illustrated in **Table 5**, below:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.26	20.711	100.0
6.14	14.386	43.4
6.41	13.783	31.8
9.69	9.116	17.4
10.93	8.091	15.5
11.41	7.750	14.2
13.01	6.802	12.1
13.74	6.441	34.9
15.79	5.609	23.0
16.35	5.419	18.5
17.80	4.978	42.8
18.34	4.834	94.1
19.05	4.654	27.7
19.80	4.481	12.5
21.28	4.171	41.5
21.75	4.084	29.4
22.26	3.990	24.4
23.04	3.858	19.4
23.51	3.782	17.2
25.08	3.548	26.9
25.46	3.496	39.3
26.22	3.396	16.7
26.61	3.347	21.0
27.72	3.216	21.8

Table 5

The crystalline salt of ponatinib and sulphuric acid was prepared with excellent purity of 99.1%.

- 5 The crystalline salt of ponatinib and succinic acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and succinic acid is characterised by a FTIR spectrum comprising characteristic peaks at 570, 651, 747, 1113, 1141, 1317, 1538, 1663, 1715 and 3308 cm^{-1} wavenumbers, shown in **Figure 18**. The solid-state NMR spectrum is shown in **Figure 19**.
- 10 The crystalline salt of ponatinib and succinic acid according to the invention has the characteristic XRPD pattern as shown in **Figure 20**. The salt of ponatinib and succinic acid has the following most characteristic powder diffraction peaks illustrated in **Table 6**, below:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.59	11.644	100.0
10.90	8.110	14.1
11.61	7.616	21.4
13.03	6.788	90.8
14.86	5.956	43.7
15.32	5.780	39.1
17.02	5.206	25.4
17.28	5.129	20.3
17.63	5.028	14.5
19.20	4.619	66.5

20.44	4.341	19.0
22.38	3.969	22.9
22.90	3.880	18.8
23.61	3.766	84.2
24.21	3.673	17.6
25.13	3.541	31.0
26.11	3.410	94.7
28.30	3.151	38.3
29.40	3.036	21.9
31.34	2.852	14.4

Table 6

The crystalline salt of ponatinib and succinic acid o was prepared with excellent purity of 98.7%.

5 The crystalline salt of ponatinib and *p*-toluenesulphonic acid according to the present invention can be characterized by an FTIR spectroscopy and a solid-state NMR investigations. The crystalline salt of ponatinib and *p*-toluenesulphonic acid is characterised by a FTIR spectrum comprising characteristic peaks at 567, 680, 749, 1000, 1141, 1161, 1231, 1420, 2217 and 3296 cm⁻¹ wavenumbers, shown in **Figure 21**. The solid-state NMR spectrum is shown in **Figure 23**.

10 The crystalline salt of ponatinib and *p*-toluenesulphonic acid according to the invention has the characteristic XRPD pattern as shown in **Figure 24**. The salt of ponatinib and *p*-toluenesulphonic acid has the following most characteristic powder diffraction peaks illustrated in **Table 7**, below:

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
6.66	13.264	100.0
9.03	9.781	17.0
9.84	8.983	10.1
10.48	8.431	48.5
11.18	7.911	17.8
13.07	6.766	30.5
13.41	6.597	23.2
14.29	6.192	30.0
16.06	5.513	50.1
16.83	5.264	18.3
18.03	4.916	17.1
19.22	4.614	30.0
20.00	4.435	38.6
20.44	4.340	25.0
21.00	4.227	22.3
22.38	3.970	20.6
23.79	3.738	22.7
24.18	3.678	93.6
24.95	3.566	21.2
28.71	3.107	28.1

Table 7

15 The crystalline salt of ponatinib and *p*-toluenesulphonic acid was prepared with excellent purity of 98.5%.

In another aspect of the invention, the novel salts of ponatinib with an acid component selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid are in an amorphous state or in a substantially amorphous state. The word „substantially” is understood as comprising at least 5 of 95% by weight of the respective solid form.

The amorphous salt of ponatinib and L-tartaric acid can be characterized by an FTIR spectroscopy and solid-state NMR investigations. **Figure 25** shows the FTIR spectrum comprising characteristic peaks at 557, 648, 1052, 1113, 1294, 1317, 1535, 1600, 1722 and 2213 cm⁻¹ wavenumbers and 10 **Figure 26** shows the solid-state NMR spectrum.

The salt of ponatinib and L-tartaric acid according to the invention has the characteristic XRPD pattern as shown in **Figure 27**. The salt of ponatinib and L-tartaric acid is an essentially amorphous phase.

The amorphous salt of ponatinib and L-tartaric acid was prepared with excellent purity of 98.8%.

The salt of ponatinib and maleic acid can be characterized by an FTIR spectroscopy and solid-state NMR investigations. **Figure 28** shows the FTIR spectrum comprising characteristic peaks at 669, 746, 985, 1118, 1155, 1295, 1319, 1538, 1718 and 2947 cm⁻¹ wavenumbers and **Figure 29** shows the solid-state NMR spectrum.

The salt of ponatinib and maleic acid according to the invention has the characteristic XRPD pattern as shown in **Figure 30**. The salt of ponatinib and maleic acid is essentially amorphous phase.

The amorphous salt of ponatinib and maleic acid was prepared with purity of 96.7%.

The novel salts according to the present invention can be used for preparation of pharmaceutical formulations which can be used for the treatment of leukaemia, especially chronic myeloid leukaemia (CML) as well as Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL). The formulations can be for oral or parenteral administration, or for any way of administration known in the state of the art. The oral formulations can be e.g. in the form of tablets, capsules, minitabets, film-strips and any other known form, preferably in the form of tablets or capsules.

The used analytical methods were performed as follows:

Analysis – XRPD (X-Ray Powder Diffractometry)

Diffractograms were obtained with laboratory X'PERT PRO MPD PANalytical diffractometer, used radiation CuK α (λ = 1.542Å).

Generator settings:

- excitation voltage 45 kV
- anodic current 40 mA.

Scan description:

- scan type – gonio
- measurement range 2 - 40° 2 θ
- step size 0.01° 2 θ
- step time: 0.5 s.

Samples were measured as received on Si plate (zero background holder).

Incident beam optics: programmable divergence slits (irradiated length 10 mm). 10 mm mask. 1/4° anti-scatter fixed slit, 0.02 rad Soller slits.

5 Diffracted beam optics: X'Celerator detector, scanning mode, active length 2.122°. 0.02 rad Soller slits, anti-scatter slit 5.0 mm. Ni filter.

Analysis – FTIR (Fourier-Transformed Infra-Red) spectroscopy

FTIR spectra were recorded by Nicolet Thermo 6700 spectrometer.

General settings:

- 10 Number of sample scans: 45
 Number of background scans: 45
 Resolution: 4.000
 Sample gain: 4.0
 Optical velocity: 0.6329
15 Aperture: 100.00

Analysis – NMR

For ¹H NMR spectra the Bruker NMR spectrometer AVANCE 250 MHz and DMSO as solvent were used. The stoichiometry of salts were determined from integrals of corresponding signals of API and coformer.

¹³C CP-MAS ss NMR spectra were measured on Bruker 400 WB spectrometer in 4 mm rotors with 13 kHz spinning frequency. The spectra of salts were compared with the spectrum of initial API because the formation of a salt should be accompanied by changes of positions of signals of API and by the presence of signals of coformer.

Examples

Example 1

Preparation of salt of ponatinib and benzoic acid

30 100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of 2-propanol by heating to 50°C. 23 mg (0.188 mmol) of benzoic acid was dissolved in 0.5 mL of 2-propanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

35 Yield: 77 mg (63%)

¹H-NMR analysis showed a 1:1 stoichiometry of ponatinib and benzoic acid.

Example 2

Preparation of salt of ponatinib and citric acid

100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of ethanol by heating to 50°C. 36.5 mg (0.190 mmol) of citric acid was dissolved in 0.5 mL of ethanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

5 The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 56 mg (41%)

¹H-NMR analysis showed a 1:1 stoichiometry of ponatinib and citric acid.

Example 3

Preparation of salt of ponatinib and fumaric acid

10 100 mg (0.188 mmol) of ponatinib was dissolved in 15 mL of 2-propanol by heating to 50°C. 22 mg (0.189 mmol) of fumaric acid was dissolved in 0.5 mL of 2-propanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

15 Yield: 86 mg (71%)

¹H-NMR analysis showed a 2:1 stoichiometry of ponatinib and fumaric acid.

Example 4

Preparation of salt of ponatinib and phosphoric acid

20 100 mg (0.188 mmol) of ponatinib was dissolved in 15 mL of methanol by heating to 50°C. 13 µL (0.190 mmol) of phosphoric acid (85% solution) was diluted with 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

25 Yield: 57 mg (48%)

³¹P-NMR analysis confirmed the presence of phosphoric acid.

Example 5

Preparation of salt of ponatinib and sulphuric acid

30 100 mg (0.188 mmol) of ponatinib was dissolved in 15 mL of methanol by heating to 50°C. 10.5 µL (0.190 mmol) of sulphuric acid (96% solution) was diluted with 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

35 The solution at 40°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 38 mg (32%)

Example 6

Preparation of salt of ponatinib and succinic acid

40 100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of methanol by heating to 50°C. 22.5 mg (0.190 mmol) of succinic acid was dissolved in 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 34 mg (28%)

¹H-NMR analysis showed a 1:1 stoichiometry of ponatinib and succinic acid.

5 Example 7

Preparation of salt of ponatinib and *p*-toluenesulphonic acid

100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of methanol by heating to 60°C. 36 mg (0.189 mmol) of *p*-toluenesulphonic acid was dissolved in 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 60°C.

- 10 The solution at 60°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 88 mg (65%)

¹H-NMR analysis showed a 1:1 stoichiometry of ponatinib and *p*-toluenesulphonic acid.

15 Example 8

Preparation of salt of ponatinib and L-tartaric acid

100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of methanol by heating to 50°C. 28.5 mg (0.190 mmol) of L-tartaric acid was dissolved in 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

- 20 The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 45 mg (35%)

¹H-NMR analysis showed a 1:1 stoichiometry of ponatinib and L-tartaric acid.

Example 9

- 25 Preparation of salt of ponatinib and maleic acid

100 mg (0.188 mmol) of ponatinib was dissolved in 3 mL of methanol by heating to 50°C. 22 mg (0.190 mmol) of maleic acid was dissolved in 0.5 mL of methanol at room temperature and the solution of the counterion was drop-wise added to the solution of the API of 50°C.

- 30 The solution at 50°C is stirred for 1 hour in closed vial, cooled back to room temperature and stirred overnight the resulting suspension was filtered off and dried at laboratory condition.

Yield: 55 mg (45%)

¹H-NMR analysis showed a 2:1 stoichiometry of ponatinib and maleic acid.

Claims:

1. A pharmaceutically acceptable salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and at least one acid component, selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid.
5
2. A salt according to the claim 1, wherein the salt is crystalline or amorphous.
3. A process of preparation of the salts according to the claims 1-2, the process comprising the steps a-h:
10
 - a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;
 - 15 b/ addition of the acid component, selected from the group consisting of benzoic acid, citric acid, fumaric acid, L-tartaric acid, maleic acid, phosphoric acid, sulphuric acid, succinic acid and *p*-toluenesulphonic acid, in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;
 - 20 c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;
 - d/ cooling the mixture of the step c/ to the room temperature;
 - e/ stirring the mixture of the step d/ overnight at the room temperature;
 - 25 f/ filtration of the suspension formed in the step e/;
 - g/ drying the crystals obtained in the step f/ at laboratory conditions;
 - 30 h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.
4. The process according to the claim 3, wherein the temperature used in the steps a/ and c/ is 50°C.
5. The process according to the claim 3 or 4, wherein the solvent is selected from the group consisting of methanol, ethanol and 2-propanol.
6. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and benzoic acid.
35
7. The salt according to the claim 6, wherein the salt is crystalline or amorphous.
8. The salt according to any of the claims 6-7, having characteristic absorptions at 2936, 2701, 2218, 1670, 1529, 1315, 1152, 1122, 1103 and 789 cm⁻¹ wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.
- 40 9. The salt according to any of the claims 6-8, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks, using radiation CuK α (λ = 1.542Å), at a reflection angle 2 θ ($\pm$ 0.2° 2 θ) of 6.5, 11.5, 16.0, 17.0, 23.9 and 28.2.
10. A process for preparation of the salt according to claims 6 – 9, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

5 b/ addition of the benzoic acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

10 d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

15 f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

20 11. The process according to the claim 10, wherein the used solvent is 2-propanol.

12. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and citric acid.

13. The salt according to the claim 12, wherein the salt is crystalline or amorphous.

25 14. The salt according to any of the claims 12-13, having characteristic absorptions at 593, 793, 1052, 1121, 1160, 1316, 1593, 1733, 2212 and 2839 cm⁻¹ wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

30 15. The salt according to any of the claims 12-14, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks, using radiation CuK α (λ = 1.542Å), at a reflection angle 2 θ ($\pm$ 0.2° 2 θ) of 5.6, 12.6, 14.2, 17.0 and 25.3.

16. A process for preparation of the salt according to claims 12-15, the process comprising the steps a-h:

35 a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

b/ addition of the citric acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

40 c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

45 e/ stirring the the mixture of the step d/ overnight at the room temperature;

f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

17. The process according to the claim 16, wherein the used solvent is ethanol.

5

18. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and fumaric acid.

19. The salt according to the claim 18, wherein the salt is crystalline or amorphous.

10

20. The salt according to any of the claims 18-19, having characteristic absorptions at 609, 670, 840, 1125, 1161, 1289, 1599, 1672, 2213 and 3067 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

21. The salt according to any of the claims 18-20, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks using radiation $\text{CuK}\alpha$ ($\lambda = 1.542\text{\AA}$), at a reflection angle 2θ ($\pm 0.2^\circ 2\theta$) of 13.7, 14.9, 17.5, 18.8, 19.9 and 24.3.

15

22. A process for preparation of the salt according to claims 18-21, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

20

b/ addition of the fumaric acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

25

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

30

f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

35

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

23. The process according to the claim 22, wherein the used solvent is 2-propanol.

24. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and phosphoric acid.

40

25. The salt according to the claim 24, wherein the salt is crystalline or amorphous.

26. The salt according to any of the claims 24-25, having characteristic absorptions at 644, 803, 849, 904, 1083, 1121, 1250, 1423, 1652 and 2428 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

27. The salt according to any of the claims 24-26, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks using radiation $\text{CuK}\alpha$ ($\lambda = 1.542\text{\AA}$), at a reflection angle 2θ ($\pm 0.2^\circ 2\theta$) of 8.3, 12.4, 14.8, 16.5, 19.3, 22.4 and 26.8.

28. A process for preparation of the salt according to claims 24-27, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

b/ addition of the phosphoric acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

29. The process according to the claim 28, wherein the used solvent is methanol.

30. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and sulphuric acid.

31. The salt according to the claim 30, wherein the salt is crystalline or amorphous.

32. The salt according to any of the claims 30-31, having characteristic absorptions at 577, 745, 796, 1107, 1167, 1421, 1542, 1667, 2475 and 3018 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

33. The salt according to any of the claims 30-32, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks using radiation $\text{CuK}\alpha$ ($\lambda = 1.542\text{\AA}$), at a reflection angle 2θ ($\pm 0.2^\circ 2\theta$) of 4.3, 6.1, 13.7, 18.3, 21.3 and 25.5.

34. A process for preparation of the salt according to claims 30-33, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

b/ addition of the sulphuric acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

f/ filtration of the suspension formed in the step e/;

5 g/ drying the crystals obtained in the step f/ at laboratory conditions;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

35. The process according to the claim 34, wherein the used solvent is methanol.

10

36. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and succinic acid.

37. The salt according to the claim 36, wherein the salt is crystalline or amorphous.

15 38. The salt according to any of the claims 36-37, having characteristic absorptions at 570, 651, 747, 1113, 1141, 1317, 1538, 1663, 1715 and 3308 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

39. The salt according to any of the claims 36-38, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks using radiation $\text{CuK}\alpha$ ($\lambda = 1.542\text{\AA}$), at a reflection angle $2\theta (\pm 0.2^\circ 2\theta)$ of 7.6, 13.0, 19.2, 23.6 and 26.1.

20 40. A process for preparation of the salt according to claims 36-39, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

25

b/ addition of the succinic acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

30

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

35 f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

40 h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

41. The process according to the claim 40, wherein the used solvent is methanol.

42. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and *p*-toluenesulphonic acid.

45 43. The salt according to the claim 42, wherein the salt is crystalline or amorphous.

44. The salt according to any of the claims 42-43, having characteristic absorptions at 567, 680, 749, 100, 1141, 1161, 1231, 1420, 2217 and 3296 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

45. The salt according to any of the claims 42-44, wherein the salt is in crystalline form characterised by an X-Ray Powder Diffraction pattern having characteristic peaks using radiation $\text{CuK}\alpha$ ($\lambda = 1.542\text{\AA}$), at a reflection angle $2\theta (\pm 0.2^\circ 2\theta)$ of 6.7, 10.5, 16.1, 20.0 and 24.

46. A process for preparation of the salt according to claims 42-45, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

b/ addition of the *p*-toluenesulphonic acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions ;

h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

47. The process according to the claim 46, wherein the used solvent is methanol.

48. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and L-tartaric acid.

49. The salt according to the claim 48, wherein the salt is crystalline or amorphous.

50. The salt according to any of the claims 48-49, having characteristic absorptions at 557, 648, 1052, 1113, 1294, 1317, 1535, 1600, 1722 and 2213 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

51. The salt according to any of the claims 48-50, wherein the salt is in an amorphous form.

52. A process for preparation of the salt according to claims 48-51, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

b/ addition of the L-tartaric acid acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

5 f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

10 h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

53. The process according to the claim 46, wherein the used solvent is methanol.

54. A salt of 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide (ponatinib) and maleic acid.

15 55. The salt according to the claim 54, wherein the salt is crystalline or amorphous.

56. The salt according to any of the claims 54-55, having characteristic absorptions at 669, 746, 985, 1118, 1155, 1295, 1319, 1538, 1718 and 2947 cm^{-1} wavenumbers in Fourier-Transformed Infrared spectroscopic analysis.

57. The salt according to any of the claims 54-56, wherein the salt is in an amorphous form.

20 58. A process for preparation of the salt according to claims 54-57, the process comprising the steps a-h:

a/ dissolving the 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl] benzamide in a solvent selected from the group consisting of C1-C4-alkyl alcohols and any their mixtures by heating to 40-60°C;

25

b/ addition of the maleic acid acid in 1 equimolar ratio dissolved in the same solvent that was used in the step a/ to the solution formed in the step a/;

c/ stirring the solution obtained in the step b/ at 40-60°C for 1 hour;

30

d/ cooling the mixture of the step c/ to the room temperature;

e/ stirring the the mixture of the step d/ overnight at the room temperature;

35 f/ filtration of the suspension formed in the step e/;

g/ drying the crystals obtained in the step f/ at laboratory conditions;

40 h/ optionally, recrystallization by dissolving the crystals in a solvent selected from the group consisting of C1-C4 alkyl alcohols and repetition of the steps of c/ - g/.

59. The process according to the claim 46, wherein the used solvent is methanol.

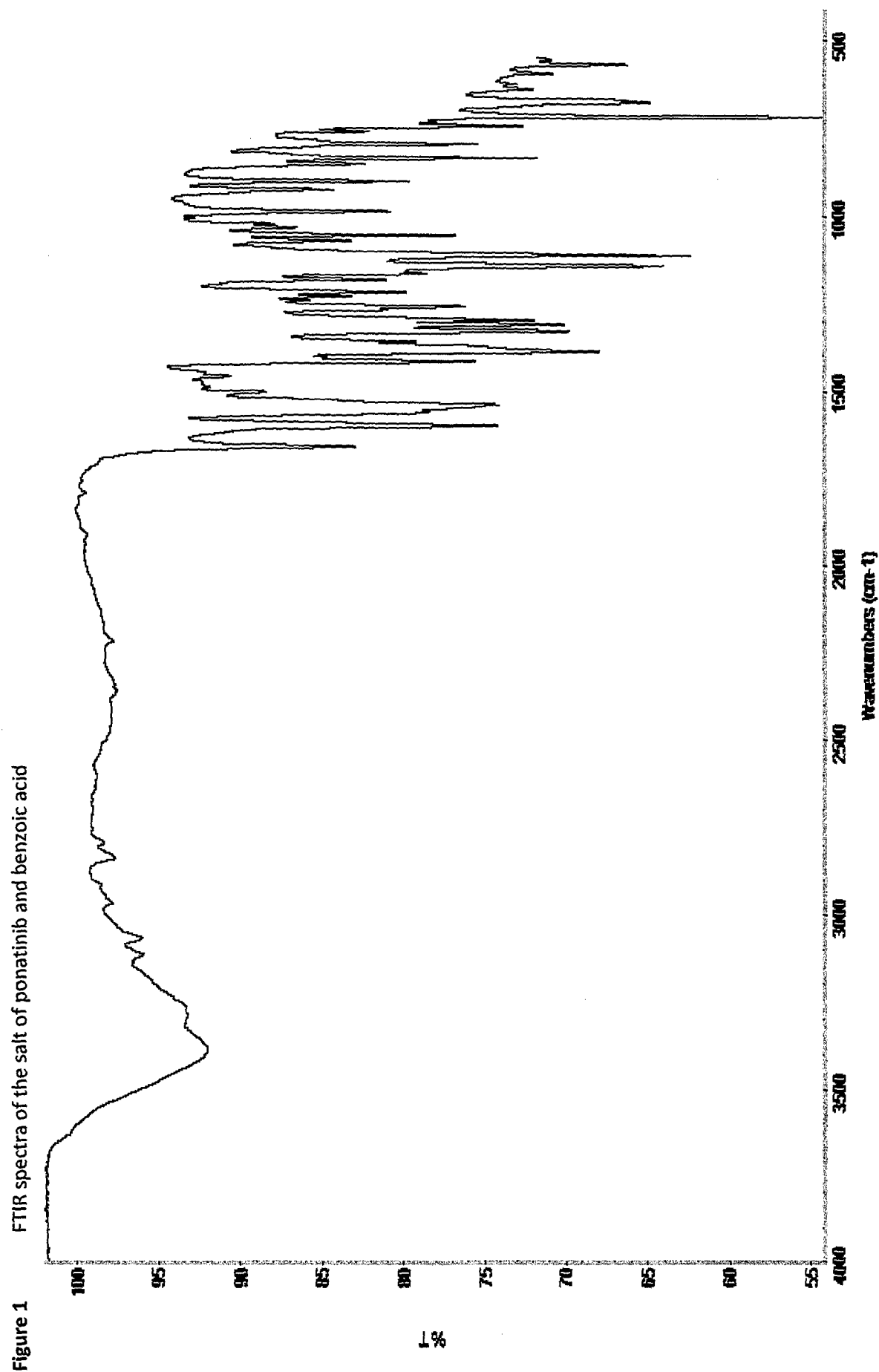


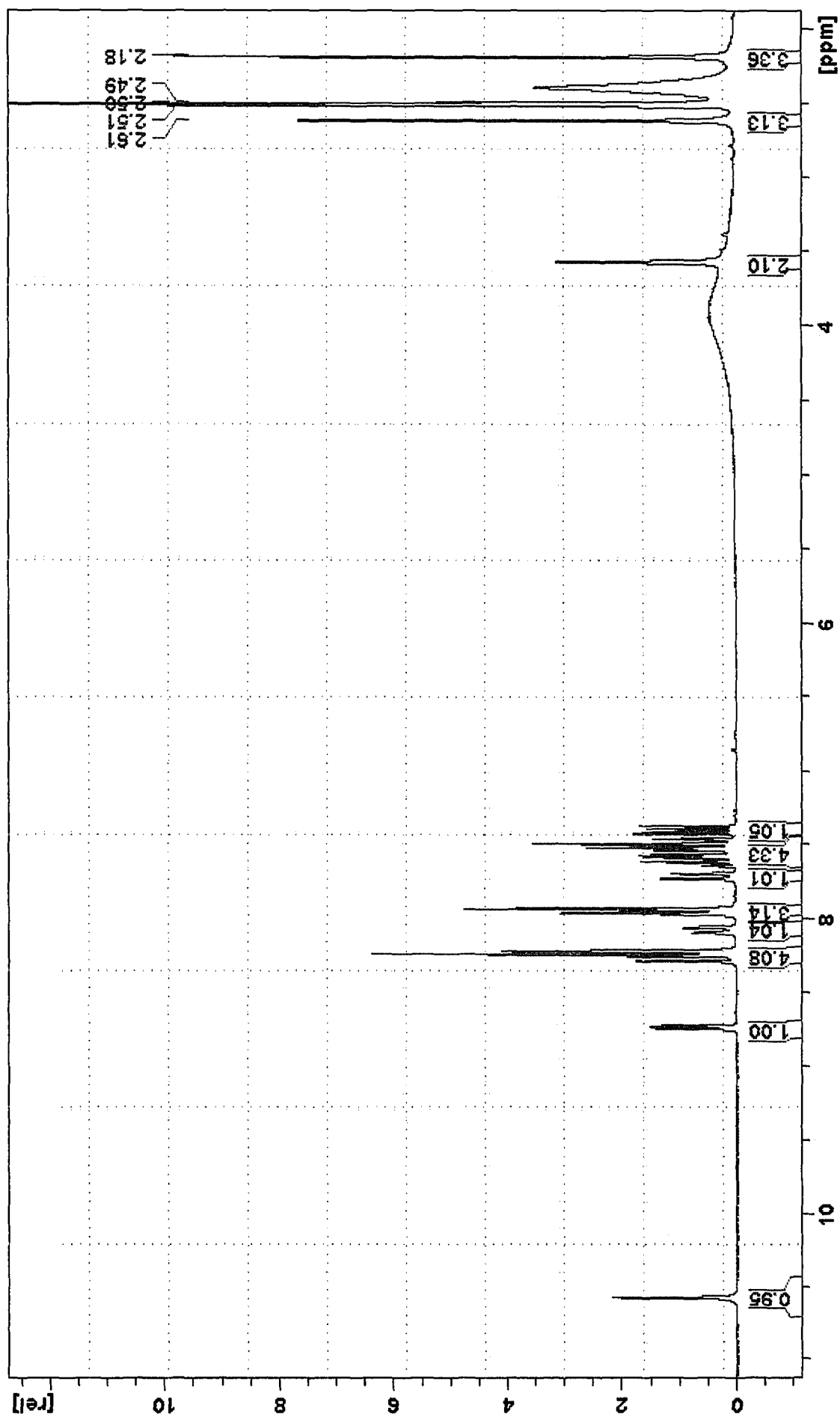
Figure 2 ^1H -NMR spectra the salt of ponatinib and benzoic acid

Figure 3 ssNMR spectra the salt of ponatinib and benzoic acid

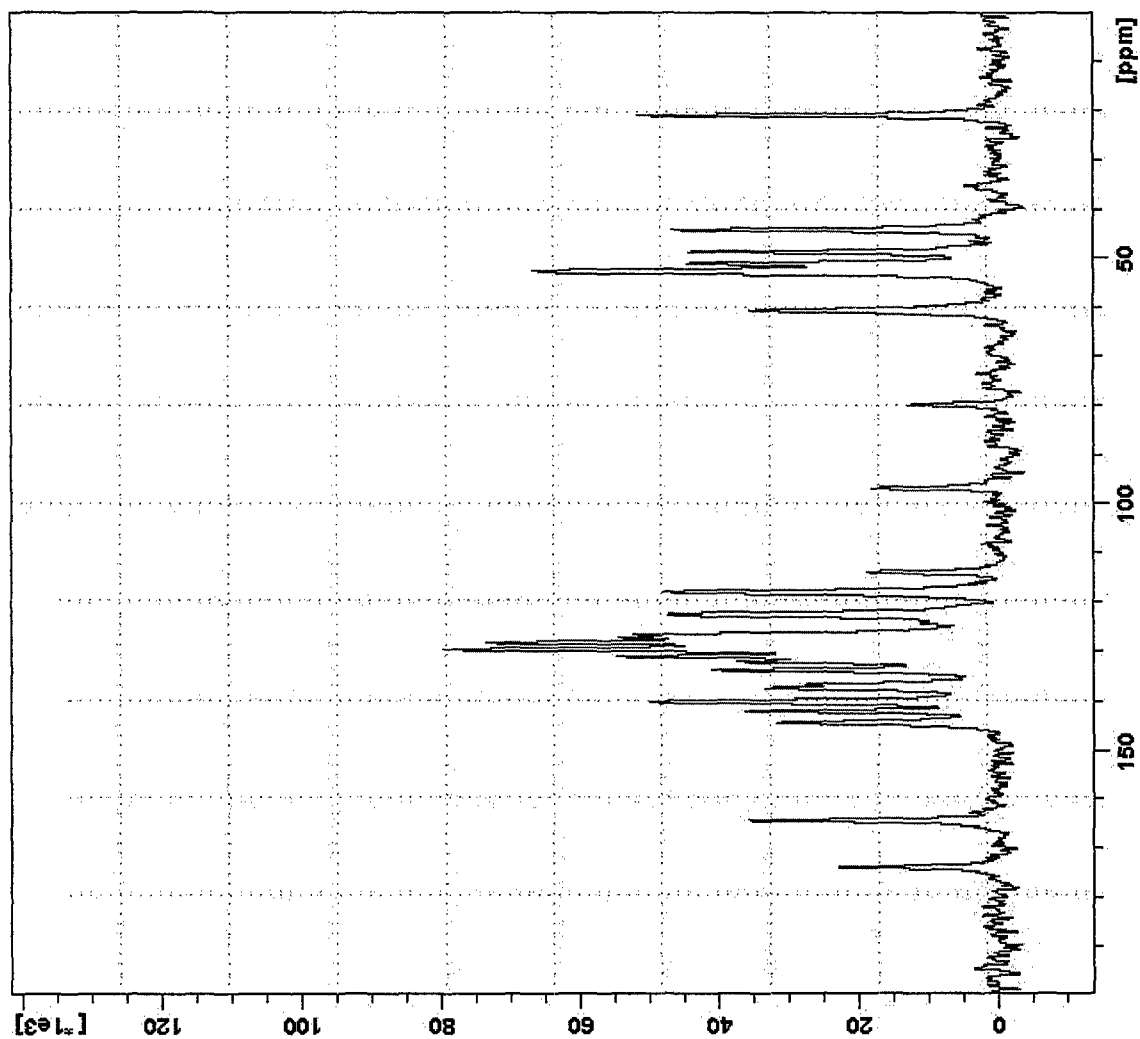


Figure 4 XRPD pattern of the salt of ponatinib and benzoic acid

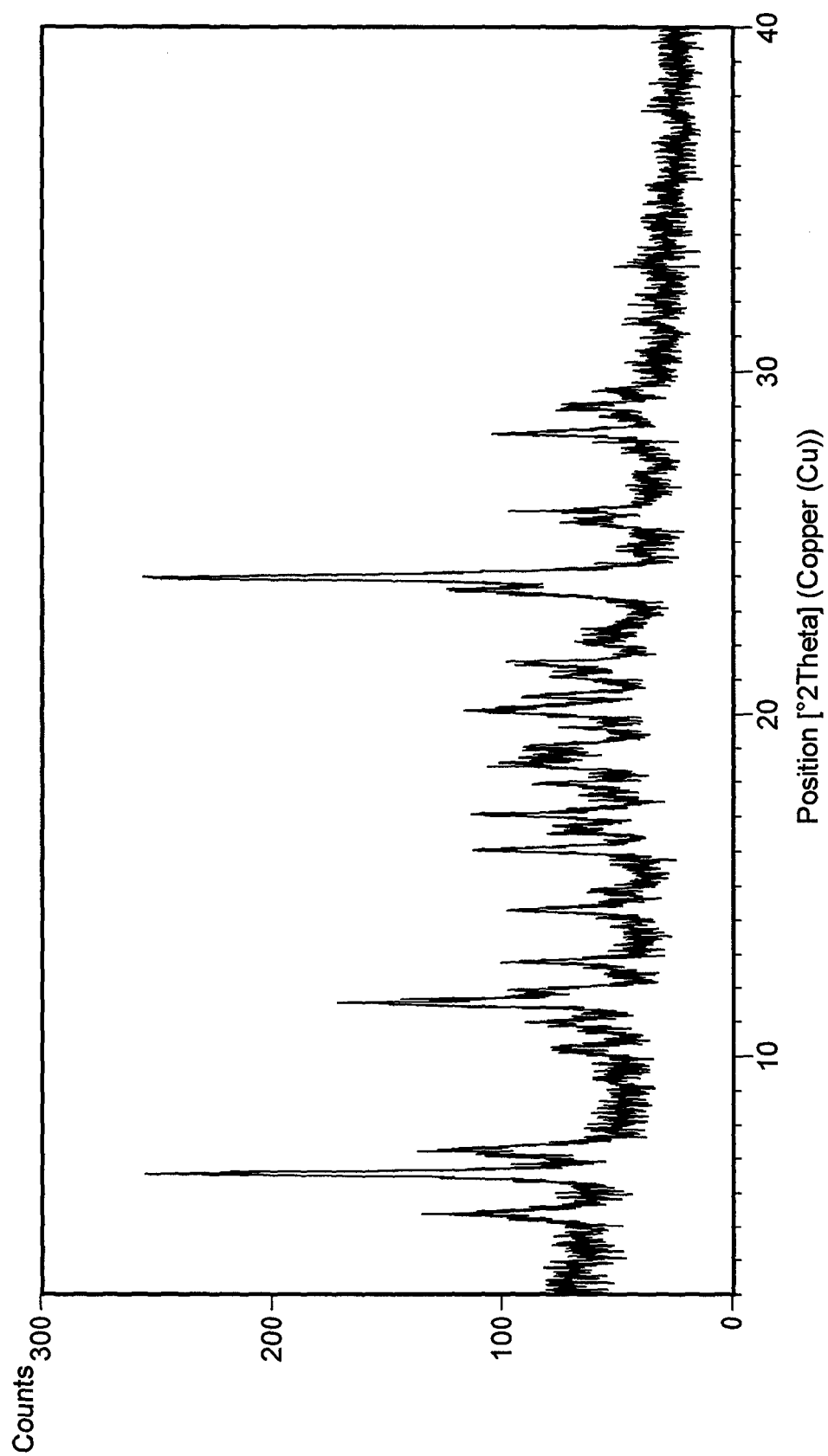
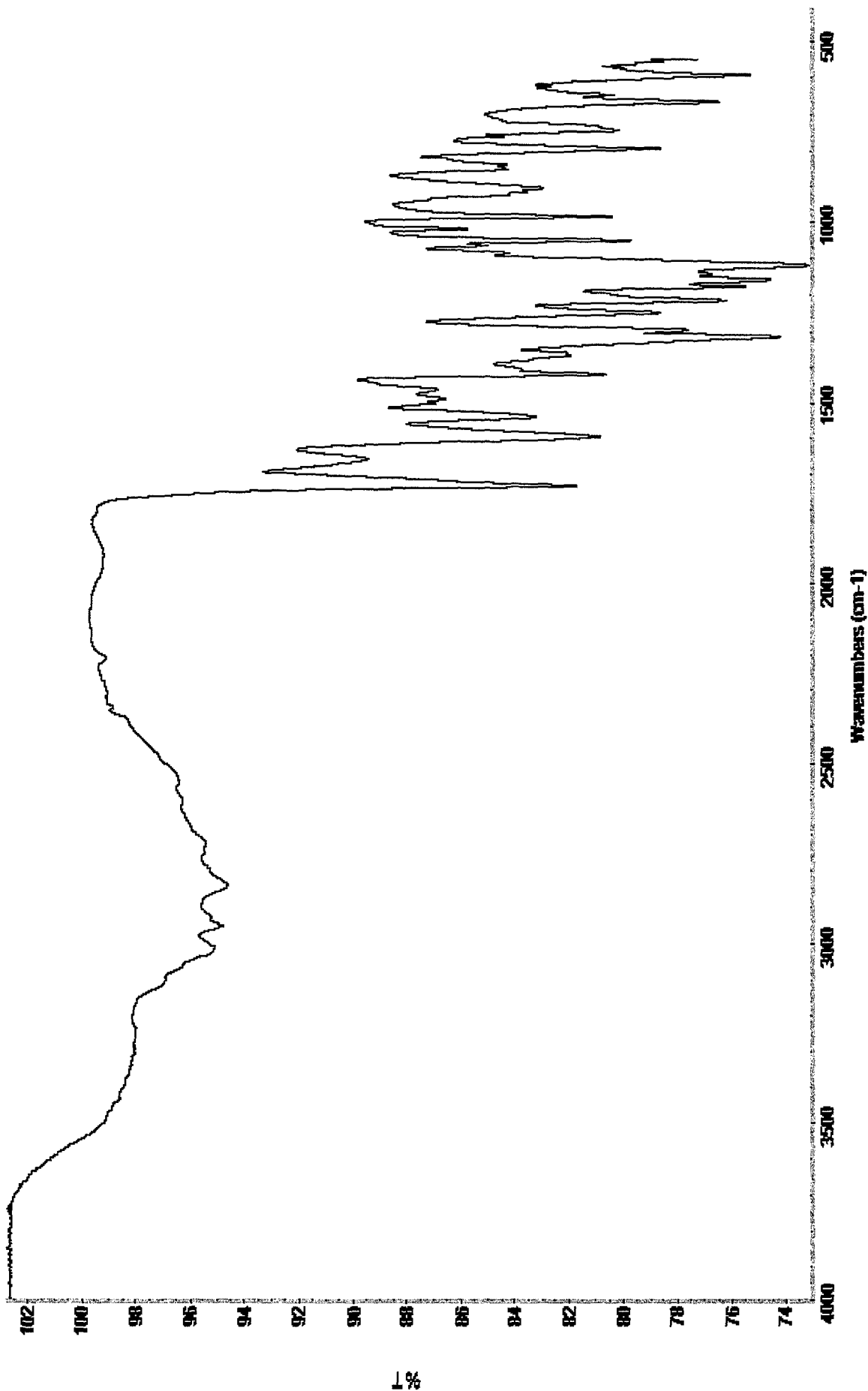


Figure 5 FTIR spectra of the salt of ponatinib and citric acid



ssNMR spectra the salt of ponatinib and citric acid

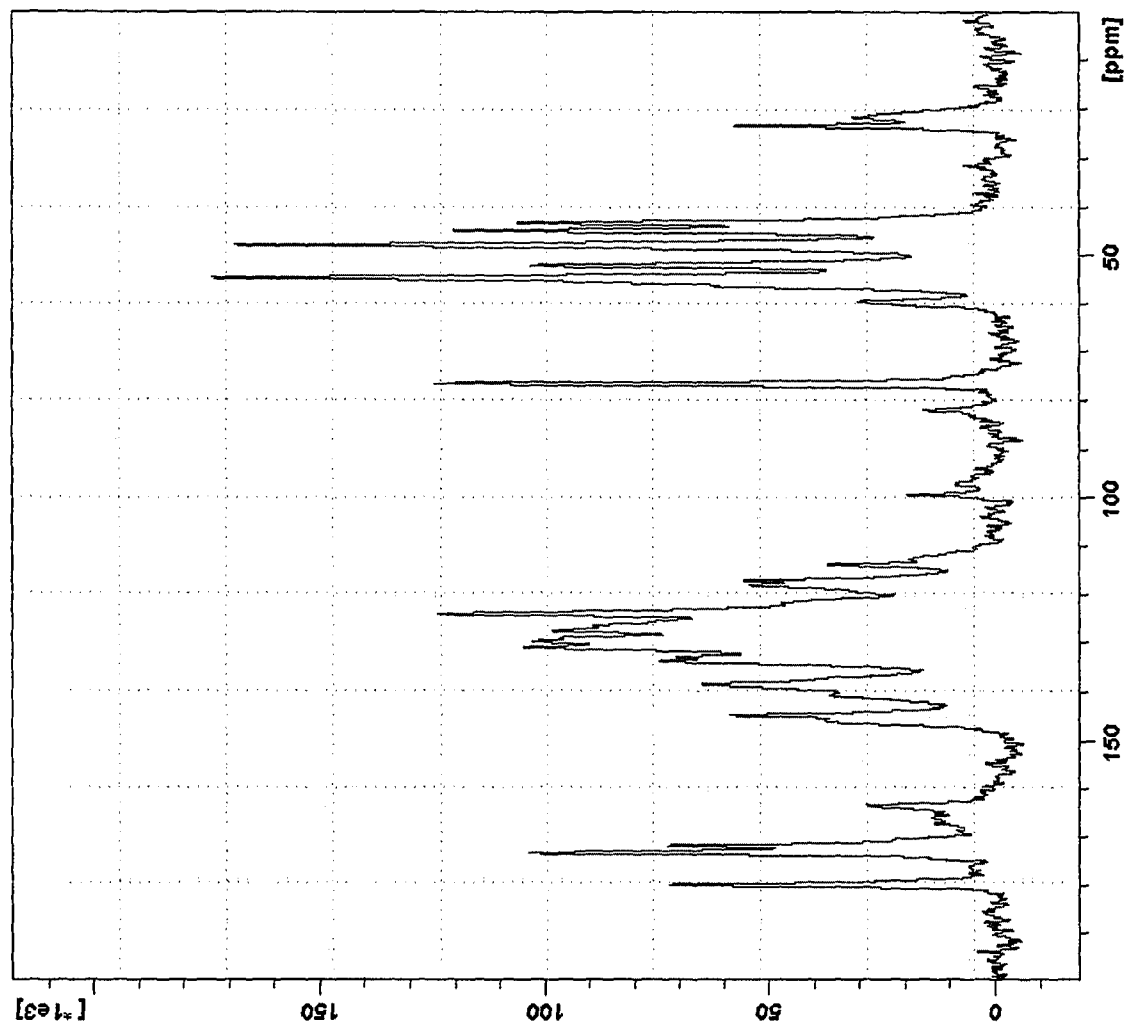


Figure 6

Figure 7 XRPD pattern of the salt of ponatinib and citric acid

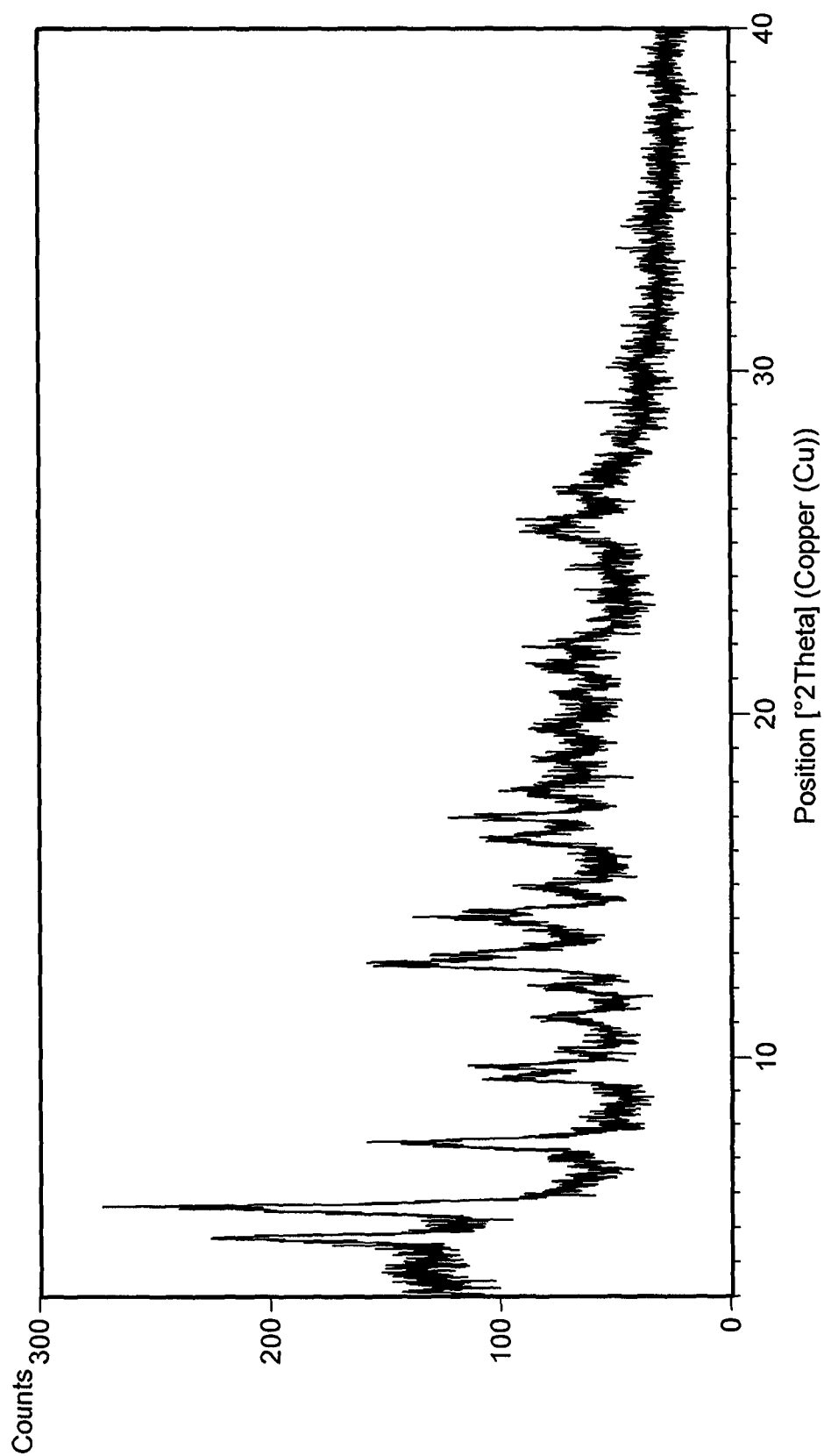


Figure 8 FTIR spectra of the salt of ponatinib and fumaric acid

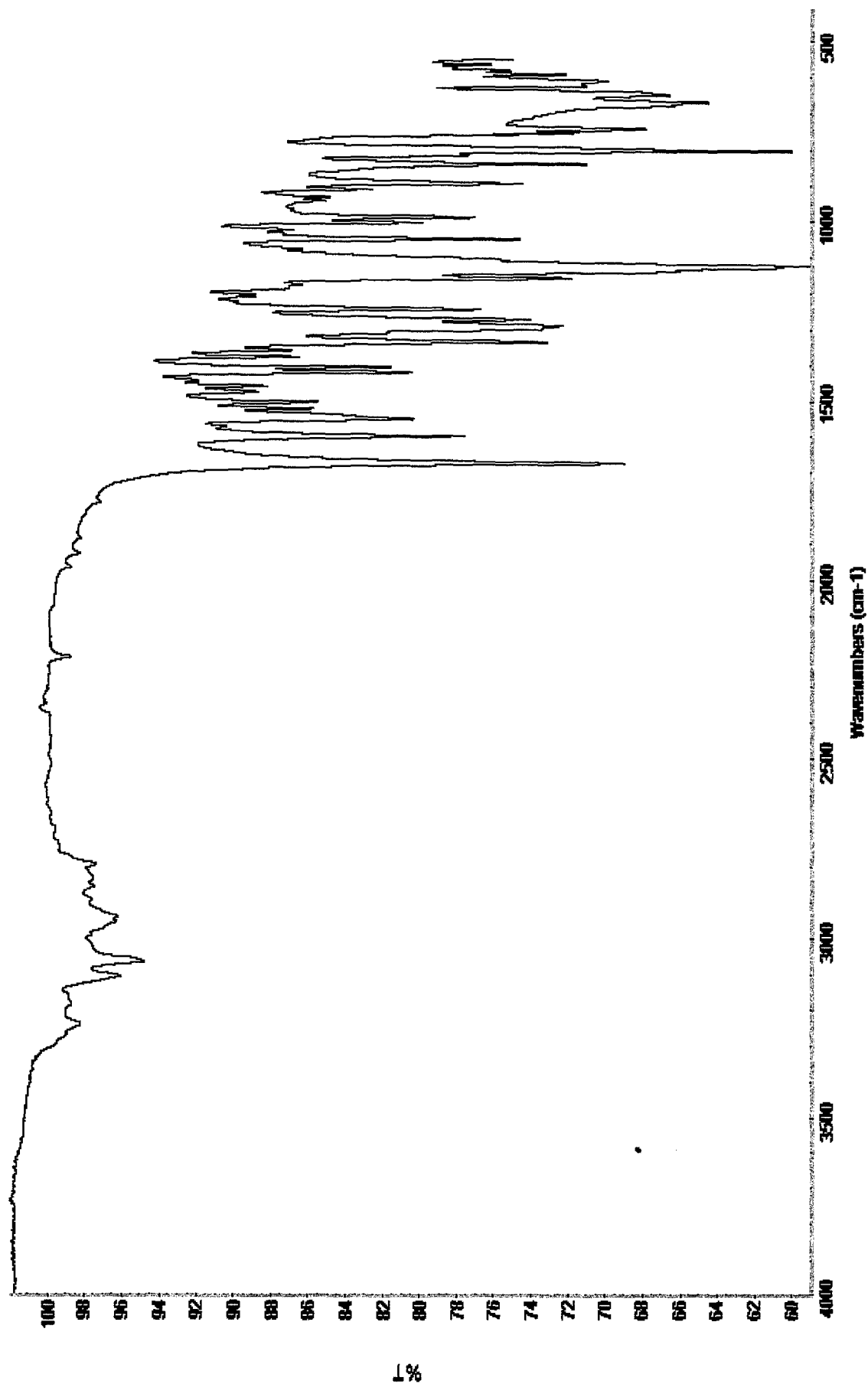


Figure 9 ¹H-NMR spectra the salt of ponatinib and fumaric acid

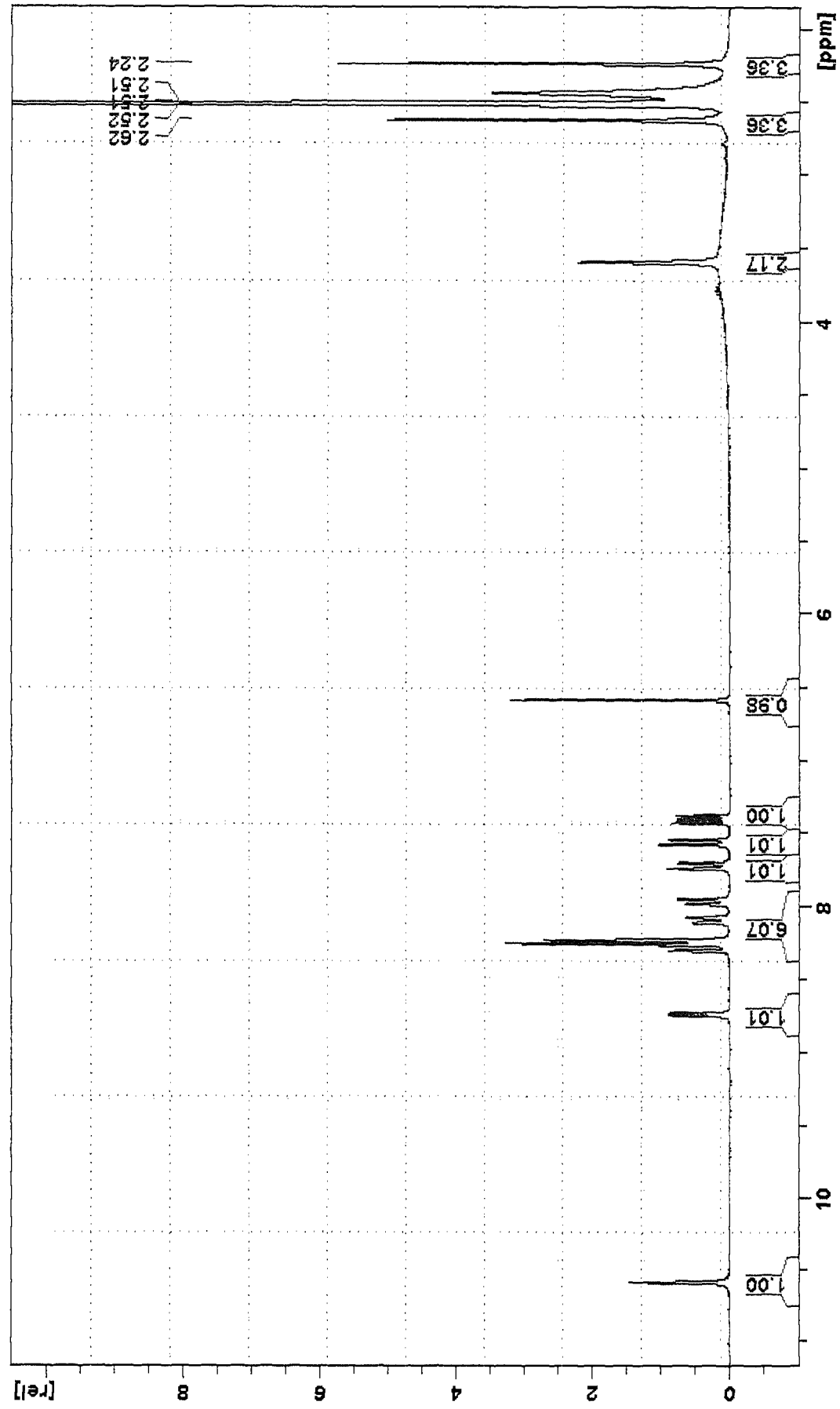


Figure 10 ssNMR spectra the salt of ponatinib and fumaric acid

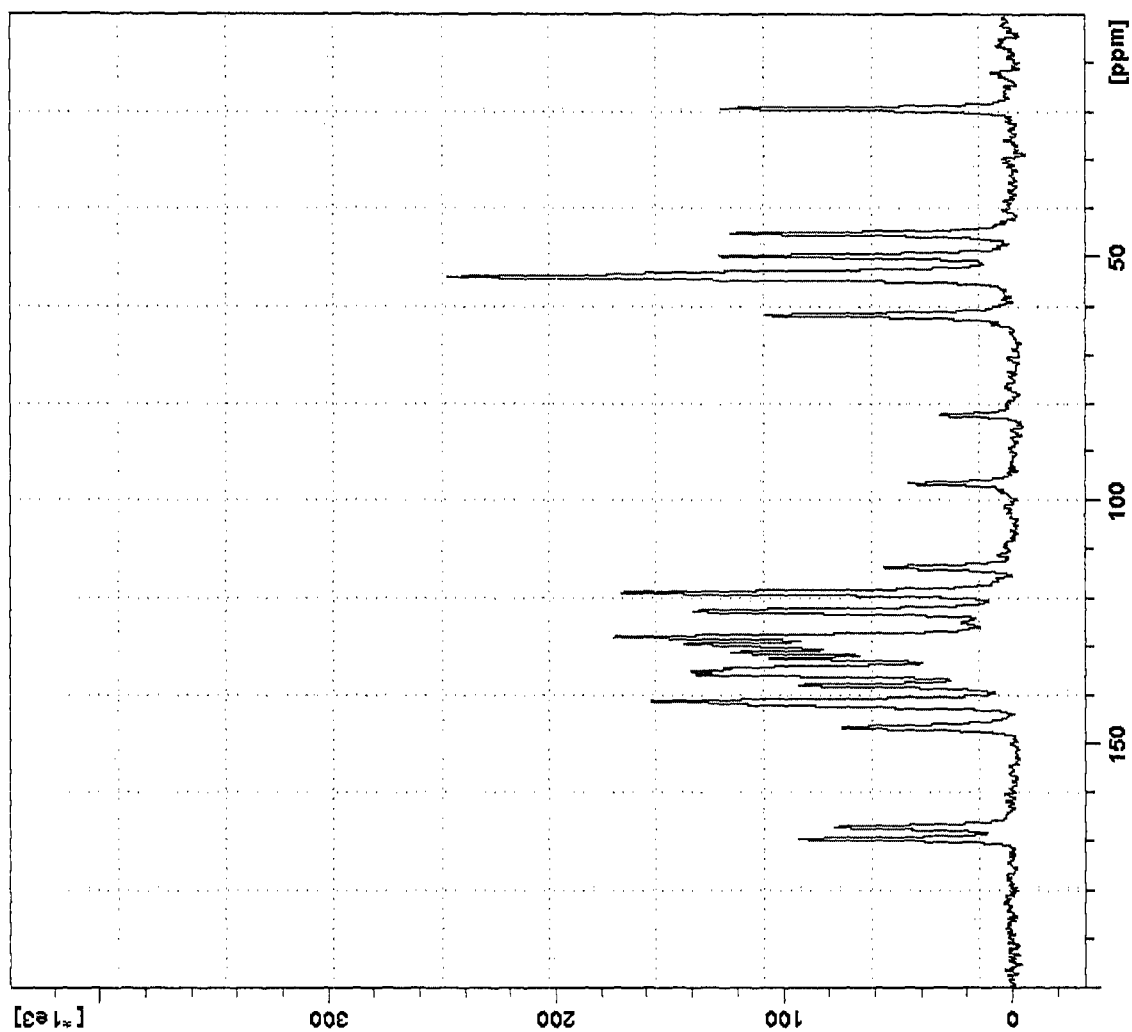


Figure 11 XRPD pattern of the salt of ponatinib and fumaric acid

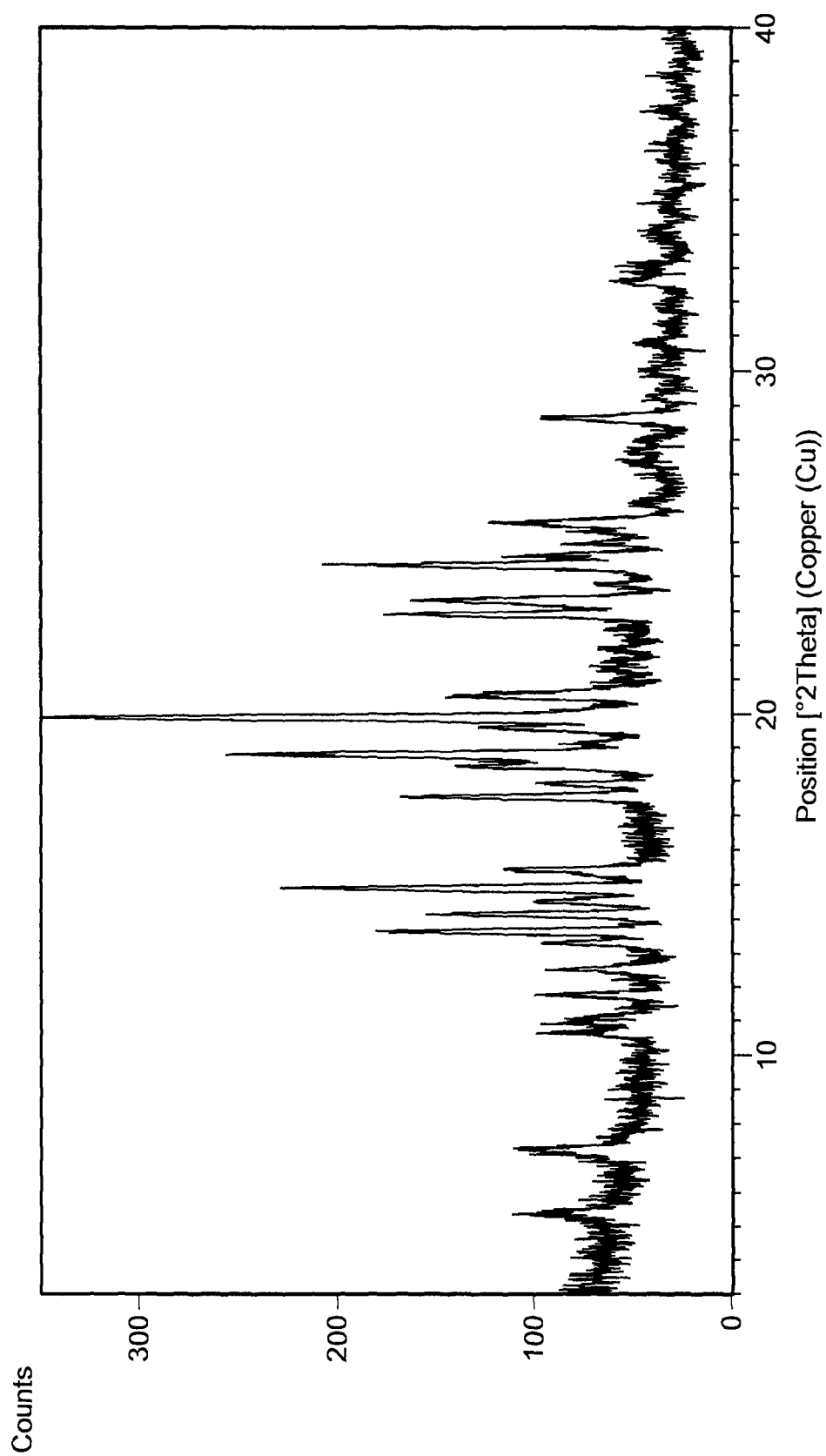


Figure 12 FTIR spectra of the salt of ponatinib and phosphoric acid

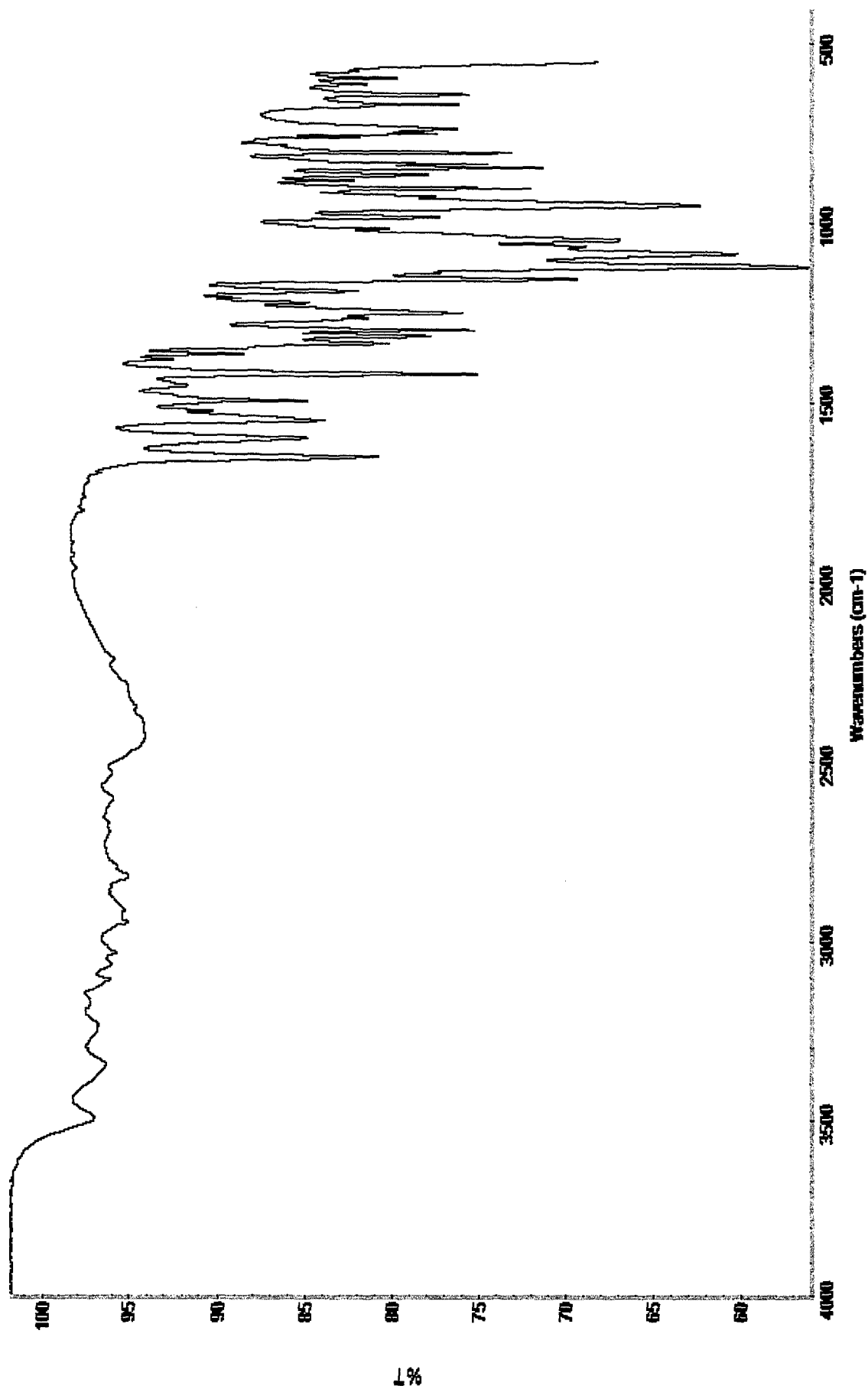


Figure 13 ssNMR spectra the salt of ponatinib and phosphoric acid

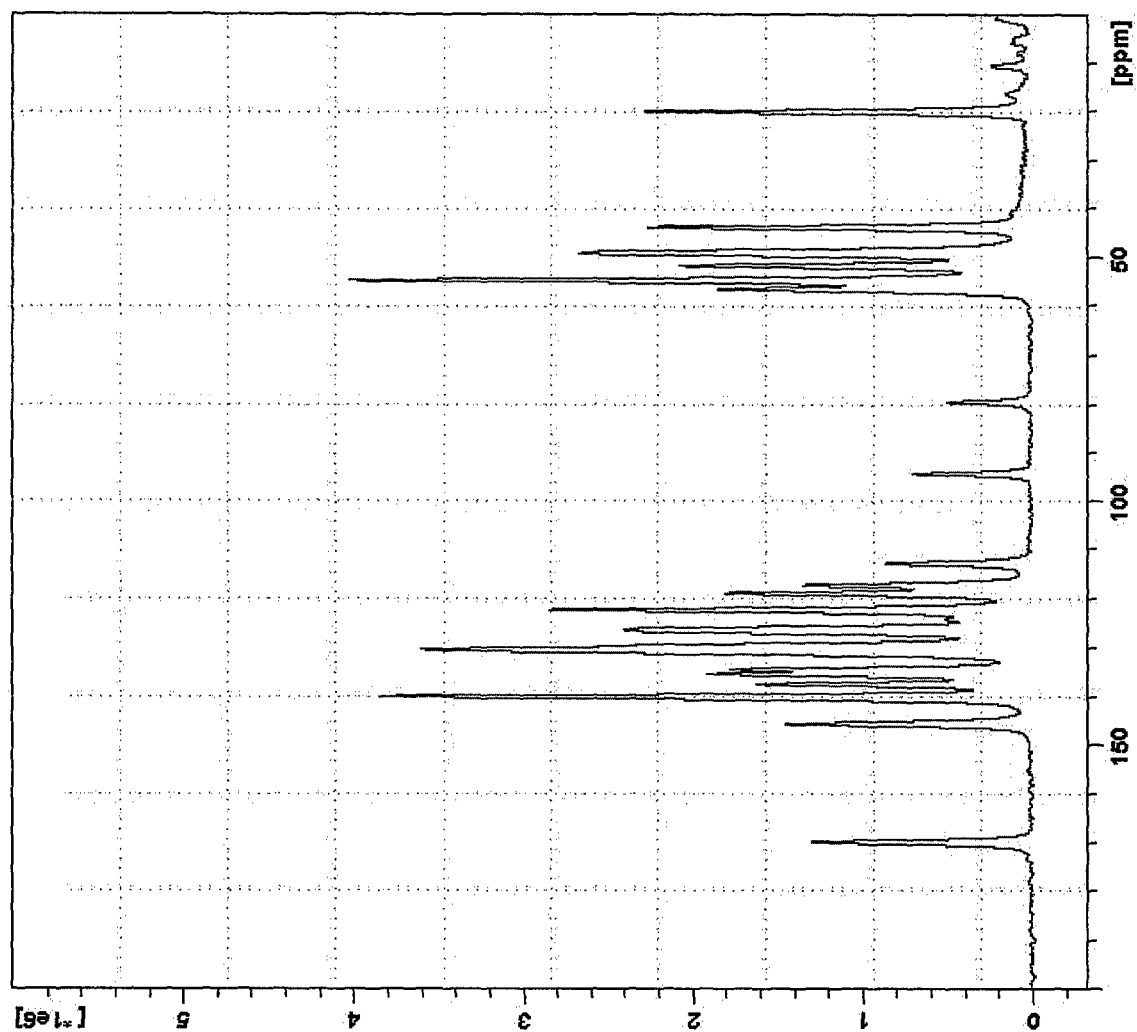


Figure 14 XRPD pattern of the salt of ponatinib and phosphoric acid

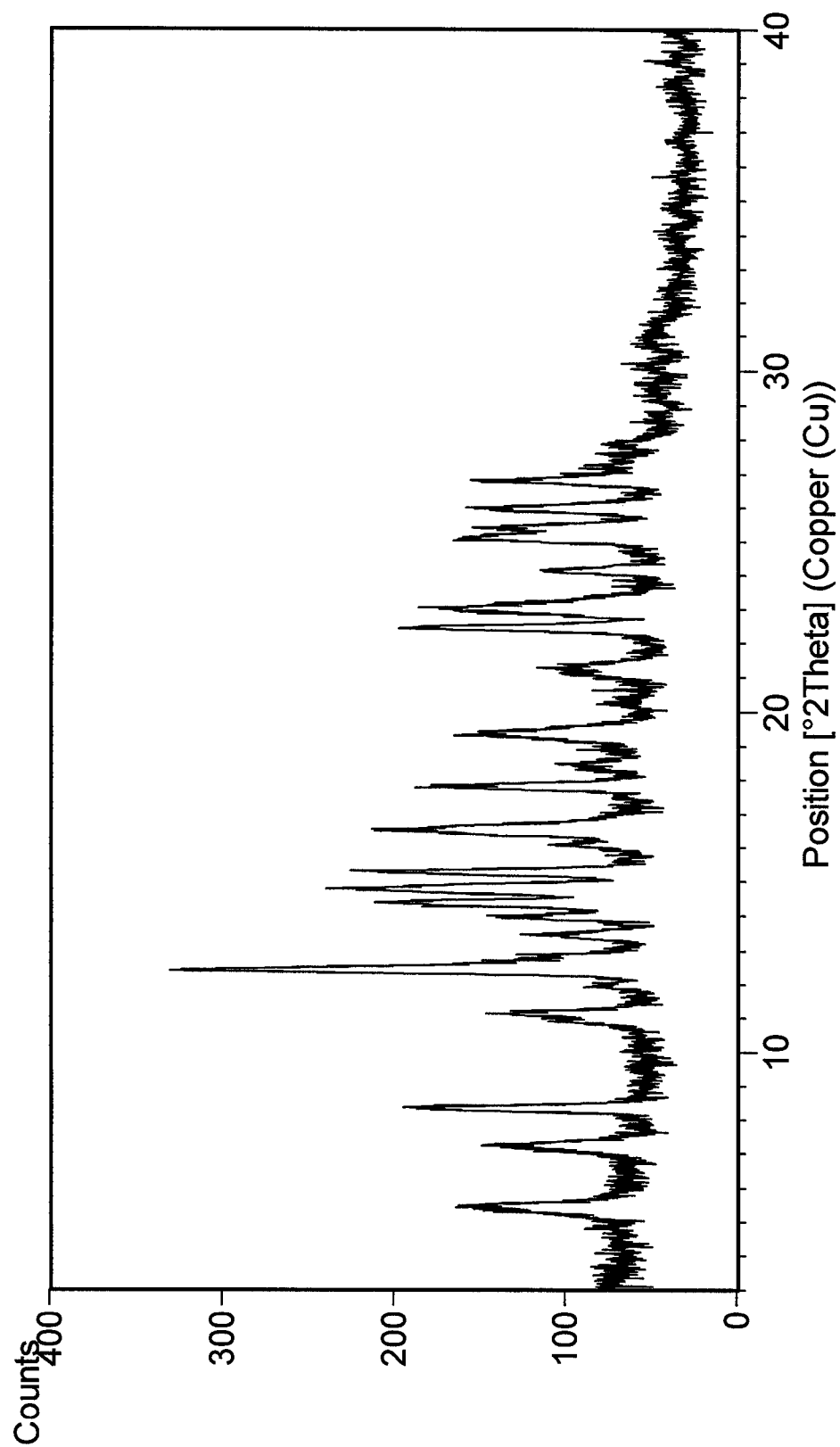


Figure 15 FTIR spectra of the salt of ponatinib and sulphuric acid

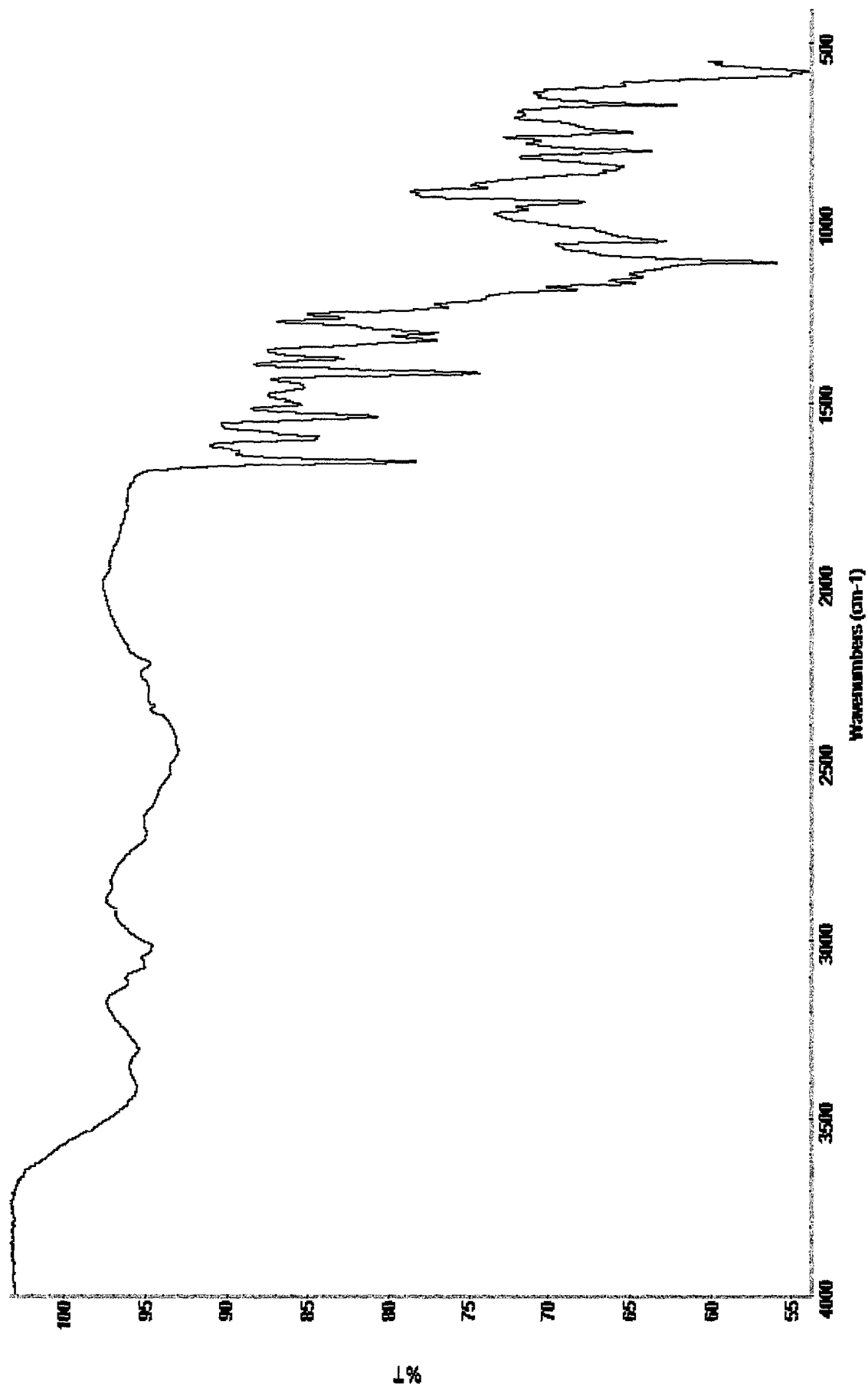


Figure 16 ssNMR spectra the salt of ponatinib and p sulphuric acid

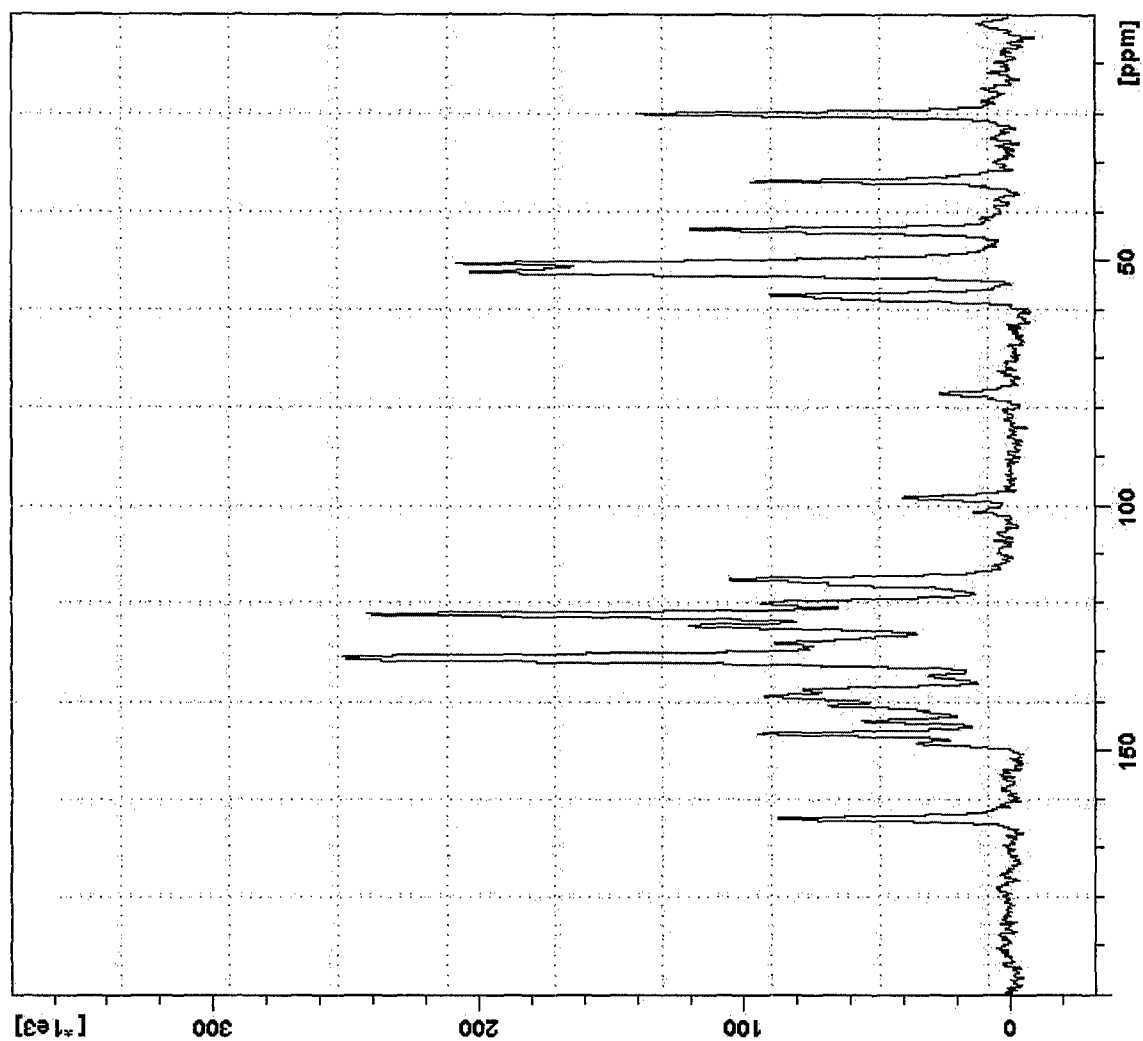
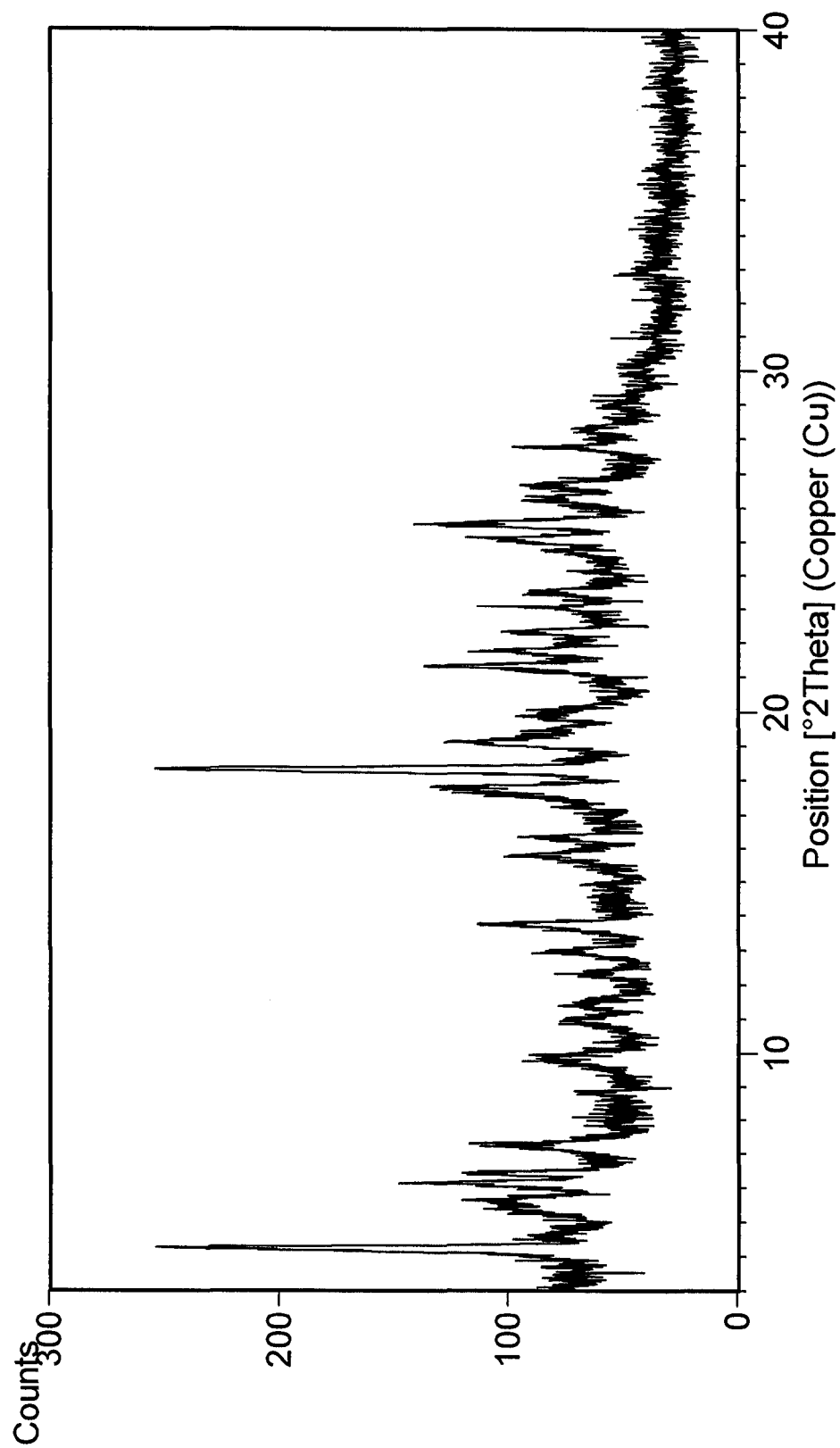


Figure 17 XRPD pattern of the salt of ponatinib and sulphuric acid



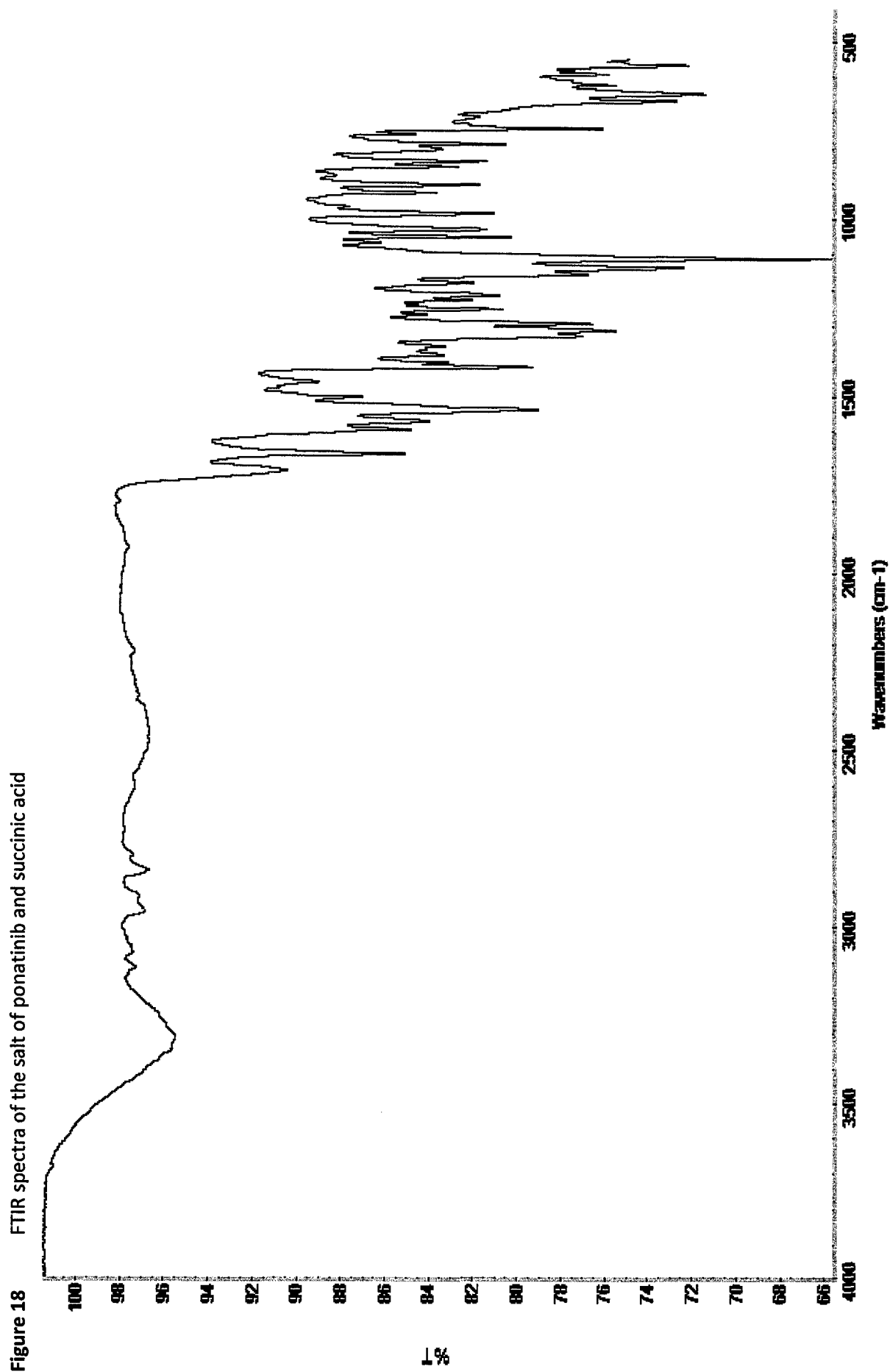


Figure 19 ssNMR spectra the salt of ponatinib and succinic acid

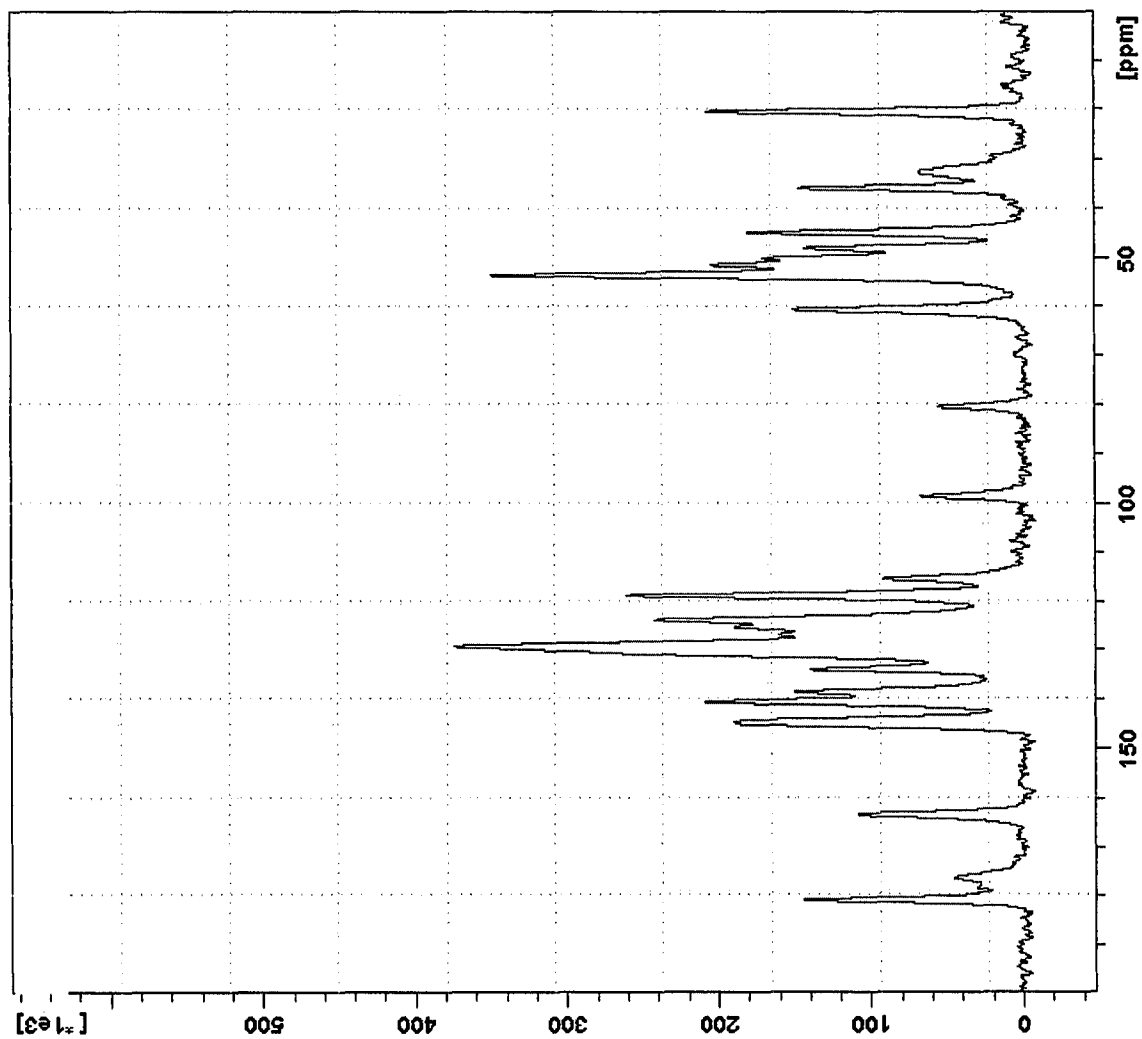
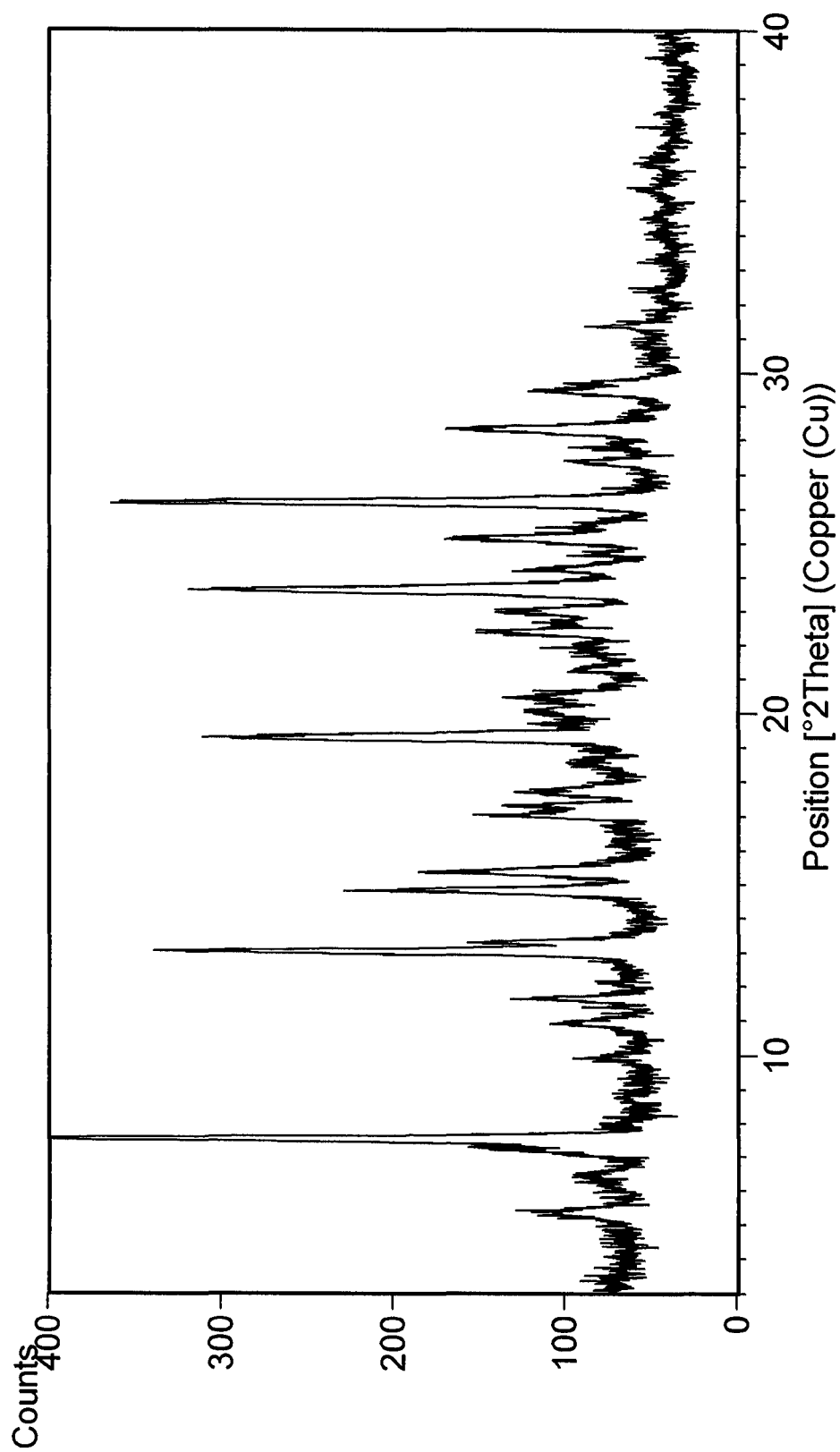


Figure 20 XRPD pattern of the salt of ponatinib and succinic acid



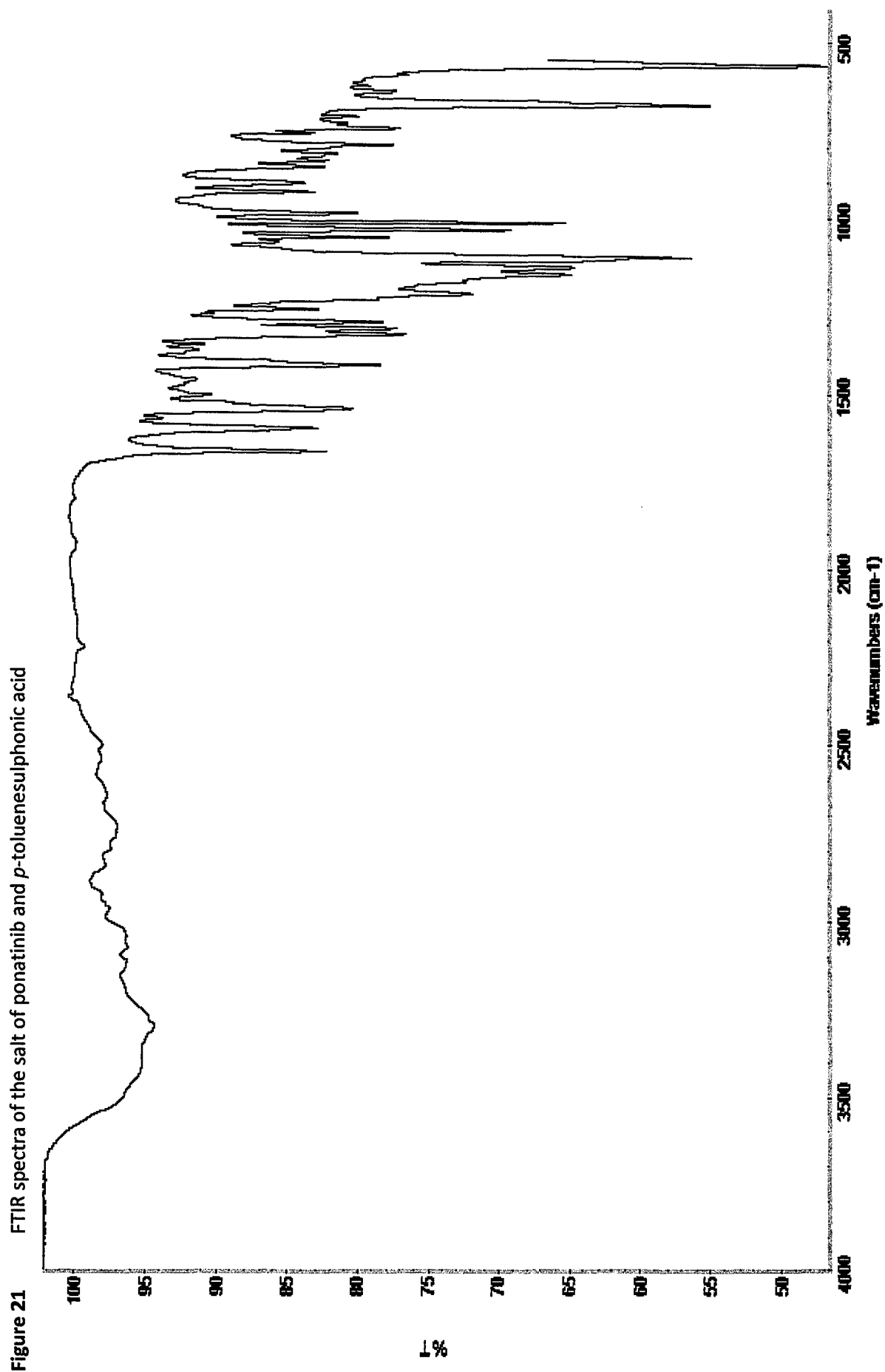


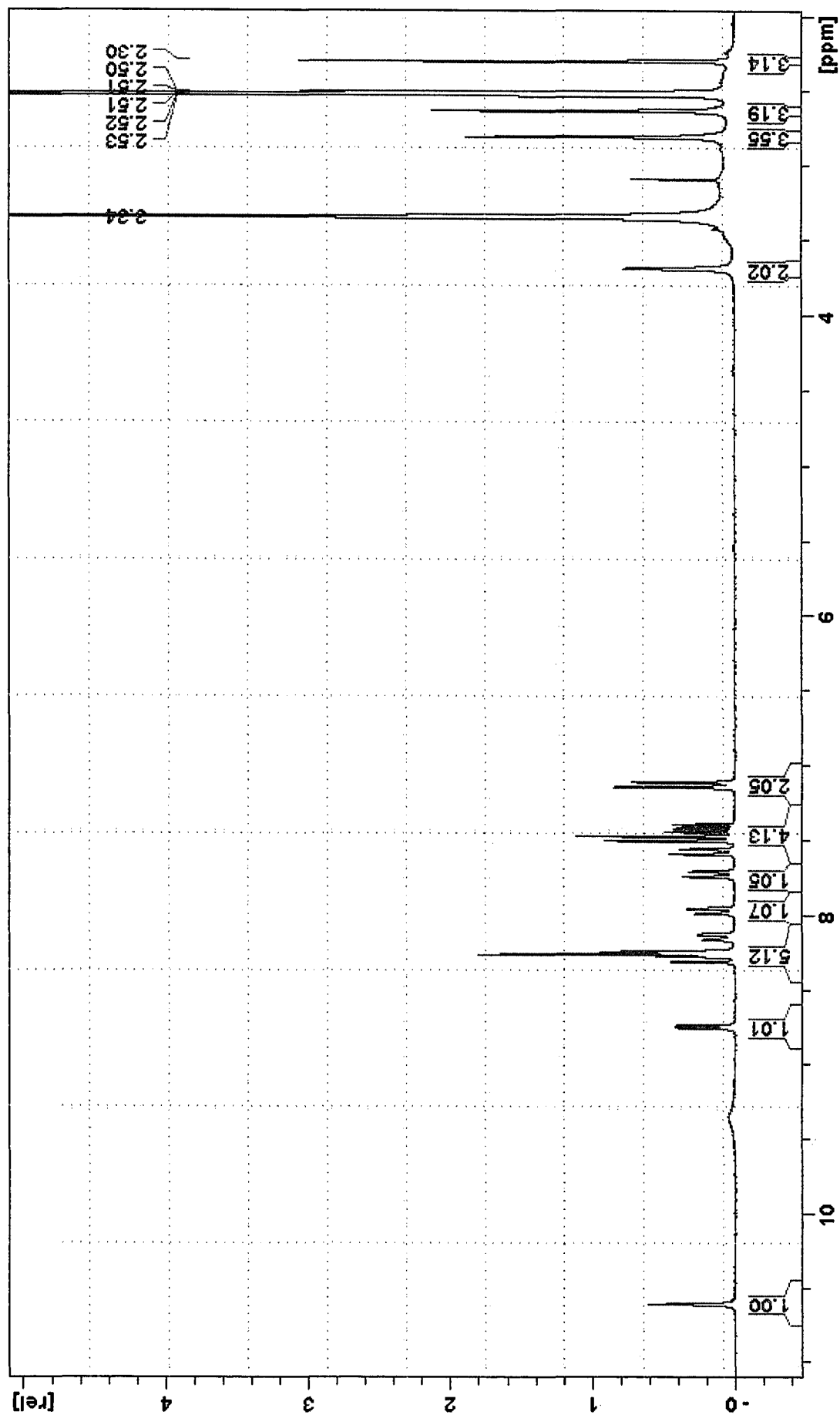
Figure 22 ^1H -NMR spectra the salt of ponatinib and *p*-toluenesulphonic acid

Figure 23 ssNMR spectra the salt of ponatinib and *p*-toluenesulphonic acid

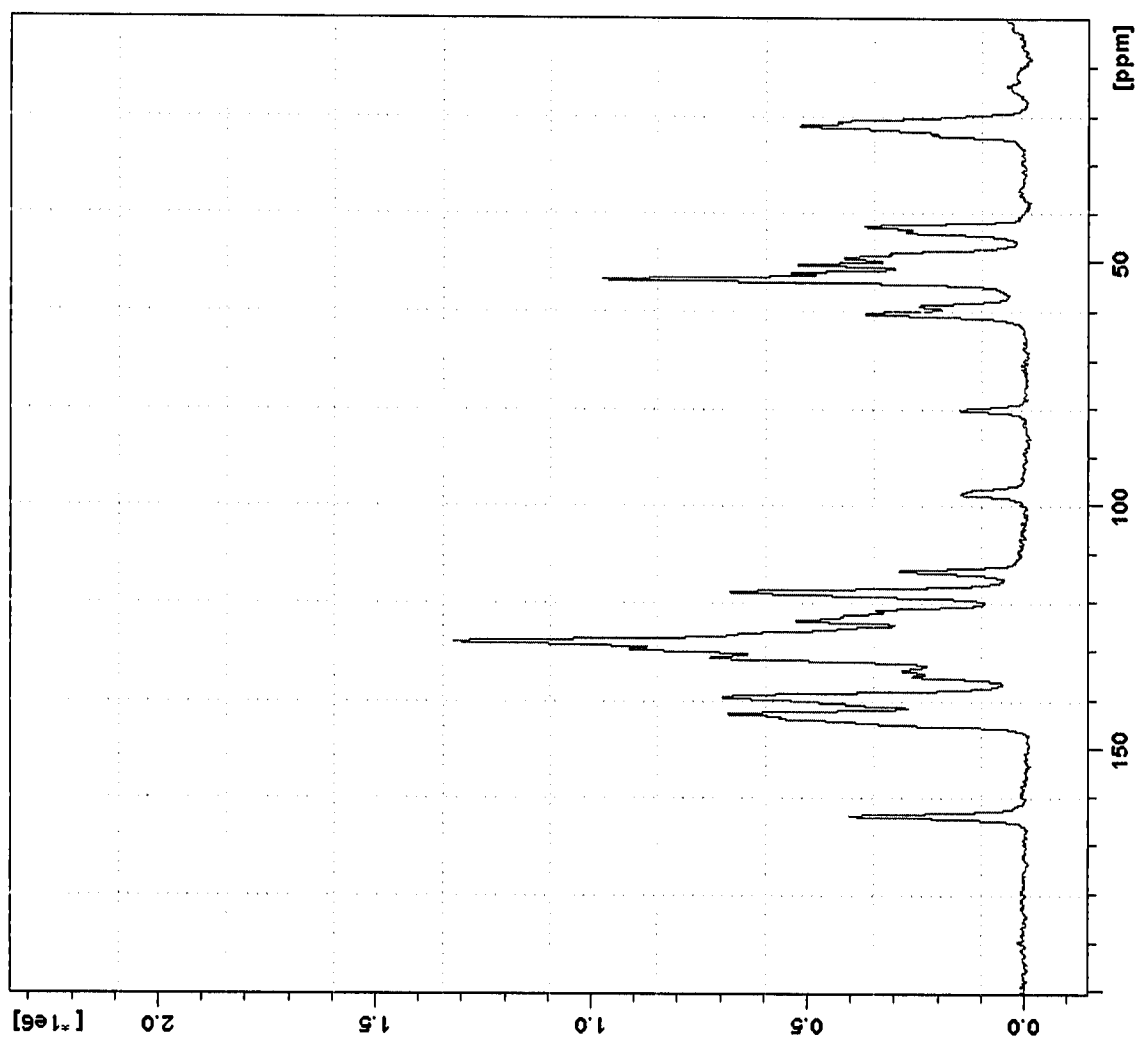


Figure 24 XRPD pattern of the salt of ponatinib and *p*-toluenesulphonic acid

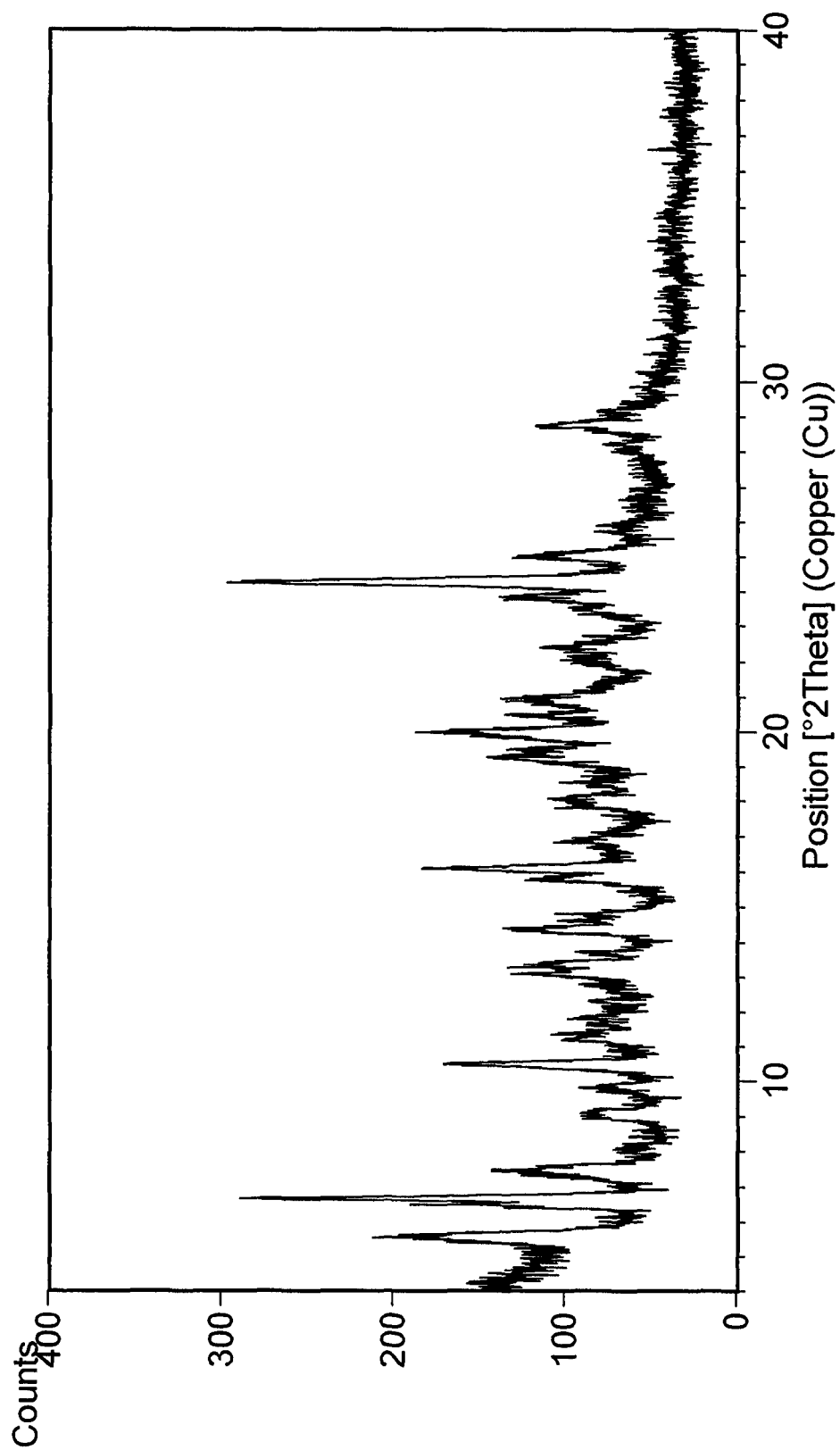


Figure 25 FTIR spectra of the salt of ponatinib and L-tartaric acid

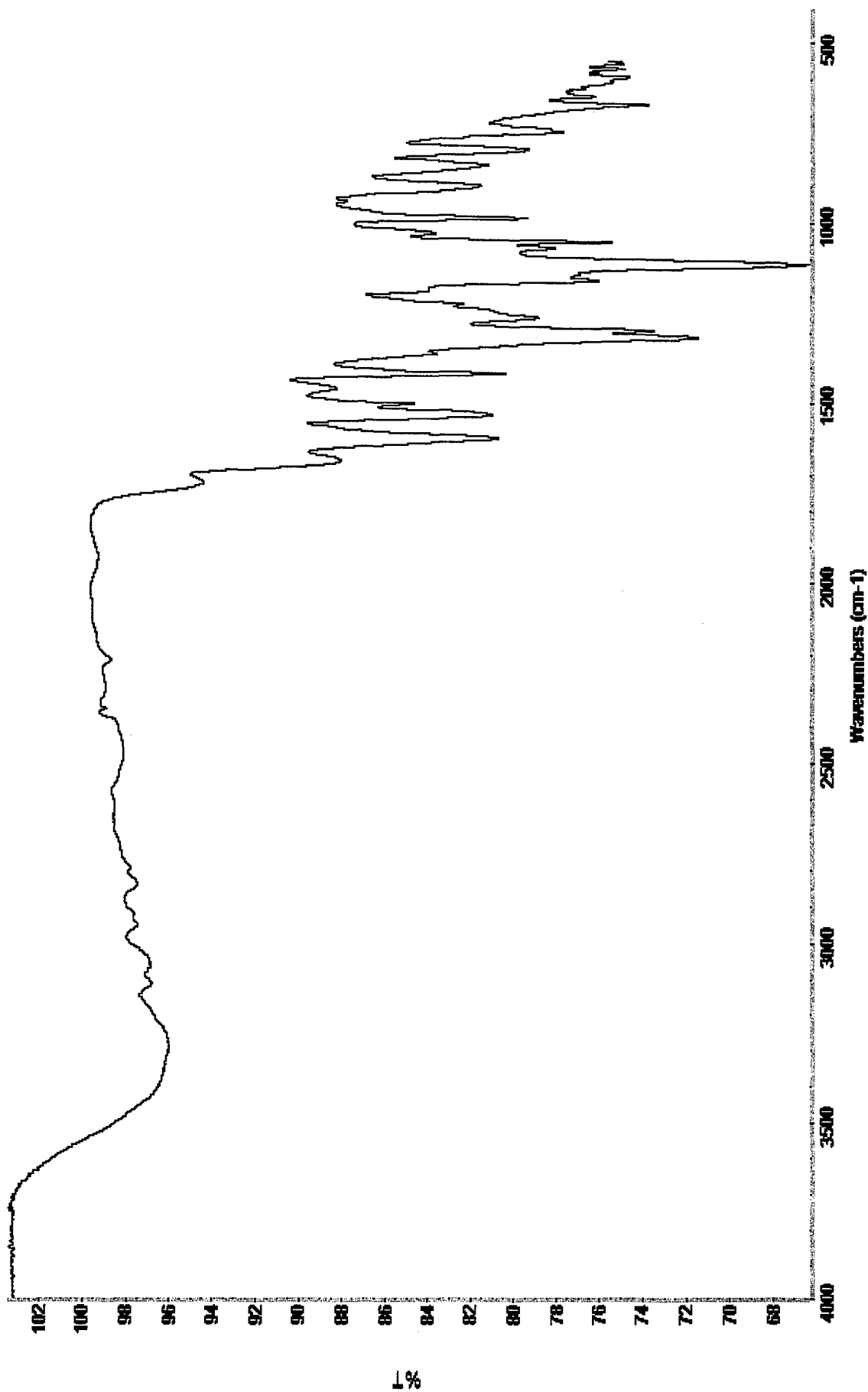


Figure 26 ssNMR spectra the salt of ponatinib and L-tartaric acid

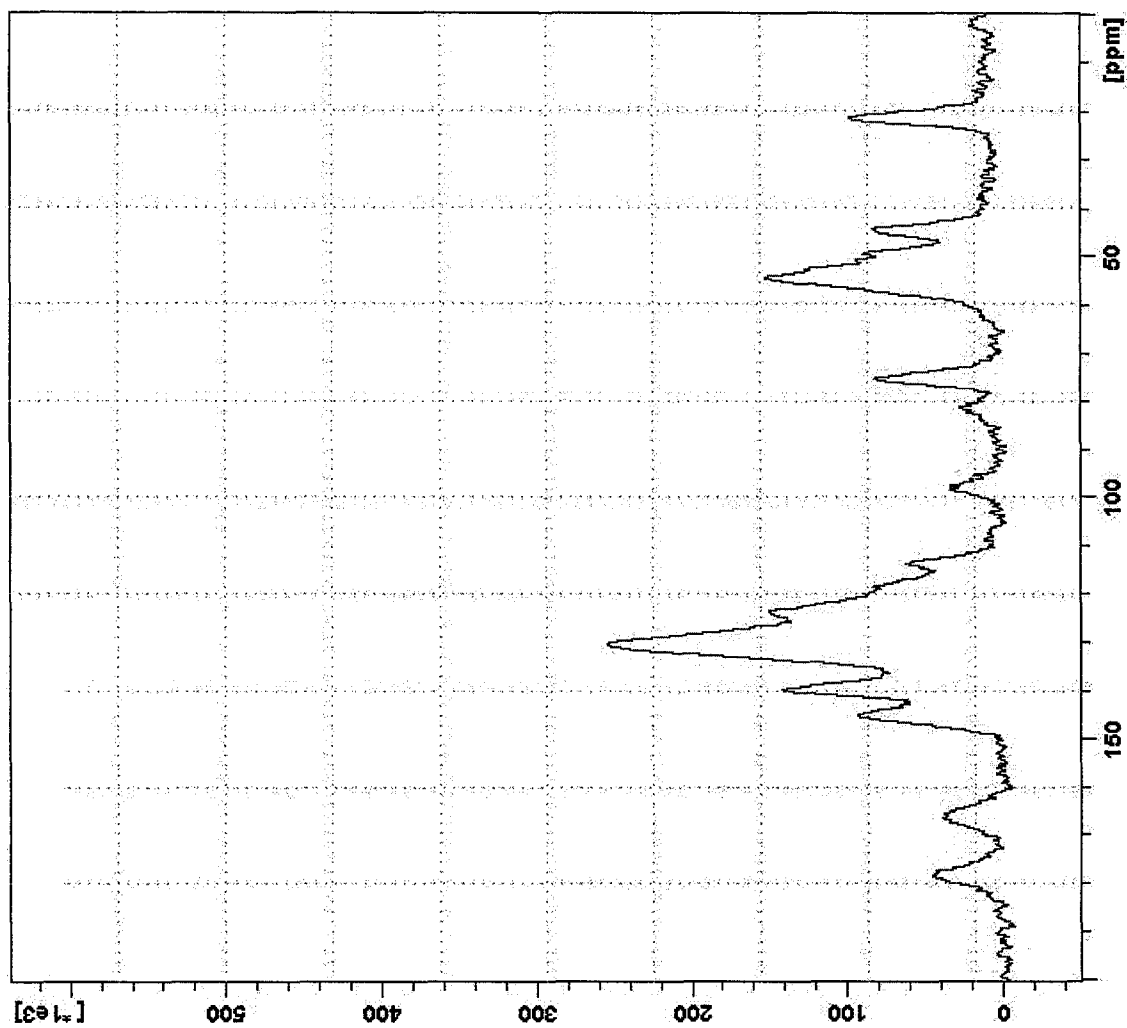
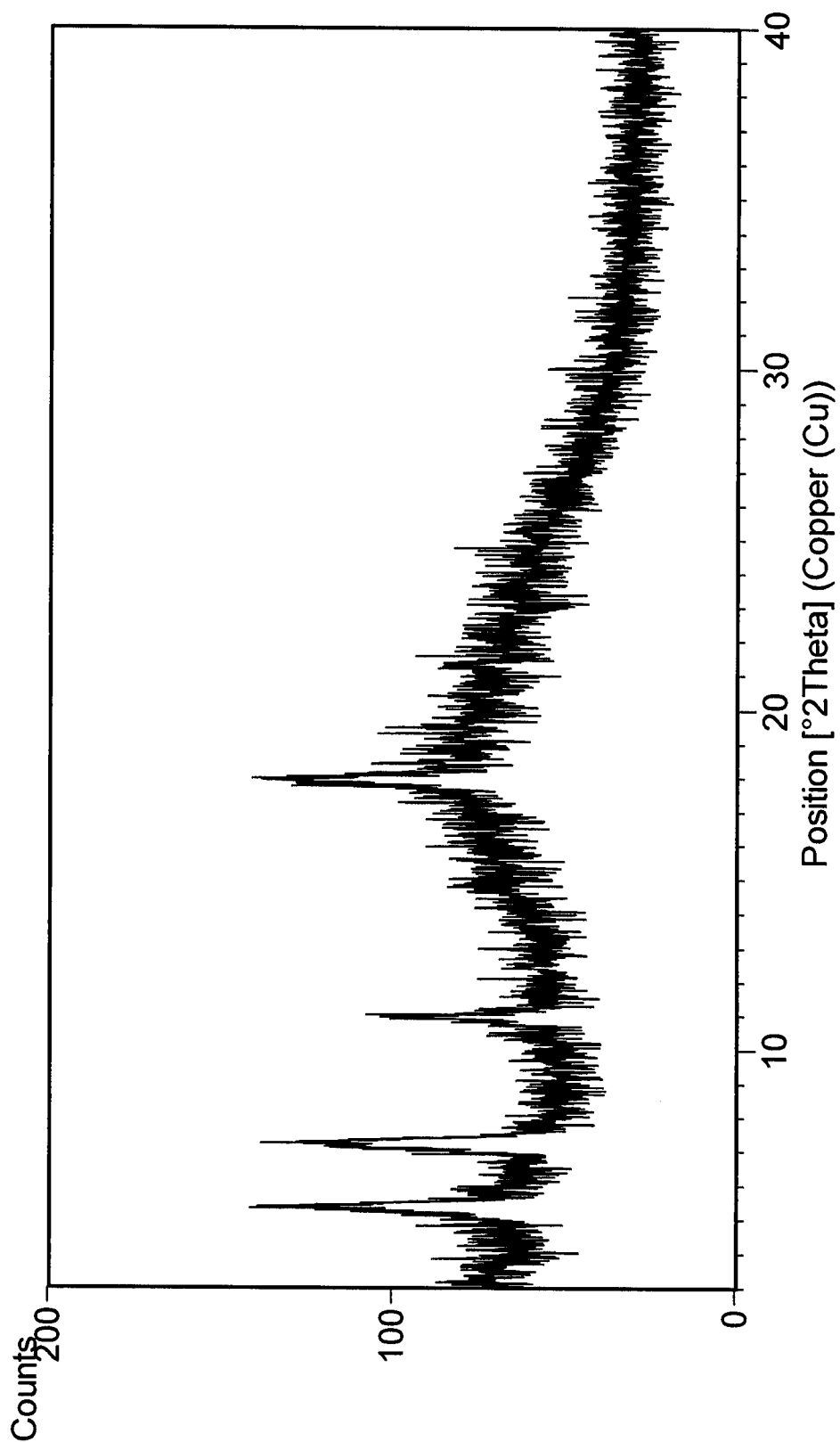


Figure 27 XRPD pattern of the salt of ponatinib and L-tartaric acid



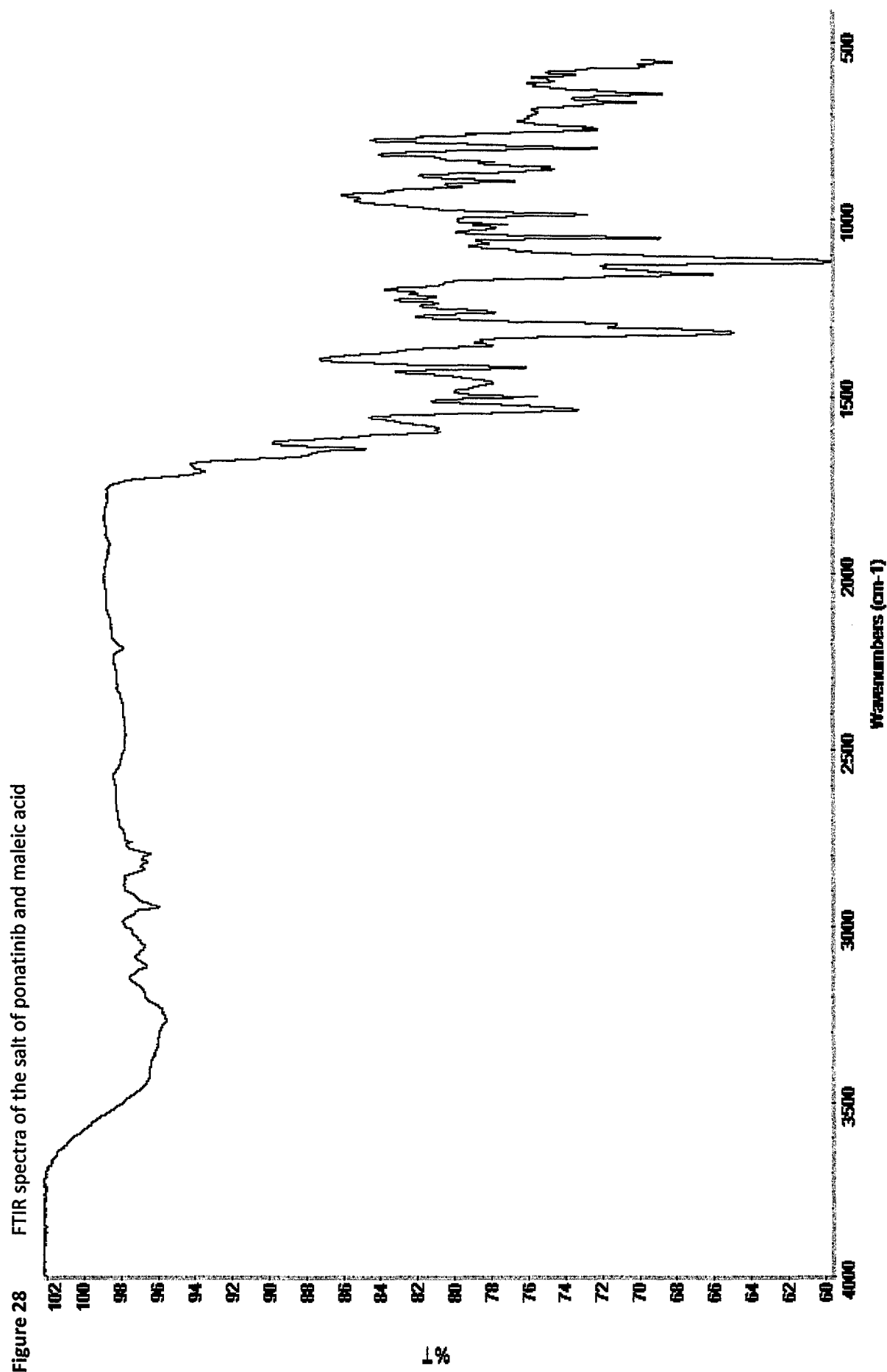


Figure 29 ssNMR spectra the salt of ponatinib and maleic acid

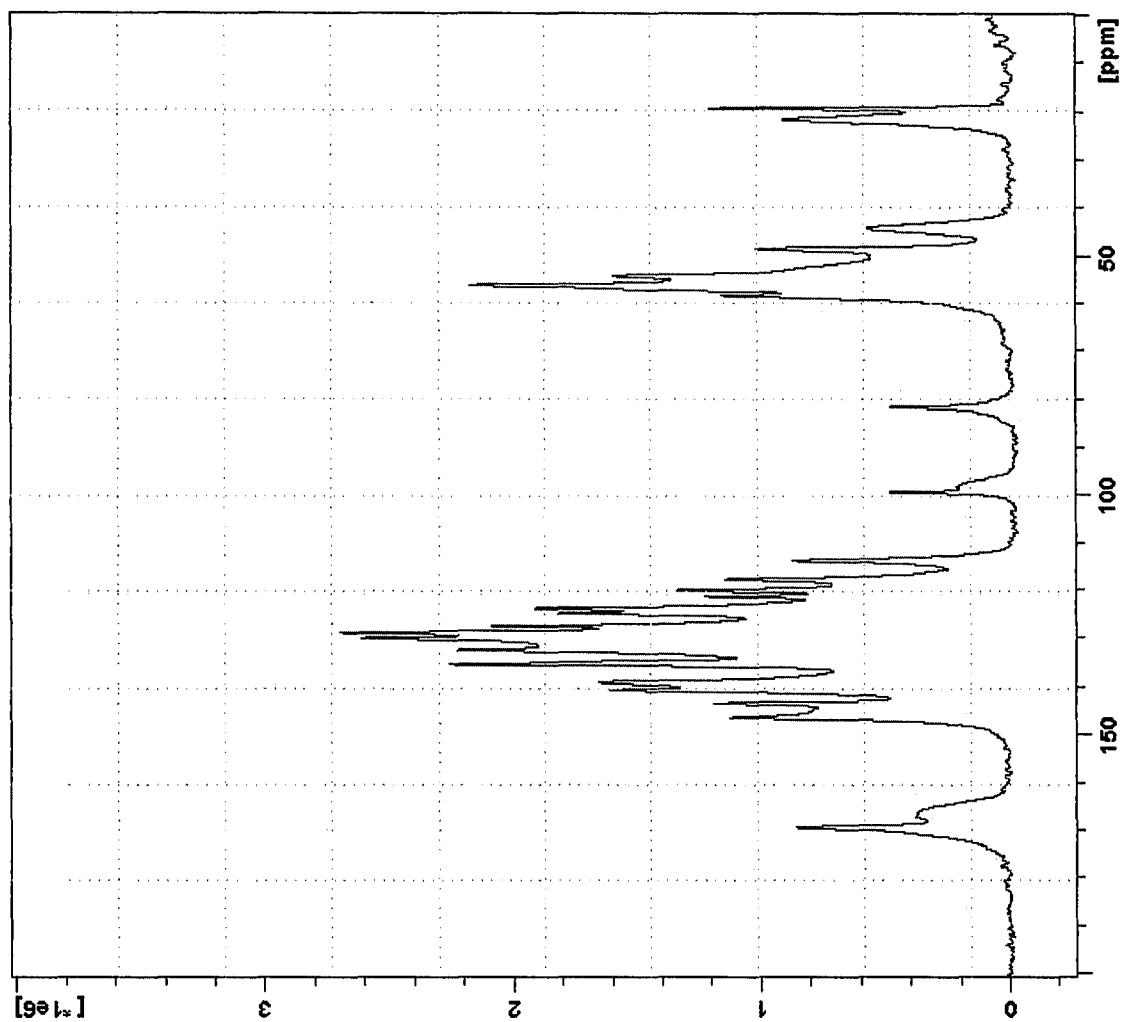
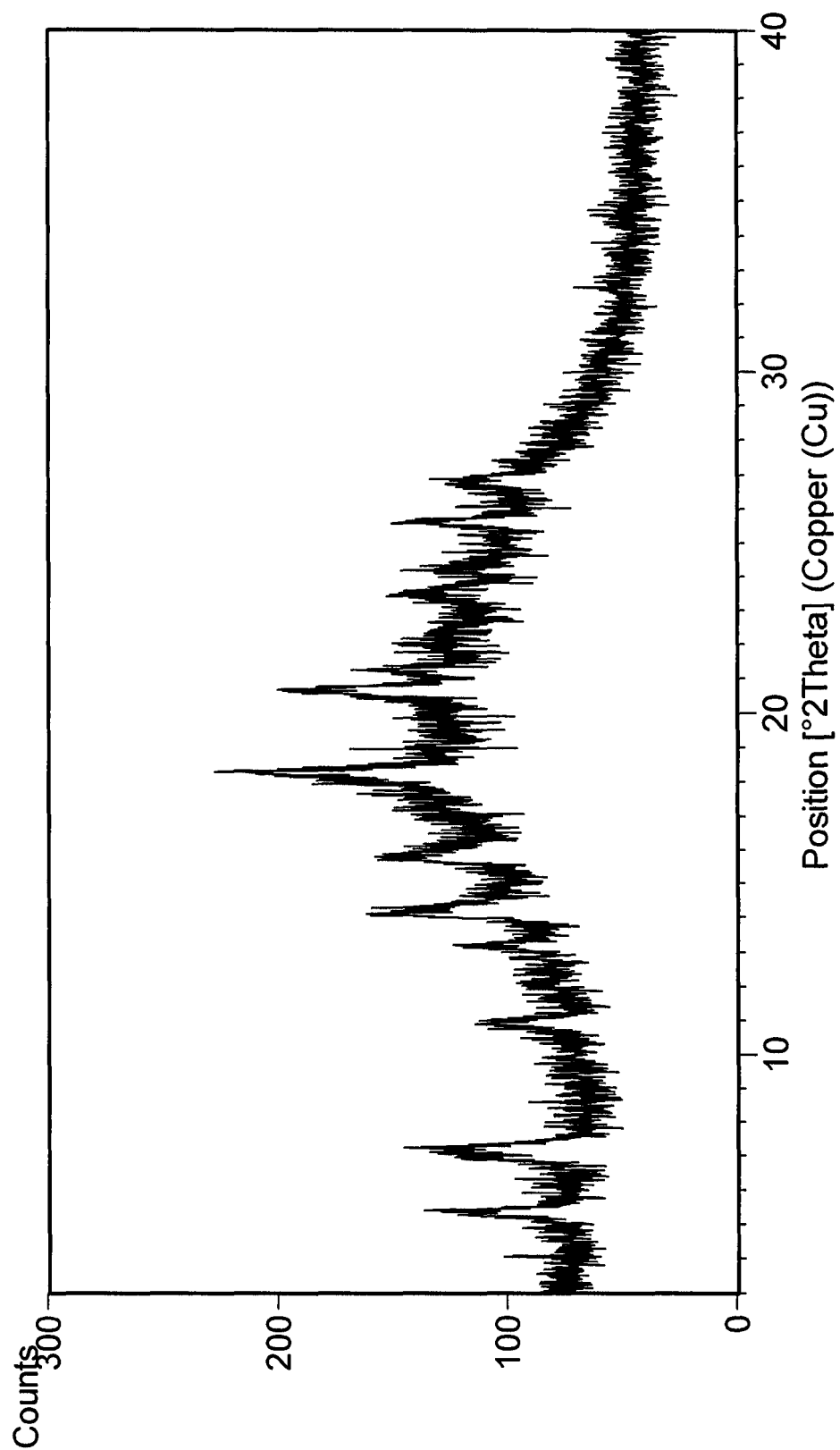


Figure 30 XRPD pattern of the salt of ponatinib and maleic acid



INTERNATIONAL SEARCH REPORT

International application No

PCT/CZ2013/000163

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/5025 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

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, 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 2011/053938 A1 (ARIAD PHARMA INC [US]; HUANG WEI-SHENG [US]; RIVER VICTOR M [US]; CLAC) 5 May 2011 (2011-05-05)	1,2,6-9, 12-15, 18-21, 24-27, 30-33, 36-39, 42-45, 48-51, 54-57
Y	the whole document, in particular the claims; page 1, lines 4-8; page 29, lines 8-15; scheme 1, step 6; page 44, line 1 - page 45, line 3 ----- -/--	1-59



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

19 March 2014

Date of mailing of the international search report

27/03/2014

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Authorized officer

Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000163

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 2007/075869 A2 (ARIAD PHARMACEUTICALS, INC.) 5 July 2007 (2007-07-05) cited in the application	1,2,6-9, 12-15, 18-21, 24-27, 30-33, 36-39, 42-45, 48-51, 54-57
Y	the whole document, in particular the claims; example 16; page 36 -----	1-59
A	HUANG WEI-SHENG ET AL: "Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-{ 4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 53, no. 12, 24 June 2010 (2010-06-24) , pages 4701-4719, XP002615777, ISSN: 0022-2623, DOI: 10.1021/JM100395Q [retrieved on 2010-06-01] the whole document for AP24534, i.e. compound 20g; tri-HCl salt thereof, see preparation of compound 24a on page 4717 -----	1-59

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/CZ2013/000163

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011053938	A1	05-05-2011	
		AU 2010313152 A1	19-04-2012
		CA 2777128 A1	05-05-2011
		CN 102770129 A	07-11-2012
		CR 20120202 A	12-06-2012
		EA 201290255 A1	30-04-2013
		EP 2493460 A1	05-09-2012
		JP 2013509444 A	14-03-2013
		KR 20120115237 A	17-10-2012
		US 2012316137 A1	13-12-2012
		US 2013178622 A1	11-07-2013
		WO 2011053938 A1	05-05-2011

WO 2007075869	A2	05-07-2007	
		AU 2006331673 A1	05-07-2007
		BR PI0621098 A2	02-04-2013
		CA 2634923 A1	05-07-2007
		CN 103044432 A	17-04-2013
		DK 1973545 T3	25-02-2013
		EA 200870116 A1	30-10-2009
		EP 1973545 A2	01-10-2008
		EP 2495016 A1	05-09-2012
		ES 2403206 T3	16-05-2013
		JP 5200939 B2	05-06-2013
		JP 2009521462 A	04-06-2009
		JP 2013064004 A	11-04-2013
		KR 20080081191 A	08-09-2008
		LU 92327 I2	05-02-2014
		PT 1973545 E	11-02-2013
		US 2007191376 A1	16-08-2007
		US 2012135986 A1	31-05-2012
		US 2013196979 A1	01-08-2013
		US 2013231337 A1	05-09-2013
		WO 2007075869 A2	05-07-2007
