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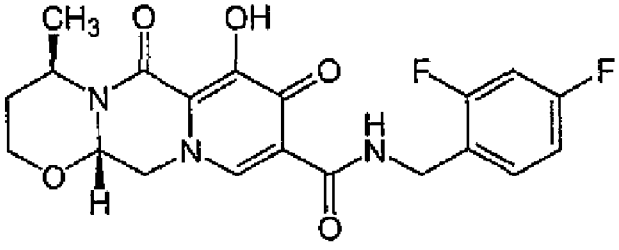
(54) Title: SOLID FORMS OF DOLUTEGRAVIR SALTS AND A METHOD OF THEIR PREPARATION



(I)

(57) Abstract: The invention relates to solid forms of salts of dolutegravir of formula I, (4*R*,12a*S*)-*N*-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide, a method of their preparation and their use in a dosage form. For example, solid forms of dolutegravir with amines (e.g.diethylamine, *N,N'*-dibenzylethylenediamine, meglumine, ethanolamine, diethanolamine, tromethamine, *tert*-butylamine), potassium, magnesium and calcium are well usable. These salts can be conveniently used to increase purity of dolutegravir and its stabilization in terms of chemical as well as polymorphic purity.

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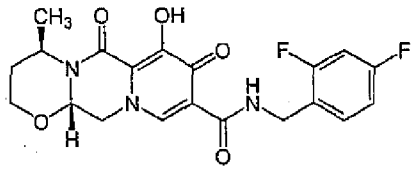
Solid forms of dolutegravir salts and a method of their preparation

Technical Field

The invention relates to new solid forms of salts of dolutegravir (**I**), (4*R*,12a*S*)-*N*-(2,4-difluorobenzyl)-7-hydroxy-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazine-9-carboxamide, a method of their preparation and their use in a dosage form. For example, solid forms of dolutegravir with amines (e.g. diethylamine, *N,N'*-dibenzylethylenediamine, meglumine, ethanolamine, diethanolamine, tromethamine, *tert*-butylamine), potassium, magnesium and calcium are well usable. These salts can be conveniently used to increase purity of dolutegravir and its stabilization in terms of chemical as well as polymorphic purity.



(**I**)

Dolutegravir is indicated, in combination with other retroviral medications, for the treatment of adult and adolescent patients over 12 years of age infected by the human immunodeficiency virus (HIV). Dolutegravir inhibits HIV integrase by binding to the active site of the integrase and by blocking the transfer processes of integration of retroviral deoxyribonucleic acid (DNA), which is important for the replication cycle of HIV.

Background Art

Dolutegravir has first been mentioned in the patent application WO2006116764, which does not mention any details of the character of the solid form of the product. On the other hand, the patent application WO2010068253 describes crystalline sodium salts of dolutegravir, the anhydrous salt and the monohydrate. There, these salts are characterized with the use XRPD and IR. The anhydrous sodium salt in a crystalline form is also included in the original medicinal product Tivicay. The last known solid form, i.e. the amorphous sodium salt of dolutegravir, is described in the patent application WO2013038407, using the XRPD, DSC,

TGA, IR and Raman spectroscopy methods. Preparation of other salts has not been published yet.

Disclosure of Invention

Dolutegravir very readily forms salts with amines, e.g. with diethylamine, *N,N'*-dibenzylethylenediamine, meglumine, tromethamine, ethanolamine, diethanolamine, *tert*-butylamine and amino acids. The amine binds to dolutegravir in the molar ratio of the amine to dolutegravir of 2:1 to 1:4, however ideally in the molar ratios of 1:1 or 1:2. Further, the potassium, magnesium and calcium salts of dolutegravir have been prepared, which can be further used for the development and production of a particular dosage form and a particular medicinal product.

Detailed description of the invention

Dolutegravir forms salts with aliphatic and aromatic amines as well as potassium, magnesium and calcium salts. Useful salts with amines may include diethylamine, *N,N'*-dibenzylethylenediamine, meglumine, tromethamine, ethanolamine, diethanolamine, *tert*-butylamine and the whole group of amino acids. Advantages of the salts of dolutegravir with amines consist in their easy preparation and high proneness to crystallization. Dolutegravir very readily forms salts with amines and the resulting salts have, unlike the magnesium or calcium salt, a crystalline character.

The benefits of using the salts of dolutegravir with amines consist in the possibility to increase the chemical purity during crystallization and possible re-crystallizations. Thus, dolutegravir gets stabilized in terms of chemical as well as polymorphic purity. Table 1 summarizes the chemical purity values of the starting dolutegravir and of the prepared salts of dolutegravir with amines after the first crystallization.

Table 1: Chemical purity of dolutegravir and its salts with amines

	chemical purity (HPLC)
dolutegravir (starting)	98.2 %
diethylamine salt of dolutegravir	98.7 %
N,N'-dibenzylethylenediamine salt of dolutegravir	99.7 %
ethanolamine salt of dolutegravir	98.9 %

tromethamine salt of dolutegravir	99.5 %
lysine salt of dolutegravir	99.0 %

The salts of dolutegravir with amines were also studied with the use of load tests and subsequent verification of their chemical purity. The results of these tests are summarized in Table 2. The tests have concentrated on amines used in pharmacy, i.e. *N,N'*-dibenzylethylenediamine (benzathine), ethanolamine (olamine) and tromethamine.

Table 2: Chemical purity (HPLC) of salts of dolutegravir with amines before and after the load tests

	dolutegravir	**dolutegravir benzathine**	**dolutegravir olamine**	**dolutegravir tromethamine**
starting material	98.2 %	99.7 %	98.9 %	99.5 %
80 °C, 1 % RH, 72 hours	97.7 %	99.6 %	98.5 %	99.4 %
80 °C, 75 % RH, 72 hours	97.4 %	99.4 %	98.3 %	99.0 %
RT, 10 days, in the presence of P_2O_5	98.2 %	99.7 %	98.8 %	99.5 %
RT, 10 days, in the presence of H_2O	98.0 %	99.6 %	98.2 %	99.1 %

Formation of salts of dolutegravir with amines was confirmed with the use of analytic methods, X-ray powder diffraction, differential scanning calorimetry and by means of the solid-state nuclear magnetic resonance. The X-ray powder diffraction (XRPD) pattern of various salts of dolutegravir - with diethylamine (fig. 5), with *N,N'*-dibenzylethylenediamine (fig. 8), with ethanolamine (fig. 11), with tromethamine (fig. 15) and with lysine (fig. 18) differ from the XRPD pattern of dolutegravir (fig. 2). Similarly, the solid-state nuclear magnetic resonance (ssNMR) spectrum of various salts of dolutegravir - with diethylamine (fig. 4), with *N,N'*-dibenzylethylenediamine (fig. 7), with ethanolamine (fig. 10), with tromethamine (fig. 14) and with lysine (fig. 17) differs from the ssNMR spectra of dolutegravir (fig. 1). The following melting points were measured with the use of the differential scanning calorimetry (DSC), dolutegravir 189.5°C (fig. 3), dolutegravir salt with diethylamine 186.3°C (fig. 6), dolutegravir salt with *N,N'*-dibenzylethylenediamine 155.7°C

(fig. 9), dolutegravir salt with ethanolamine 188.4°C (fig. 12), dolutegravir salt with tromethamine 169.5°C (fig. 16) and dolutegravir salt with lysine 196.5°C (fig. 19).

The salt of dolutegravir with ethanolamine can also exist in a hydrated form; XRPD in fig. 13. This form was confirmed by the thermogravimetric analysis (TGA), according to which it contains 17% of water and 14% of ethanolamine. The anhydrous form of dolutegravir with ethanolamine contains 1% of water and 16% of ethanolamine. According to TGA, the salt of dolutegravir with diethylamine contains 1% of water and 14% of diethylamine. According to TGA, the salt of dolutegravir with *N,N'*-dibenzylethylenediamine contains 2% of water. According to TGA, the salt of dolutegravir with tromethamine contains 1% of water and the salt with lysine contains 4% of water.

Preparation of a salt of dolutegravir with an amine according to variant A comprises the following steps:

a/ dissolution and/or dispersion of a mixture of dolutegravir and an amine in a solvent or mixture of solvents;

b/ removal of the solvents from the mixture from step a/.

Preparation of a salt of dolutegravir with an amine according to variant B comprises the following steps:

a/ dissolution and/or dispersion of dolutegravir in a solvent or a mixture of solvents;

b/ addition of an amine in the solid form or in the form of a solution;

c/ removal of the solvents from the mixture from step b/.

The dissolution or dispersion according to the preparation variants A and B may be carried out in an organic solvent selected from C1 to C8 hydrocarbons (aliphatic or aromatic), C1 to C4 alcohols, C1 to C8 esters, C1 to C8 ketones, C1 to C6 ethers (acyclic or cyclic), C1 to C4 nitriles, water or their mixtures in the range from 20°C to the boiling point of the solvent or solvents. It is preferably carried out in methanol, ethanol, 1-propanol, 2-propanol, acetone, tetrahydrofuran or their mixtures. In step b/ of the preparation variant B the amine can be added in a solid form or in the form of a solution; the salt with dolutegravir is formed equally readily in both the cases. Subsequently, the mixture is usually cooled down, preferably to the range of 20°C to 30°C and left to crystallize. The salt can be isolated either directly by filtration, or concentration of the mixture, or evaporation of the solvents may follow.

Preparation of a salt of dolutegravir with an amine according to variant C is directly carried out during the formulation process, preferably directly during the wet granulation. Besides dolutegravir itself and the excipients, the respective equivalent part of the amine - diethylamine, *N,N'*-dibenzylethylenediamine, meglumine, tromethamine, ethanolamine, diethanolamine, *tert*-butylamine or lysine are charged into a homogenizer. The salt is formed during wet granulation.

Dolutegravir forms salts with amines in the molar ratios of the amine to dolutegravir in the range of 2:1 to 1:4, but ideally 1:1 to 1:2.

A salt of dolutegravir and an amine is generally produced in an 80% yield, preferably 90% yield, while the chemical purity, measured by HPLC, is not lower than that of the input dolutegravir. On the contrary, what often happens is that the chemical purity of the salt is considerably higher than the purity of the input dolutegravir. Thus, a salt of dolutegravir with an amine can be advantageously used for purification of crude dolutegravir.

The salt of dolutegravir with diethylamine exhibits a crystalline character. The X-ray powder pattern of this salt is shown in Fig. 5. The characteristic peaks are: 5.5; 11.2; 14.3; 16.8; 19.1 and 24.4 ± 0.2 °2-theta. Diffraction peaks with a higher relative intensity than 15% are shown in Table 3.

Table 3: Diffraction peaks of the salt of dolutegravir with diethylamine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
5.55	15.925	38.0
7.39	11.951	4.2
10.32	8.563	31.2
11.15	7.927	100.0
11.97	7.386	10.2
14.27	6.203	49.7
14.80	5.980	8.3
15.81	5.602	7.4
16.78	5.279	29.3
19.14	4.634	70.5
20.58	4.312	8.1
21.05	4.218	19.5

21.95	4.047	17.9
22.84	3.891	5.4
23.30	3.814	8.5
24.40	3.645	21.1
25.64	3.472	12.1
28.08	3.175	10.2
28.84	3.093	5.1

The salt of dolutegravir with *N,N'*-dibenzylethylenediamine exhibits a crystalline character. The X-ray powder pattern of this salt is shown in Fig. 8. The characteristic peaks are: 7.2; 11.2; 16.6; 18.0; 21.8 and 23.6 ± 0.2 °2-theta. Diffraction peaks with a higher relative intensity than 15% are shown in Table 4.

Table 4: Diffraction peaks of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
6.04	14.631	7.2
7.17	12.320	100.0
11.16	7.920	26.5
12.13	7.293	6.4
13.11	6.748	5.6
13.57	6.518	7.7
15.81	5.600	5.8
16.56	5.348	24.6
17.36	5.103	3.4
18.01	4.921	35.3
19.27	4.602	4.9
19.98	4.441	2.5
21.79	4.075	27.9
23.55	3.775	27.8
25.13	3.541	5.1
25.87	3.441	3.3
27.92	3.193	4.5
29.80	2.996	4.9
31.25	2.860	3.2
32.27	2.772	2.5

The salt of dolutegravir with ethanolamine exhibits a crystalline character and can exist in an anhydrous or hydrated form. The X-ray powder pattern of the anhydrous form of this salt is shown in fig. 11 and that of the hydrated form in fig. 13. The characteristic peaks of the anhydrous form of the salt of dolutegravir with ethanolamine are 7.2; 12.5; 18.3; 19.6 and

23.4 ± 0.2 °2-theta; its diffraction peaks with a relative intensity higher than 15% are presented in Table 5. The characteristic peaks of the hydrated form of the salt of dolutegravir with ethanolamine are 6.9; 11.5; 19.7 and 22.2 ± 0.2 °2-theta; its diffraction peaks with a relative intensity higher than 15% are presented in Table 6.

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Table 5: Diffraction peaks of the anhydrous salt of dolutegravir with ethanolamine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
7.19	12.290	100.0
9.61	9.199	28.4
12.54	7.053	40.6
15.11	5.858	9.1
18.26	4.854	35.6
19.06	4.653	15.0
19.57	4.532	28.6
20.52	4.324	16.2
21.36	4.157	4.6
22.39	3.968	10.5
23.42	3.795	16.4
26.19	3.400	11.6
27.90	3.196	7.1
28.53	3.127	4.7
31.35	2.852	5.2
34.34	2.609	1.7
35.12	2.553	2.5

Table 6: Diffraction peaks of the hydrated form of the salt of dolutegravir with ethanolamine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
6.90	12.798	100.0
7.76	11.388	8.3
11.52	7.674	35.6
13.16	6.721	3.6
14.86	5.957	3.1
17.52	5.058	4.7
18.54	4.782	5.9
19.41	4.570	10.8
19.67	4.510	13.6
20.44	4.341	3.4
22.19	4.002	8.5

23.50	3.783	5.1
24.77	3.591	3.9
26.15	3.406	2.8
26.56	3.354	2.9
27.91	3.194	2.7
28.35	3.146	2.9

The salt of dolutegravir with tromethamine exhibits a crystalline character. The X-ray powder pattern of this salt is shown in Fig. 15. The characteristic peaks are: 7.9; 15.6; 20.7; 22.4; 2.8; 26.0 and 26.8 ± 0.2 °2-theta. Diffraction peaks with a higher relative intensity than 15% are shown in Table 7.

Table 7: Diffraction peaks of the salt of dolutegravir with tromethamine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
5.19	17.012	6.2
7.86	11.245	100.0
10.35	8.538	10.3
11.42	7.741	6.2
15.55	5.694	70.2
16.11	5.496	13.8
17.66	5.019	22.5
18.91	4.690	8.3
20.19	4.394	21.0
20.69	4.289	37.6
21.00	4.226	14.5
22.43	3.961	27.0
23.34	3.808	9.4
23.73	3.747	9.6
25.05	3.553	27.0
25.99	3.426	46.1
26.77	3.328	35.7
28.29	3.152	5.7
30.62	2.918	3.0
32.15	2.782	4.0
32.69	2.737	8.3

The salt of dolutegravir with lysine exhibits a crystalline character. The X-ray powder pattern of this salt is shown in Fig. 18. The characteristic peaks are 7.3; 9.6; 13.8; 17.2; 2.8; 23.0 and 25.4° 2theta. Diffraction peaks with a higher relative intensity than 15% are shown in Table 8.

Table 8: Diffraction peaks of the salt of dolutegravir with lysine

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
7.33	12.043	100.0
9.58	9.229	50.2
9.99	8.851	23.3
13.85	6.390	19.8
14.37	6.159	6.5
14.69	6.025	8.2
17.16	5.163	17.3
18.50	4.791	13.5
19.19	4.623	12.3
20.02	4.433	6.9
21.41	4.146	20.5
22.13	4.013	18.6
23.04	3.857	43.3
23.81	3.733	18.0
25.44	3.498	29.1
26.31	3.384	10.7
27.17	3.280	15.8
28.87	3.090	8.7
34.23	2.617	5.4

Dolutegravir also forms salts with alkali metals and alkaline earth metals, in particular the potassium, magnesium and calcium salt, wherein the potassium salt exhibits a crystalline character and the magnesium and calcium salts exhibit an amorphous character. Differential scanning calorimetry (DSC) was applied to obtain the melting point of the potassium salt of dolutegravir of 318.6°C.

The potassium salt of dolutegravir exhibits a crystalline character. The X-ray powder pattern of this salt is shown in Fig. 20. The characteristic peaks are: 5.2; 9.0; 16.1; 21.5 and 28.3 ± 0.2° 2-theta. Diffraction peaks with a higher relative intensity than 15% are shown in Table 9.

Table 9: Diffraction peaks of the potassium salt of dolutegravir

Position [°2Th.]	Interplanar spacing [Å = 0.1 nm]	Rel. intensity (%)
5.22	16.921	88.9
6.47	13.642	10.1
7.98	11.077	54.1
9.00	9.817	100.0

9.85	8.973	16.2
11.16	7.920	15.8
12.74	6.945	11.1
13.38	6.611	9.1
13.98	6.331	13.2
14.93	5.928	11.2
16.05	5.519	23.1
18.10	4.898	14.5
19.00	4.666	8.5
20.45	4.340	23.0
21.45	4.139	30.6
21.74	4.084	28.7
22.50	3.948	19.4
24.09	3.692	14.2
24.66	3.607	22.7
25.70	3.464	20.8
26.34	3.381	9.1
28.26	3.156	45.3
29.93	2.983	7.6
30.41	2.937	11.6

The magnesium and calcium salt of dolutegravir exhibit an amorphous character. The X-ray powder pattern of the magnesium salt is shown in Fig. 21.

The potassium, magnesium and calcium salt can be prepared by mixing of dolutegravir with a reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations. This preparation may be done separately, e.g. during crystallization, or later in the formulation process, e.g. during wet granulation. When the salt is produced during the formulation process, dolutegravir together with a reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations are charged into a homogenizer besides the excipients.

If preparation of the said salts is conducted separately, in a solution, preferably during crystallization, it comprises the following steps:

a/ dissolution and/or dispersion of dolutegravir in a solvent or a mixture of solvents;

b/ addition of a reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations, in a solid form or in the form of a solution;

c/ removal of the solvents from the mixture from step b/.

The dissolution or dispersion may be carried out in an organic solvent selected from C1 to C8 hydrocarbons (aliphatic or aromatic), C1 to C4 alcohols, C1 to C8 esters, C1 to C8 ketones, C1 to C6 ethers (acyclic or cyclic), C1 to C4 nitriles, water or their mixtures in the range from

20°C to the boiling point of the solvent or solvents. It is preferably carried out in methanol, ethanol, 1-propanol, 2-propanol, acetone, water, or their mixtures. In step b/ the reagent can be added in the solid form or in the form of a solution; the salt with dolutegravir is formed equally readily in both the cases. Subsequently, the mixture is usually cooled down, preferably to the range of -20°C to 30°C, and left to crystallize. The salt can be isolated either directly by filtration, or concentration of the mixture, or evaporation of the solvents may follow.

Brief Description of Drawings

Fig. 1: ssNMR record of dolutegravir

Fig. 2: XRPD pattern of dolutegravir

Fig. 3: DSC record of dolutegravir

Fig. 4: ssNMR record of the salt of dolutegravir salt with diethylamine

Fig. 5: XRPD pattern of the salt of dolutegravir with diethylamine

Fig. 6: DSC record of the salt of dolutegravir with diethylamine

Fig. 7: ssNMR record of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine

Fig. 8: XRPD pattern of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine

Fig. 9: DSC record of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine

Fig. 10: ssNMR record of the anhydrous salt of dolutegravir with ethanolamine

Fig. 11: XRPD pattern of the anhydrous salt of dolutegravir with ethanolamine

Fig. 12: DSC record of the anhydrous salt of dolutegravir with ethanolamine

Fig. 13: XRPD pattern of the hydrated salt of dolutegravir with ethanolamine

Fig. 14: ssNMR record of the salt of dolutegravir with tromethamine

Fig. 15: XRPD pattern of the salt of dolutegravir with tromethamine

Fig. 16: DSC record of the salt of dolutegravir with tromethamine

Fig. 17: ssNMR record of the salt of dolutegravir with lysine

Fig. 18: XRPD pattern of the salt of dolutegravir with lysine

Fig. 19: DSC record of the salt of dolutegravir with lysine

Fig. 20: XRPD pattern of the potassium salt of dolutegravir

Fig. 21: XRPD pattern of the magnesium salt of dolutegravir

Examples

Dolutegravir was prepared according to the procedure published in the patent application WO2006116764. The chemical purity of dolutegravir prepared this way was 98.2% (HPLC).

The solid-state NMR spectrum (**Fig. 1**), XRPD pattern (**Fig. 2**) and DSC record (**Fig. 3**) confirm the structure of dolutegravir. ^{1}H NMR (500 MHz, dmso-*d6*): δ 1.33 (d, *J* = 7.0 Hz, 3H); 1.54 (m, 1H); 2.00 (m, 1H); 3.89 (m, 1H); 4.03 (m, 1H); 4.35 (dd, *J* = 13.8 Hz, *J* = 5.9 Hz, 1H); 4.54 (d, *J* = 6.1 Hz, 2H); 4.56 (dd, *J* = 13.8 Hz, *J* = 4.0 Hz, 1H); 4.79 (m, 1H); 5.45 (dd, *J* = 5.7 Hz, *J* = 4.2 Hz, 1H); 7.06 (td, *J* = 8.6 Hz, *J* = 2.5 Hz, 1H); 7.24 (td, *J* = 10.3 Hz, *J* = 2.5 Hz, 1H); 7.38 (m, 1H); 8.50 (s, 1H); 10.36 (t, *J* = 5.9 Hz); 12.51 (s, 1H). ^{13}C NMR (125.8 MHz, dmso-*d6*): δ 15.4; 29.3; 35.9; 44.9; 51.3; 62.2; 76.3; 104.0; 111.6; 115.6; 117.0; 122.6; 130.9; 140.9; 154.8; 160.3; 161.7; 162.5; 163.9; 170.5 (some of the signals are split due to C-F interactions).

Example 1

Preparation of the salt of dolutegravir with diethylamine

Dolutegravir (200 mg, 0.48 mmol) is dissolved together with diethylamine (70 mg, 0.95 mmol) in methanol at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently it is left to evaporate at the room temperature. 190 mg (81% yield) of the crystalline salt of dolutegravir with diethylamine in the molar ratio of 1:1 (^{1}H NMR) was obtained.

Example 2

Preparation of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine

Dolutegravir (2 g, 4.77 mmol) is dissolved together with *N,N'*-dibenzylethylenediamine (1.2 g, 5.01 mmol) in a mixture of 10 ml of tetrahydrofuran and 25 ml of methanol at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently it is left to crystallize in a refrigerator overnight. The produced crystals are aspirated and dried. 2.8 g (91% yield) of the crystalline salt of dolutegravir with *N,N'*-dibenzylethylenediamine in the molar ratio of 2:1 (^{1}H NMR) was obtained.

Example 3

Preparation of the salt of dolutegravir with ethanolamine

Dolutegravir (2 g, 4.77 mmol) is dissolved together with ethanolamine (310 mg, 5.01 mmol) in a mixture of tetrahydrofuran and methanol at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently it is left to crystallize in a refrigerator overnight. The produced crystals are aspirated and dried freely at the room

temperature. 2.20 g (94% yield) of a hydrated form of the crystalline salt of dolutegravir with ethanolamine in the molar ratio of 1:1 (^{1}H NMR) was obtained. If the crystals are dried in a vacuum drier at 40°C, an anhydrous form of the crystalline salt of dolutegravir with ethanolamine is obtained in the molar ratio of 1:1 (^{1}H NMR).

Example 4

Preparation of the salt of dolutegravir with tromethamine

Dolutegravir (2 g, 4.77 mmol) is dissolved together with tromethamine (610 mg, 5.01 mmol) in methanol at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently it is left to crystallize in a refrigerator overnight. The produced crystals are aspirated and dried. 2.4 g (92% yield) of the crystalline salt of dolutegravir with tromethamine in the molar ratio of 1:1 (^{1}H NMR) was obtained.

Example 5

Preparation of the salt of dolutegravir with *tert*-butylamine

Dolutegravir (200 mg, 0.48 mmol) is dissolved together with *tert*-butylamine (70 mg, 0.95 mmol) in a mixture of methanol and tetrahydrofuran at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently the product is left to crystallize in a refrigerator. 205 mg (87% yield) of the crystalline salt of dolutegravir with *tert*-butylamine in the molar ratio of 1:1 (^{1}H NMR) was obtained.

Example 6

Preparation of the salt of dolutegravir with lysine

Dolutegravir (400 mg, 0.95 mmol) is dissolved together with lysine (280 mg, 1.91 mmol) in a mixture of methanol and water (1:1) at an elevated temperature. The clear solution is left to slowly cool down to the room temperature and subsequently it is left to crystallize in a refrigerator. The produced crystals are aspirated and dried. 470 mg (88% yield) of the crystalline salt of dolutegravir with lysine in the molar ratio of 1:1 (^{1}H NMR) was obtained.

Example 7

Preparation of the potassium salt of dolutegravir

Dolutegravir (5,0 g, 11.92 mmol) is dissolved together with potassium hydroxide (23,8 mmol) in a mixture of methanol and water at an elevated temperature. Subsequently, the mixture is

left to cool down and crystallize in a refrigerator. The produced crystals are aspirated and dried. 4.45 g (89% yield) of the potassium salt of dolutegravir was obtained.

Example 8

Preparation of the magnesium salt of dolutegravir

Dolutegravir (500 mg, 1.19 mmol) is stirred up together with magnesium hydroxide (2.38 mmol) in a mixture of methanol and water. This mixture is stirred overnight in a suspension, then it is filtered and the crystals dried. 400 mg (80% yield) of the magnesium salt of dolutegravir was obtained.

Example 9

Preparation of the calcium salt of dolutegravir

Dolutegravir (500 mg, 1.19 mmol) is stirred up together with calcium hydroxide (2.38 mmol) in a mixture of methanol and water. This mixture is stirred overnight and subsequently left to evaporate. The crystals are dried. 490 mg (98% yield) of the calcium salt of dolutegravir was obtained.

Example 10

Preparation of the salt of dolutegravir with *N,N'*-dibenzylethylenediamine during wet granulation

The following ingredients were placed into a homogenizer: dolutegravir (5.2 g), *N,N'*-dibenzylethylenediamine (1.6 g), mannitol (14.6 g), microcrystalline cellulose (5.8 mg) and povidone (1.5 mg). The mixture was homogenized at 20 rpm for 60 min. Finally, sodium stearyl fumarate (1.0 mg) was added and the mixture was homogenized at 20 rpm for another 10 min.

Example 11

Preparation of the salt of dolutegravir with ethanolamine during wet granulation

The following ingredients were placed into a homogenizer: dolutegravir (5.2 g), ethanolamine (0.4 g), mannitol (14.6 g), microcrystalline cellulose (5.8 mg) and povidone (1.5 mg). The mixture was homogenized at 20 rpm for 60 min. Finally, sodium stearyl fumarate (1.0 mg) was added and the mixture was homogenized at 20 rpm for another 10 min.

Example 12

Preparation of the salt of dolutegravir with tromethamine during wet granulation

The following ingredients were placed into a homogenizer: dolutegravir (5.2 g), tromethamine (0.8 g), mannitol (14.6 g), microcrystalline cellulose (5.8 mg) and povidone (1.5 mg). The mixture was homogenized at 20 rpm for 60 min. Finally, sodium stearyl fumarate (1.0 mg) was added and the mixture was homogenized at 20 rpm for another 10 min.

Example 13

Pharmaceutical composition of the product - core

Substance	Amount – core /mg/
Dolutegravir olamine	70.1
Mannitol	150.0
Microcrystalline cellulose	62.0
Povidone	15.5
Sodium stearyl fumarate	12.4

The following ingredients were charged into a homogenizer: dolutegravir olamine, mannitol, microcrystalline cellulose and povidone. The mixture was homogenized at 20 rpm for 15 min. Finally, sodium stearyl fumarate was added and the mixture was homogenized at 20 rpm for another 3 min. The tabletting matter produced in the above mentioned way was compressed in a rotary tabletting machine and used for the production of cores with the approximate weight of 310 mg.

Overview of analytic methods

Measurement parameters of XRPD: The diffraction patterns were measured using an X´PERT PRO MPD PANalytical diffractometer, used radiation CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0,01° 2θ, the measurement was carried out on a flat powder sample that was applied on a Si plate. Programmable divergence slits with the irradiated area of the sample of 10 mm, 0.02 rad Soller slits and a ¼° anti-diffusion slit were used for the setting of the primary optical equipment. An X´Celerator detector with maximum opening of the detection slot, 0.02 rad

Soller slits and a 5.0 mm anti-diffusion slit were used for the setting of the secondary optical equipment.

The nuclear magnetic resonance (NMR) spectra were measured using a Bruker Avance 500 device. The ^{1}H spectra were measured at the frequency of 500.13 MHz, ^{13}C at the frequency of 125.8 MHz. The sample was measured in a deuterated solvent specified for the particular analysis, normally at 25°C (unless specified otherwise for a particular analysis). The chemical shift δ is expressed as *ppm*, the interaction constants *J* are specified in Hz. The spectra were normally referenced to the residual solvent content.

Carbon spectra of solid-state nuclear magnetic resonance (ssNMR) were measured with the use of an Avance 400 WB Bruker device, using the CP/MAS method in a 4mm rotor at the speed of 13 kHz, normally at 25°C.

The records of the differential scanning calorimetry (DSC) were measured using a DSC Pyris 1 device made by the company Perkin Elmer. The sample charge in a standard Al pot (40 µL) was between 2-4 mg and the heating rate was 10°C/min. The temperature program that was used consists of 1 min stabilization at the temperature of 20°C and then of heating up to 300°C at the heating rate of 10 °C/min. 4.0 N_2 at the flow rate of 20 ml/min was used as the carrier gas.

The records of the thermogravimetric analysis (TGA) were measured using a TGA 6 device made by the company Perkin Elmer. The sample charge in a corundum pot was 4-20 mg and the heating rate was 10°C/min. The temperature program that was used consists of 1 minute's stabilization at the temperature of 20°C and then of heating up to 250°C at the heating rate of 10°C/min. 4.0 N_2 at the flow rate of 20 ml/min was used as the carrier gas.

Chemical purity was measured with the use of liquid chromatography (HPLC):

Device: Waters Acquity UPLC, PDA detection

Sample preparation: Dissolve 4.0 mg of the tested sample in 10.0 ml of 40% acetonitrile

Column:
- dimension: l = 0.10 m, Ø = 2.1 mm
- *stationary phase:* Acquity BEH phenyl, 1.7 µm particles
- *column temperature:* 30°C.

Mobile phase: *A*: 10 mM phosphate buffer at pH 2.5

B: methanol

Gradient elution:

Time (min)	**Flow (ml / min)**	**% A**	**% B**
0	0.3	70	30
15	0.3	40	60
18	0.3	10	90
20	0.3	10	90
21	0.3	70	30
23	0.3	70	30

Detection: spectrophotometer 258 nm

Injected quantity: 1 µl

Sample temperature: 20°C

Sample concentration: 0.4 mg / ml

CLAIMS

1. The potassium, magnesium or calcium salt of dolutegravir or a salt of dolutegravir with an amine, or their solvate.

2. A salt of dolutegravir with an amine or its solvate according to claim 1.

3. A salt of dolutegravir with an amine according to claim 2, wherein the amine is of formula R^1-NH_2, R^1R^2NH or R^1NH-CH_2CH_2-NHR^2, wherein R^1, R^2 is a C1 to C8 aliphatic and/or aromatic substituent, substituted in any manner by hydroxyl or carboxyl groups, or its solvate.

4. A salt of dolutegravir with an amine according to claim 3, characterized in that the amine is selected from the group comprising diethylamine, *N,N'*-dibenzylethylenediamine, ethanolamine, tromethamine, *tert*-butylamine and lysine.

5. The salt of dolutegravir with diethylamine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 5.5; 11.2; 14.3; 16.8; 19.1 and 24.4 ± 0.2 °2-theta.

6. The salt of dolutegravir with *N,N'*-dibenzylethylenediamine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 7.2; 11.2; 16.6; 18.0; 21.8 and 23.6 ± 0.2 °2-theta.

7. The salt of dolutegravir with ethanolamine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 7.2; 12.5; 18.3; 19.6 and 23.4 ± 0.2 °2-theta.

8. A hydrated form of the salt of dolutegravir with ethanolamine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 6.9; 11.5; 19.7 and 22.2 ± 0.2 °2-theta.

9. The salt of dolutegravir with tromethamine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 7.9; 15.6; 20.7; 22.4; 26.0 and 26.8 ± 0.2 °2-theta.

10. The salt of dolutegravir with lysine according to claim 4, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 7.3; 9.6; 13.8; 17.2; 23.0 and 25.4° 2theta.

11. A salt of dolutegravir with an amine according to claims 1 to 9, characterized in that the molar ratio of the amine to dolutegravir is in the range of 2:1 to 1:4.

12. A salt of dolutegravir with an amine according to claim 10, characterized in that the molar ratio of the amine to dolutegravir is 1:1 to 1:2.

13. The potassium salt of dolutegravir or its solvate according to claim 1.

14. The potassium salt of dolutegravir according to claim 13, in a crystalline form.

15. The potassium salt of dolutegravir according to claim 14, exhibiting the following characteristic reflections in the X-ray powder pattern with the use of CuKα radiation: 5.2; 9.0; 16.1; 21.5 and 28.3 ± 0.2° 2-theta.

16. The magnesium salt of dolutegravir or its solvate according to claim 1.

17. The magnesium salt of dolutegravir according to claim 16, in an amorphous form.

18. The magnesium salt of dolutegravir according to claim 17, which is characterized by the glass transition temperature in the range of 231 to 234°C.

19. A process of preparing a salt of dolutegravir with an amine according to claims 1 to 12, comprising the following steps:

a) dissolution and/or dispersion of a mixture of dolutegravir and an amine in a solvent or mixture of solvents;

b) removal of the solvents from the mixture from step a).

20. A process of preparing a salt of dolutegravir with an amine according to claims 1 to 12, comprising the following steps:

a) dissolution and/or dispersion of dolutegravir in a solvent or a mixture of solvents;

b) addition of an amine in the solid form or in the form of a solution;

c) removal of the solvents from the mixture from step b).

21. The process according to claim 19 or 20, characterized in that the dissolution or dispersion is carried out in an organic solvent selected from C1 to C4 alcohols, C1 to C6 esters, C1 to C6 ketones, C1 to C6 ethers (acyclic or cyclic) or in their mixtures, preferably in methanol, ethanol, 1-propanol or 2-propanol, tetrahydrofuran or in their mixtures.

22. The process according to claim 21, characterized in that the removal of the solvents from the mixture is carried by lyophilization, spray drying or filtration.

23. The process according to claim 22, characterized in that the amine is selected from the group comprising diethylamine, *N,N'*-dibenzylethylenediamine, ethanolamine, diethanolamine, meglumine, tromethamine, *tert*-butylamine and lysine.

24. A process of preparing the potassium, magnesium or calcium salt of dolutegravir according to claims 1, 13 to 18, comprising the following steps:

a) dissolution and/or dispersion of dolutegravir in a solvent or a mixture of solvents;

b) addition of a reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations, in a solid form or in the form of a solution;

c) removal of the solvents from the mixture from step b).

25. The process according to claim 24, characterized in that the dissolution or dispersion is carried out in an organic solvent selected from C1 to C8 hydrocarbons (aliphatic or aromatic), C1 to C4 alcohols, C1 to C8 esters, C1 to C8 ketones, C1 to C6 ethers (acyclic or cyclic), C1 to C4 nitriles, in water or in their mixtures, preferably in methanol, ethanol, 1-propanol, 2-propanol, acetone, water, or in their mixtures.

26. The process according to claim 25, characterized in that the removal of the solvents from the mixture is carried by lyophilization, spray drying or filtration.

27. The process according to claim 26, characterized in that said reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations is potassium hydroxide, magnesium hydroxide or calcium hydroxide.

28. A pharmaceutical composition, characterized in that it contains the potassium, calcium, magnesium salt of dolutegravir and/or a salt of dolutegravir with an amine or their solvate.

29. The pharmaceutical composition according to claim 28, containing the potassium salt of dolutegravir and at least one pharmaceutically acceptable excipient.

30. The pharmaceutical composition according to claim 28, containing the calcium salt of dolutegravir and at least one pharmaceutically acceptable excipient.

31. The pharmaceutical composition according to claim 28, containing the magnesium salt of dolutegravir and at least one pharmaceutically acceptable excipient.

32. The pharmaceutical composition according to claim 28, containing a salt of dolutegravir with an amine and at least one pharmaceutically acceptable excipient.

33. The pharmaceutical composition according to claim 32, characterized in that the amine is selected from the group comprising diethylamine, *N,N'*-dibenzylethylenediamine, ethanolamine, diethanolamine, tromethamine, *tert*-butylamine and lysine.

34. The pharmaceutical composition according to any one of claims 28 to 33, characterized in that it has the form of a tablet.

35. The pharmaceutical composition according to any one of claims 28 to 34, for the use for the treatment of a retroviral infection.

36. The pharmaceutical composition according to claim 35, characterized in that the retroviral infection is the human immunodeficiency virus (HIV).

37. A process of preparing the pharmaceutical composition according to any of claims 28 to 36, characterized in that dolutegravir or its solvate is mixed with an amine, producing the salt of dolutegravir with the respective amine *in-situ*.

38. The process according to claim 37, characterized in that said amine is of formula R^1-NH_2, R^1R^2NH or R^1NH-CH_2CH_2-NHR^2, where R^1, R^2 is a C1 to C8 aliphatic and/or aromatic substituent, substituted in any manner by hydroxyl or carboxyl groups, or its solvate.

39. The process according to claim 38, characterized in that said amine is selected from the group comprising diethylamine, *N,N'*-dibenzylethylenediamine, ethanolamine, tromethamine, *tert*-butylamine and lysine.

40. The process of preparing the pharmaceutical composition according to any one of claims 28 to 36, characterized in that dolutegravir or its salt is mixed with a suitable compound containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations, producing the potassium, calcium or magnesium salt of dolutegravir *in-situ*.

41. The process according to claim 40, characterized in that said reagent containing potassium (K^+), magnesium (Mg^{2+}) or calcium (Ca^{2+}) cations is potassium hydroxide, magnesium hydroxide or calcium hydroxide.

42. The process according to any one of claims 37 to 41, characterized in that said composition is prepared by wet granulation.

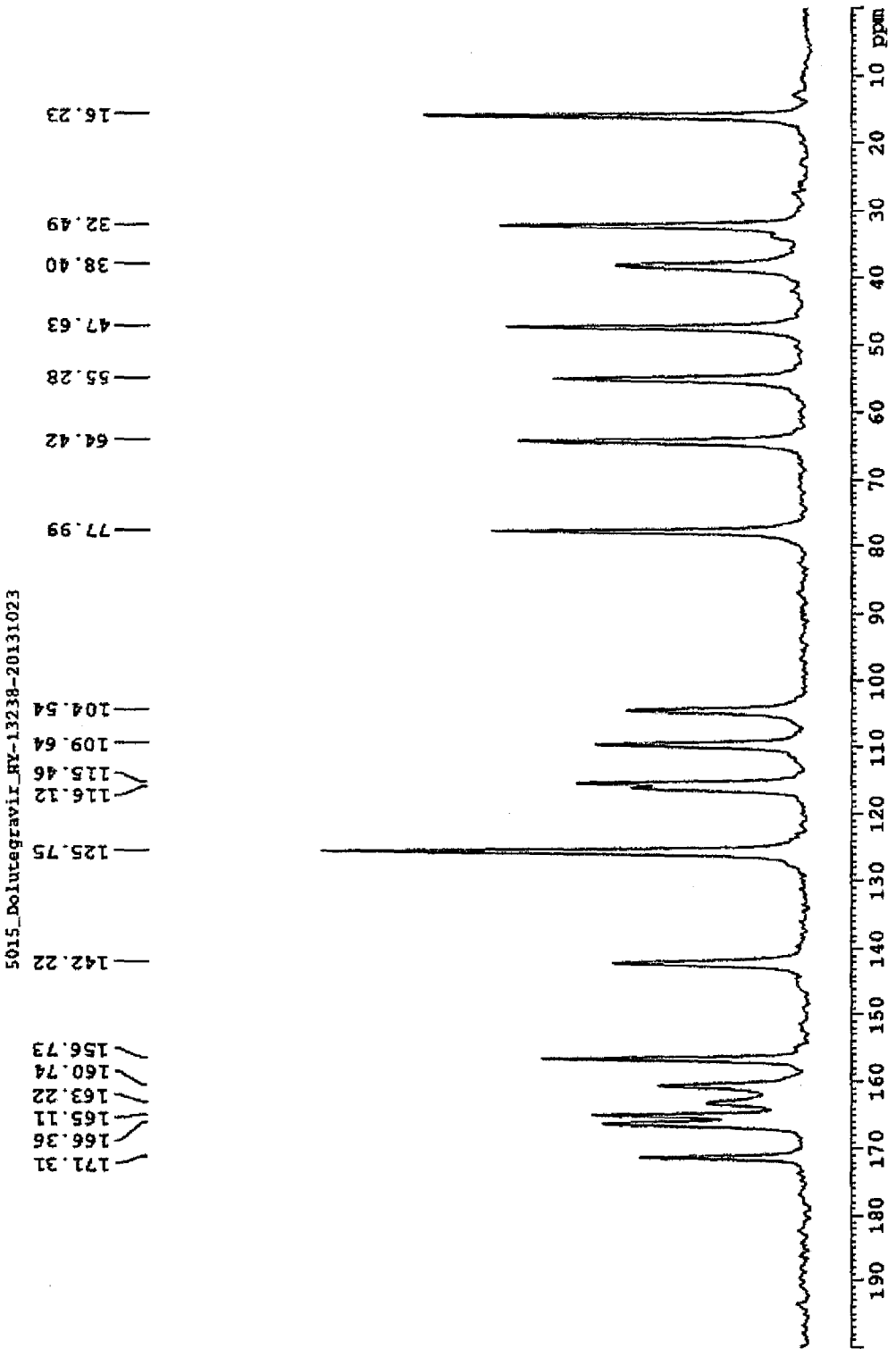
43. The potassium, calcium or magnesium salt of dolutegravir and/or a salt of dolutegravir with an amine according to any one of claims 1 to 18, for the use for the treatment of a retroviral infection.

44. The potassium, calcium or magnesium salt of dolutegravir and/or a salt of dolutegravir with an amine according to claim 43, wherein the said retroviral infection is the human immunodeficiency virus (HIV).

45. Use of the potassium, calcium or magnesium salt of dolutegravir and/or a salt of dolutegravir with an amine according to claims 1 to 18, in a process of preparing dolutegravir of a high chemical purity of at least 99.85% according to HPLC.

Drawings

Fig. 1



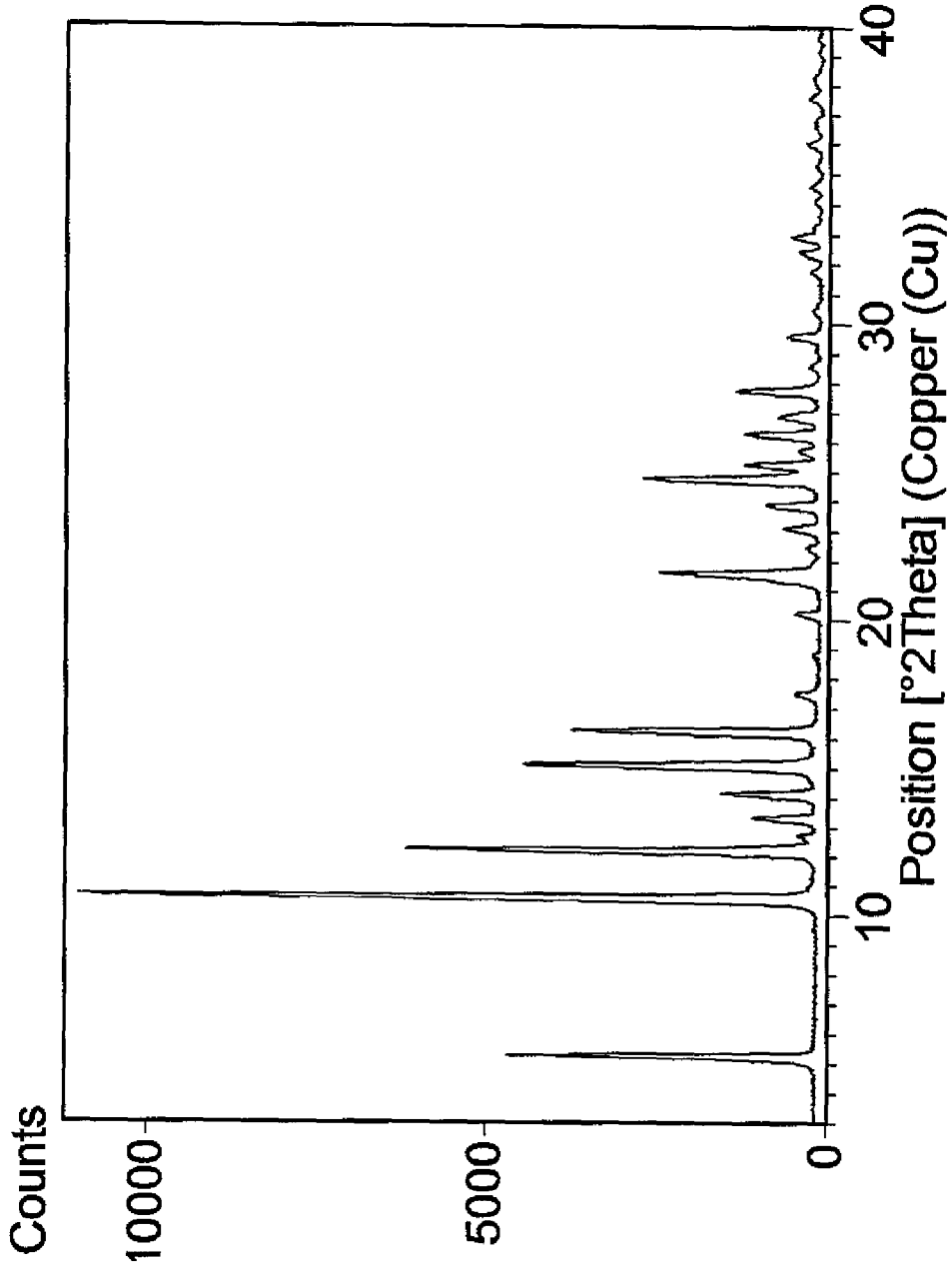
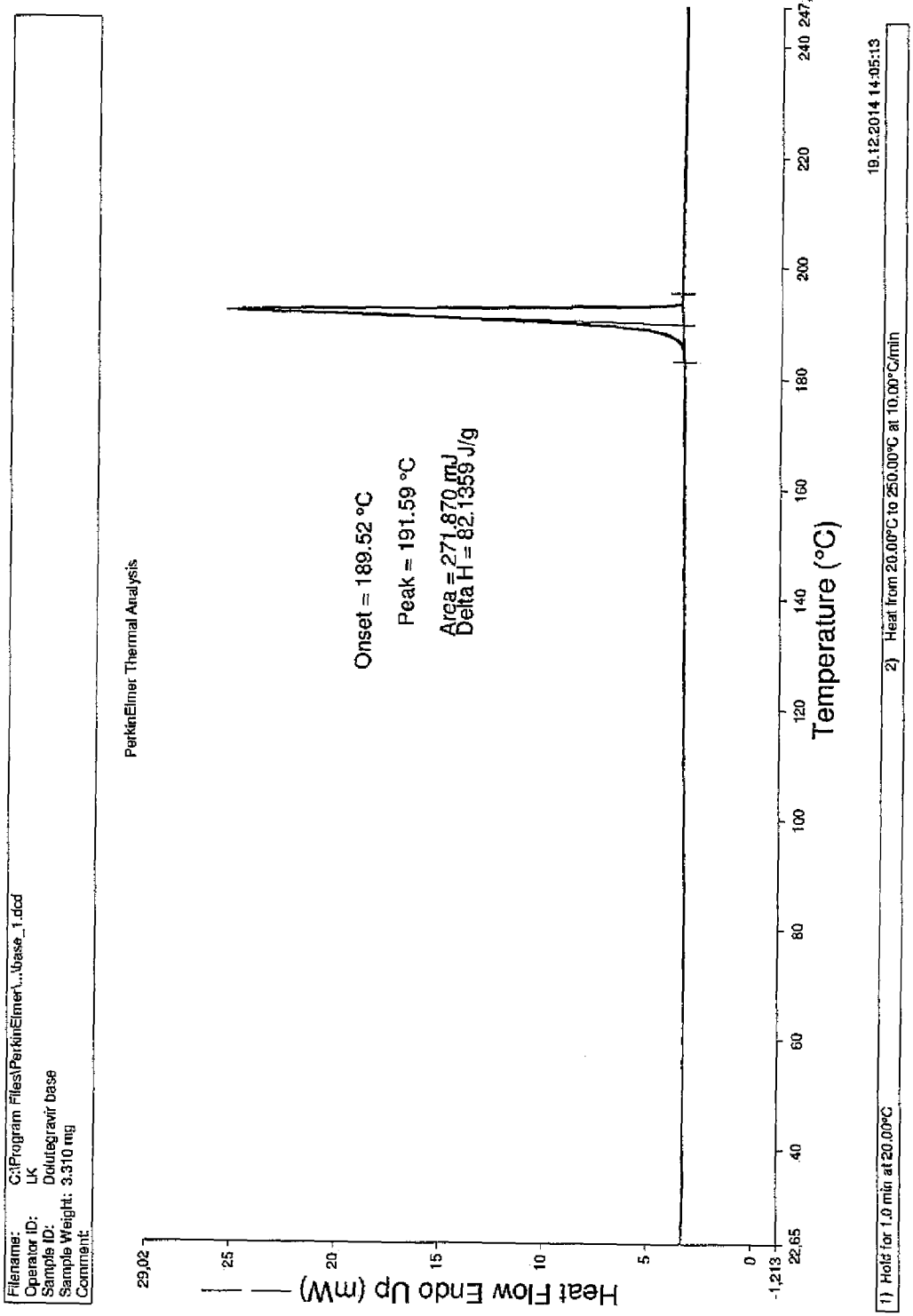


Fig. 2

Fig. 3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Delta H = 82.1359 J/g
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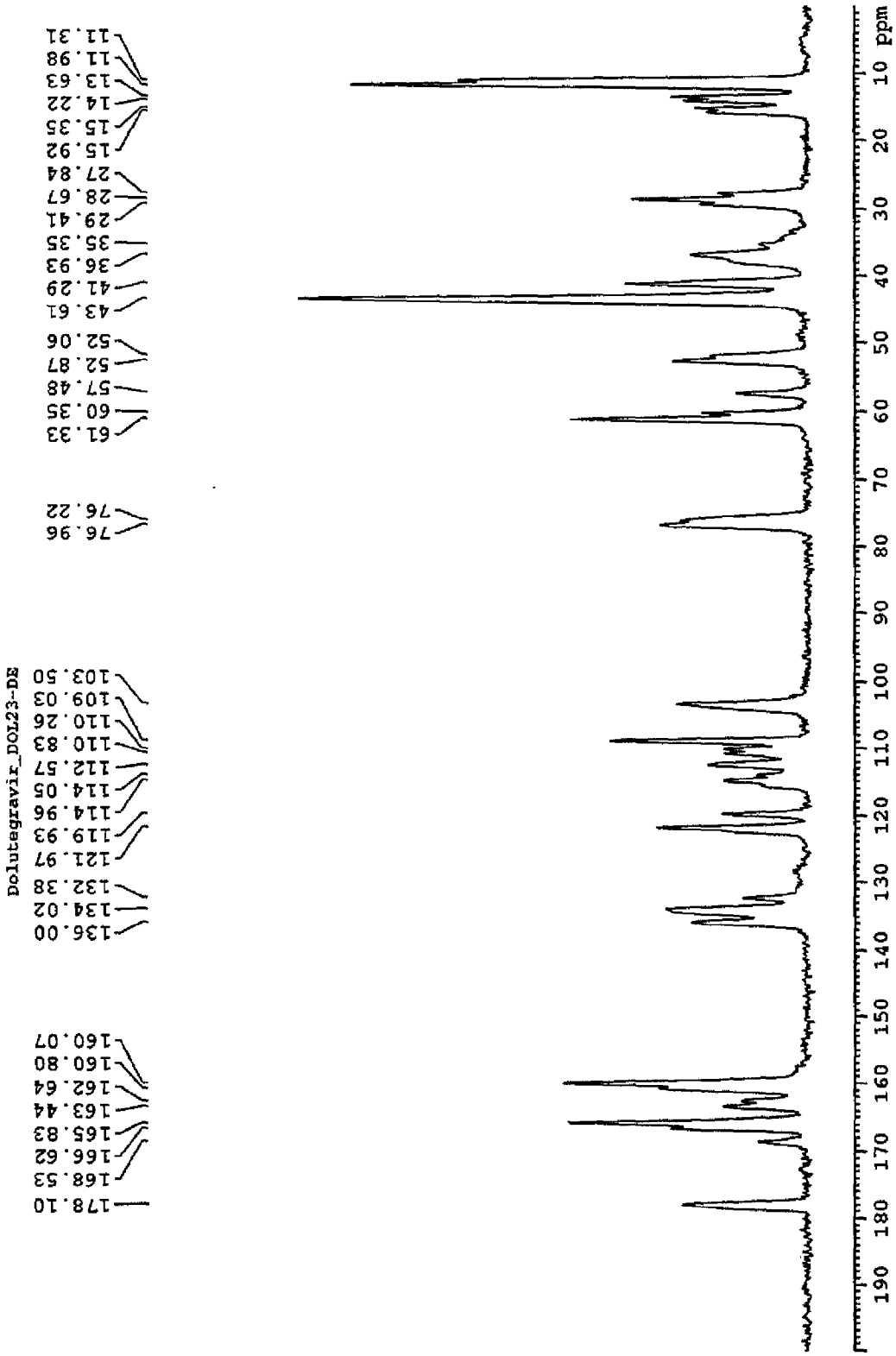
2) Heat from 20.00°C to 250.00°C at 10.00°C/min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35.35
36.93
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52.06
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60.35
61.33
76.22
76.96
103.50
109.03
110.26
110.83
112.57
114.05
114.96
119.93
121.97
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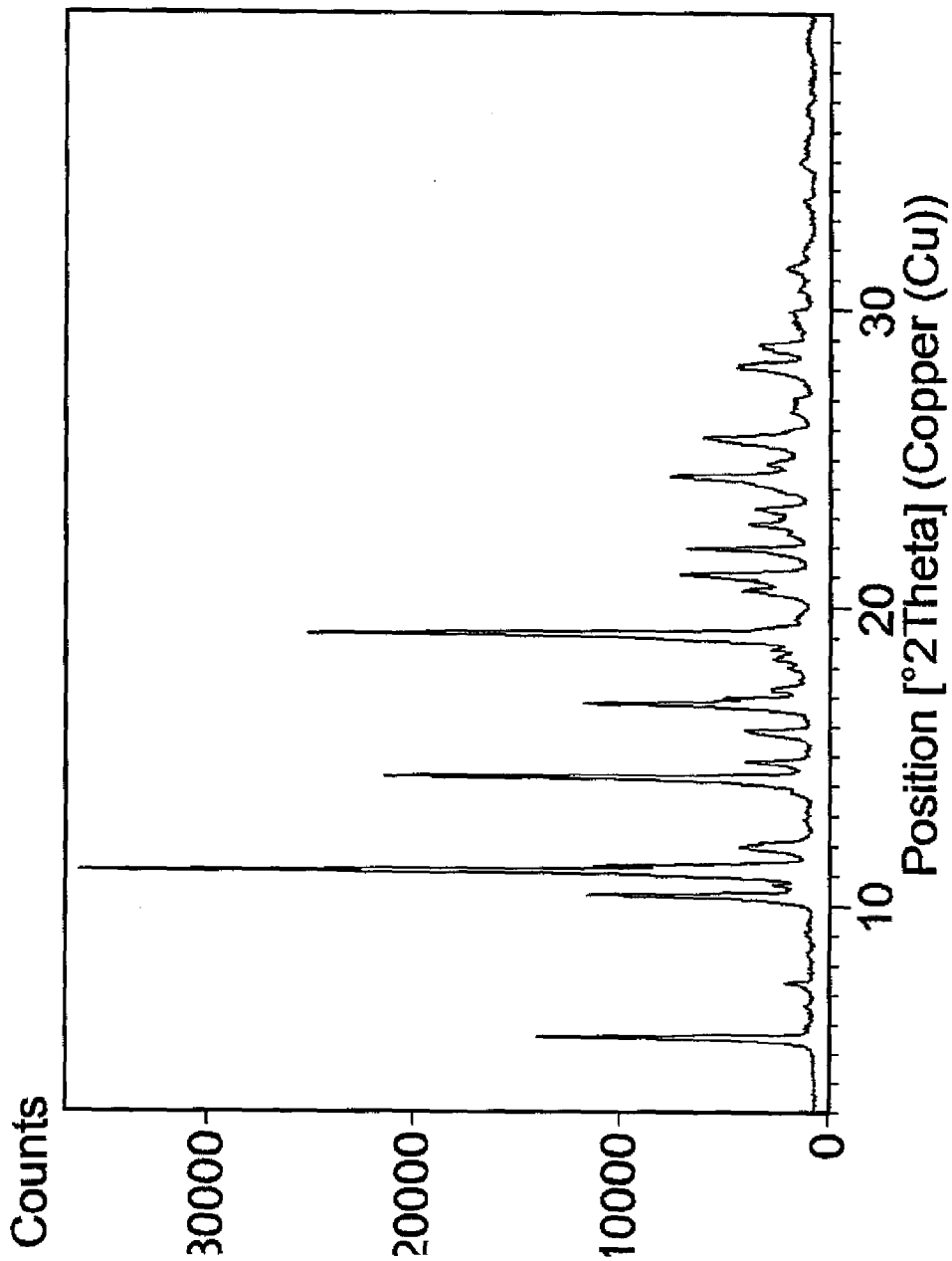
ppm

Fig. 4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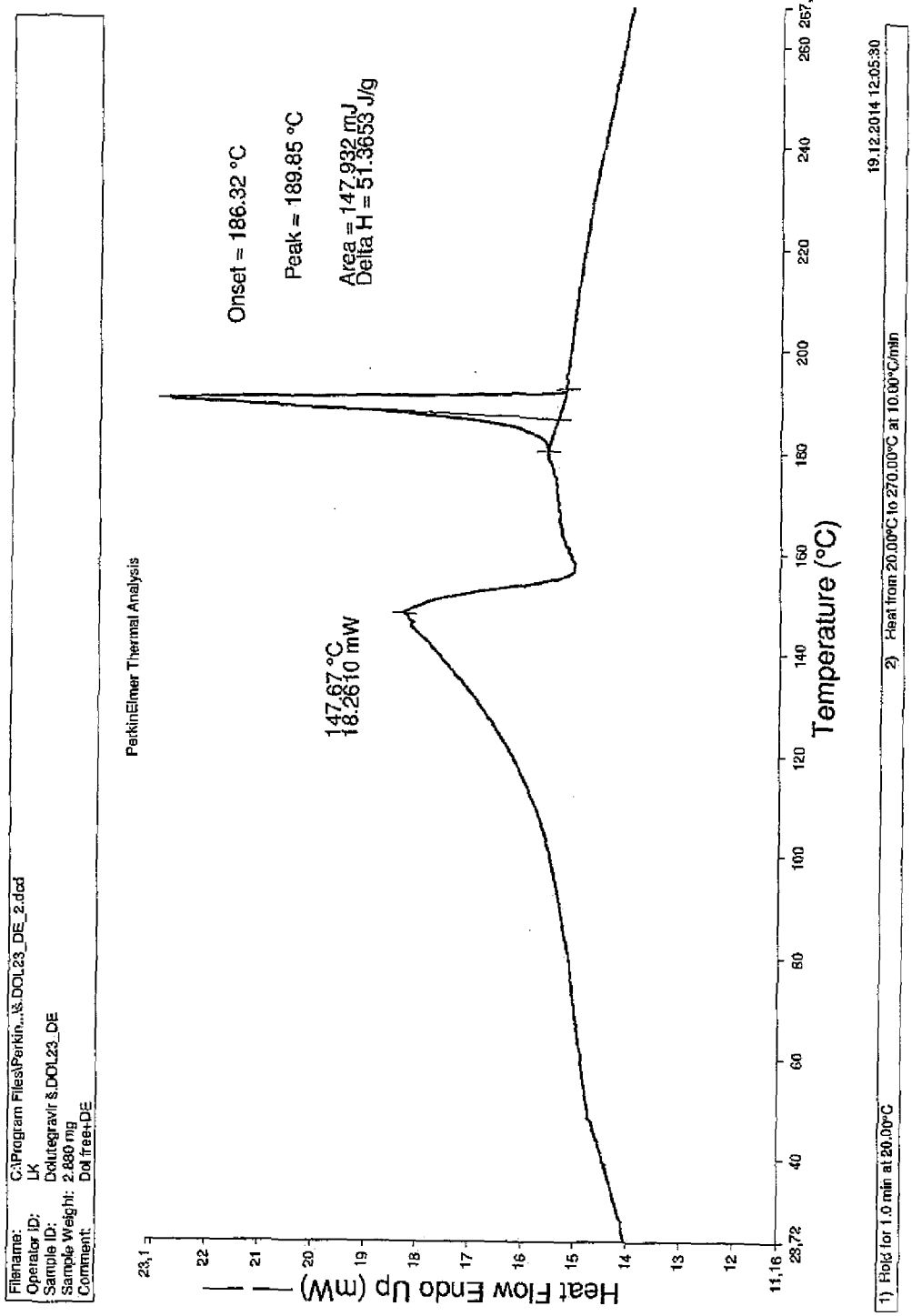
20
30
Position [°2Theta] (Copper (Cu))

Fig. 5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Operator ID: LK
Sample ID: Dolutegravir 8.DOL23_DE
Sample Weight: 2.880 mg
Comment: Dol free-DE
PerkinElmer Thermal Analysis
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Peak = 189.85 °C
Area = 147.932 mJ
Delta H = 51.3653 J/g
147.67 °C
18.2610 mW
Heat Flow Endo Up (mW)
Temperature (°C)
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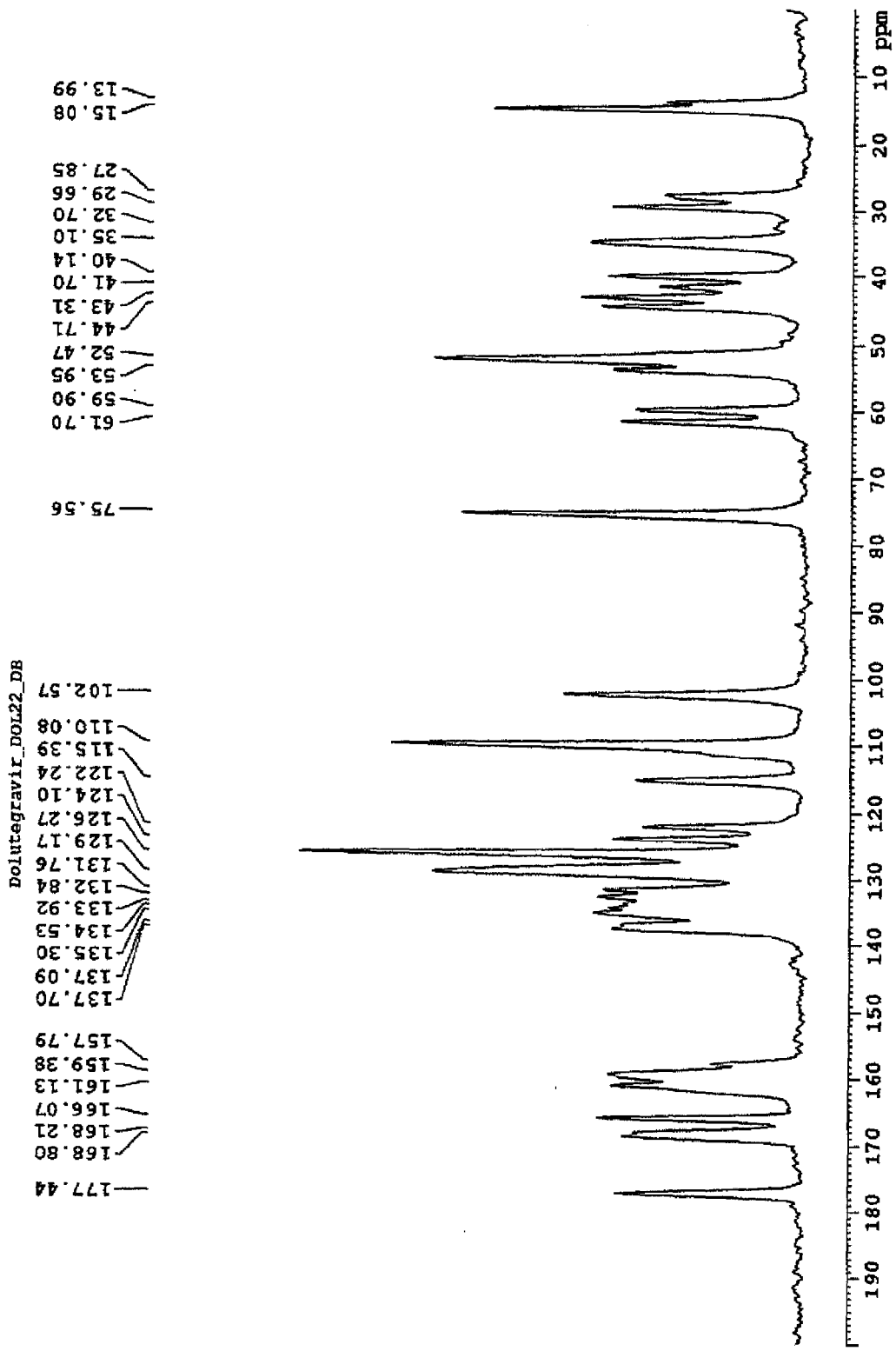
1) Hold for 1.0 min at 20.00°C
2) Heat from 20.00°C to 270.00°C at 10.00°C/min

Fig. 6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15.08
27.85
29.66
32.70
35.10
40.14
41.70
43.31
44.71
52.47
53.95
59.90
61.70
75.56
102.57
110.08
115.39
122.24
124.10
126.27
129.17
131.76
132.84
133.92
134.53
135.30
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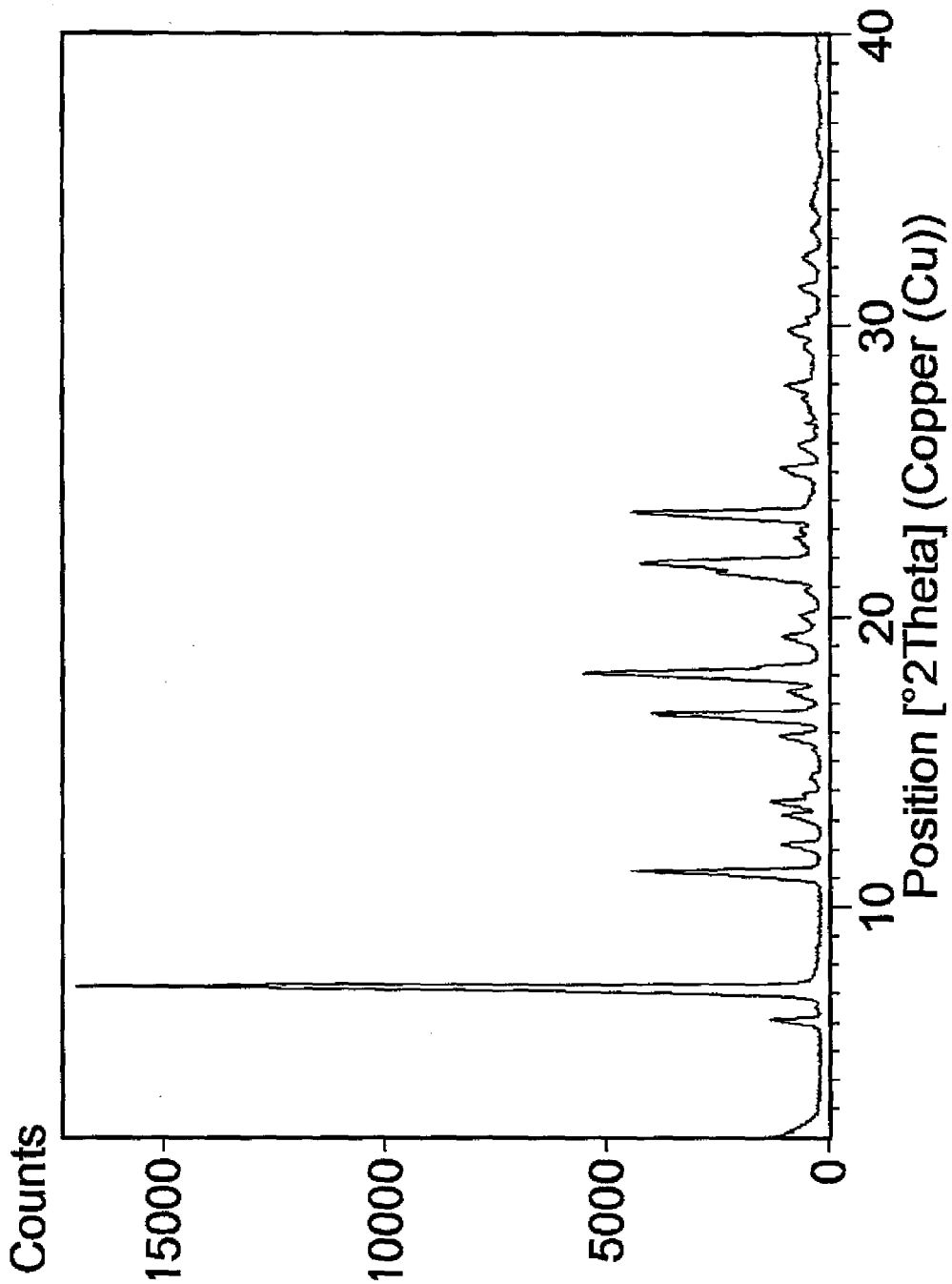
168.21
168.80
177.44
10 ppm

Fig. 7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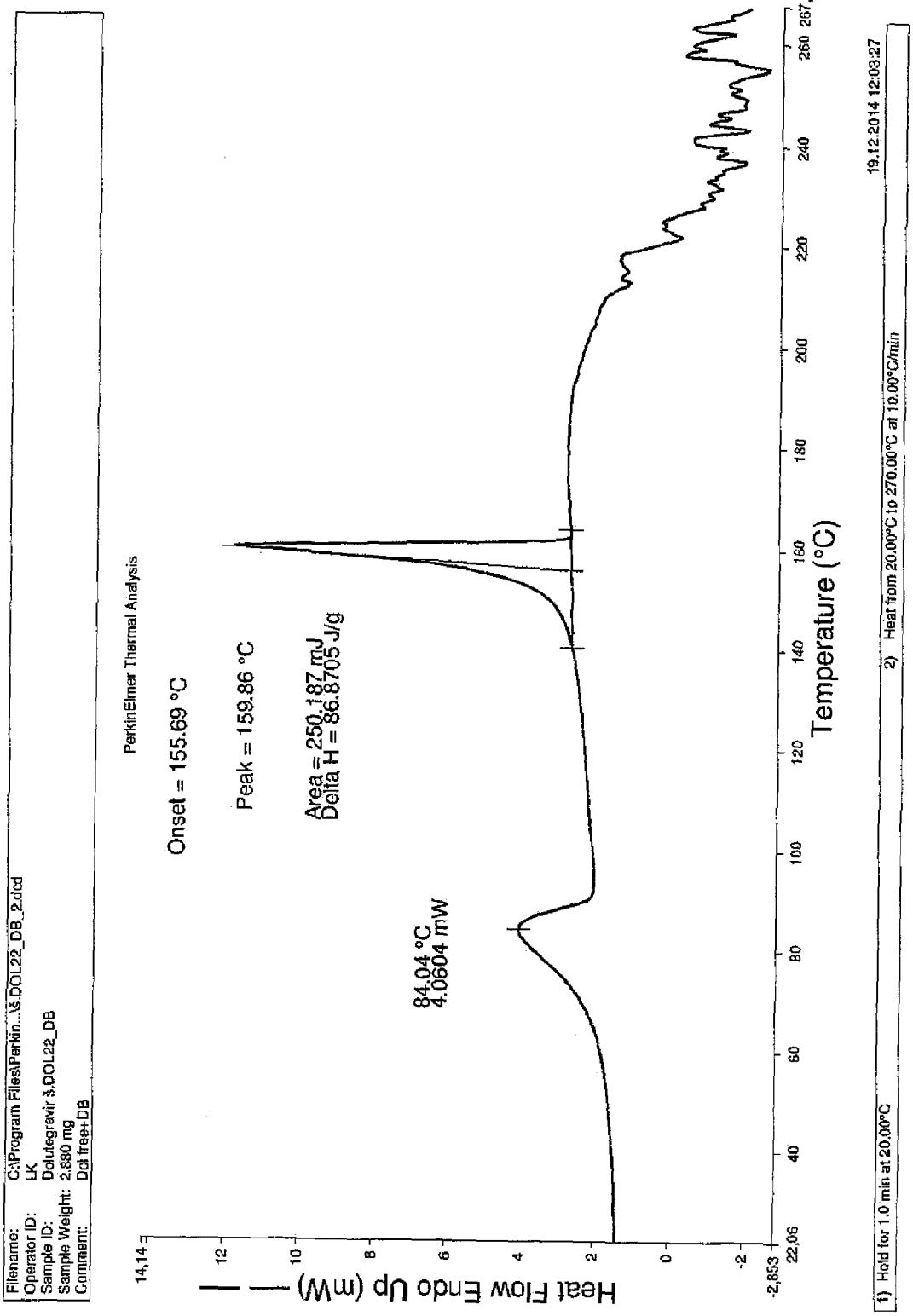
10
20
30
40
Position [°2Theta] (Copper (Cu))

Fig. 8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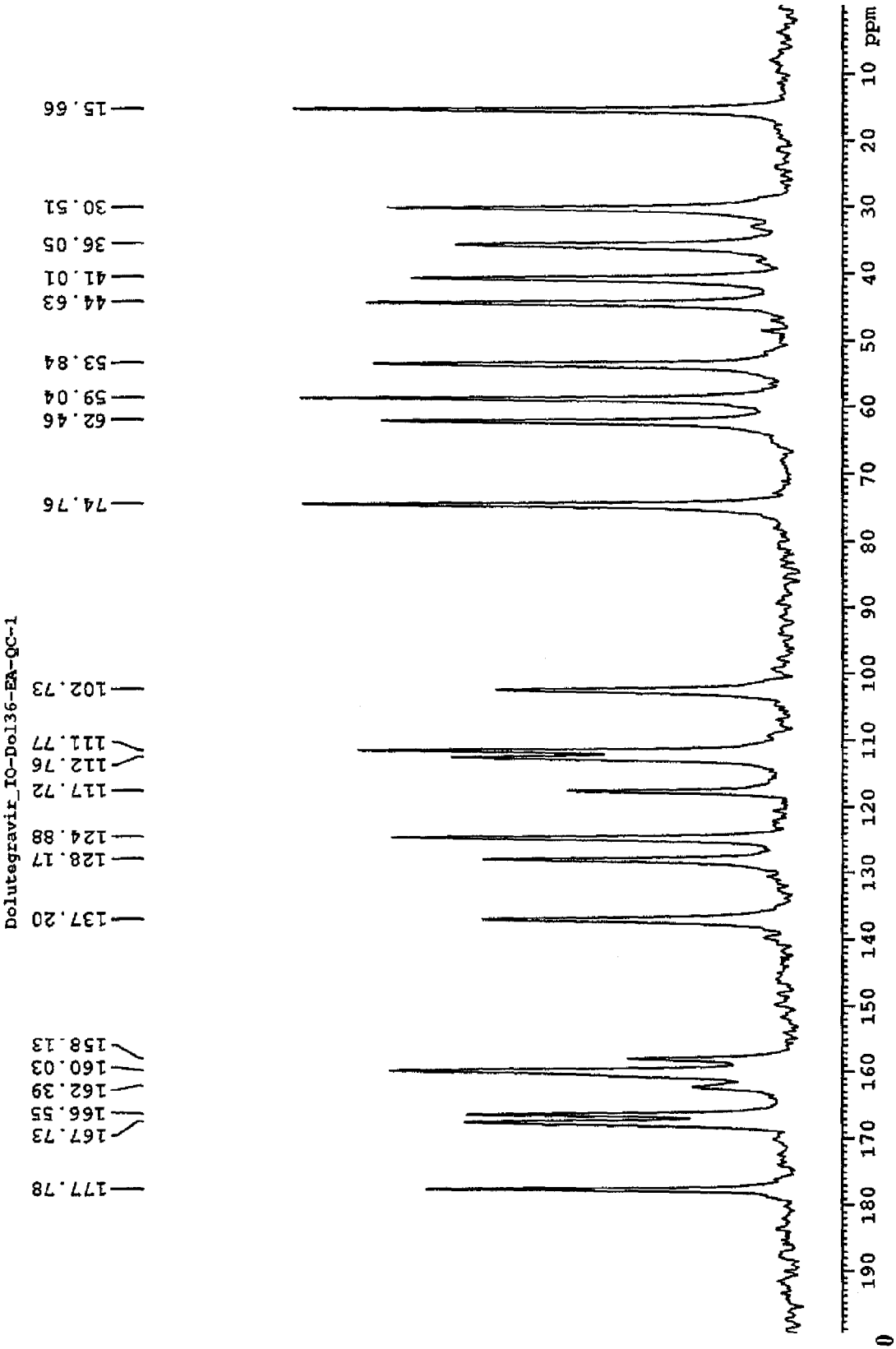
Sample Weight: 2.880 mg
Comment: Dol free+DB
PerkinElmer Thermal Analysis
Onset = 155.69 °C
Peak = 159.86 °C
Area = 250.187 mJ
Delta H = 86.8705 J/g
84.04 °C
4.0604 mW
Heat Flow Endo Up (mW)
Temperature (°C)
1) Hold for 1.0 min at 20.00°C
2) Heat from 20.00°C to 270.00°C at 10.00°C/min
19.12.2014 12:03:27

Fig. 9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36.05
41.01
44.63
53.84
59.04
62.46
74.76
102.73
111.77
112.76
117.72
124.88
128.17
137.20
158.13
160.03
162.39
166.55
167.73
177.78
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

Fig. 10

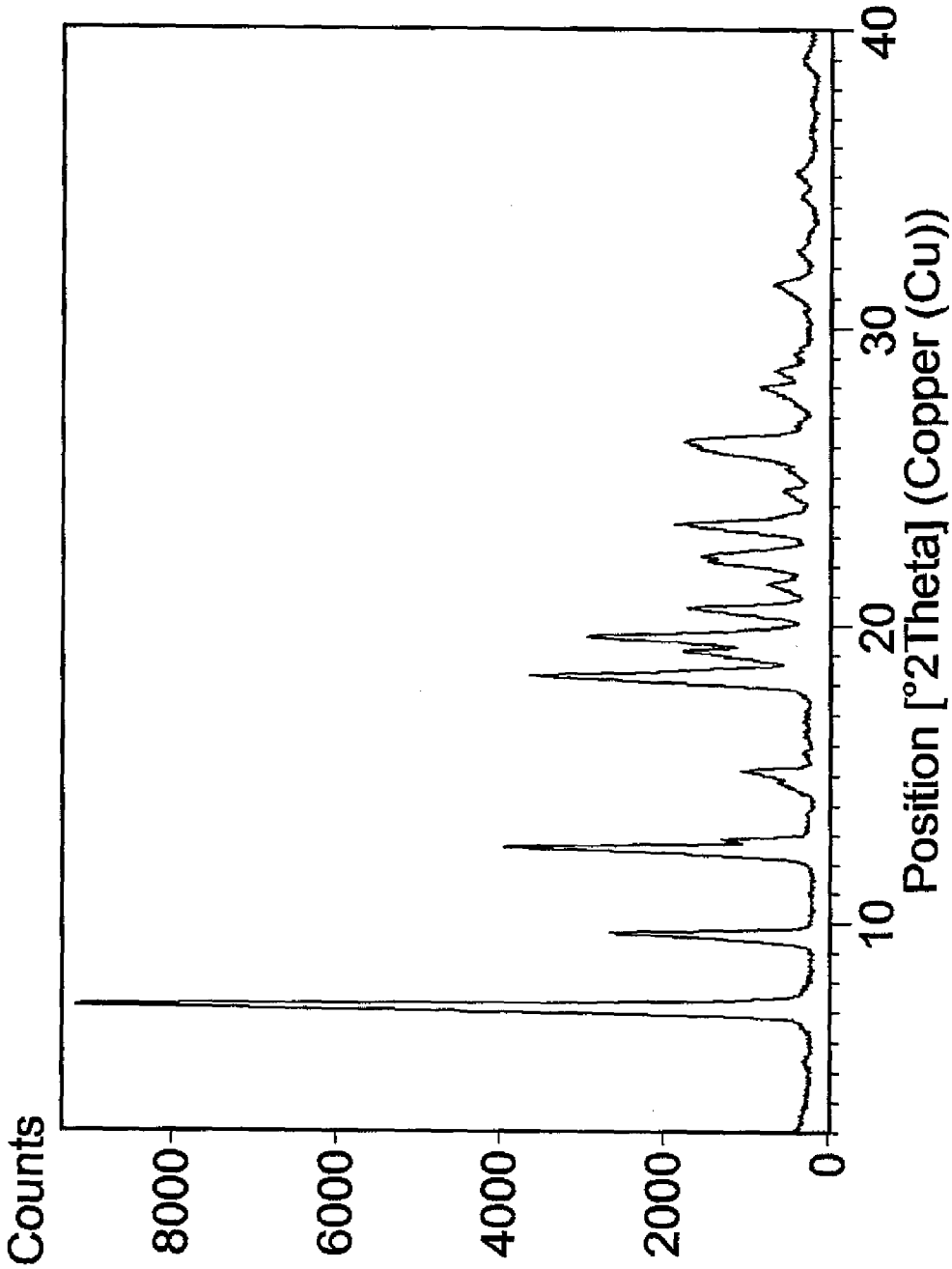
Counts
8000
6000
4000
2000
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

Fig. 11

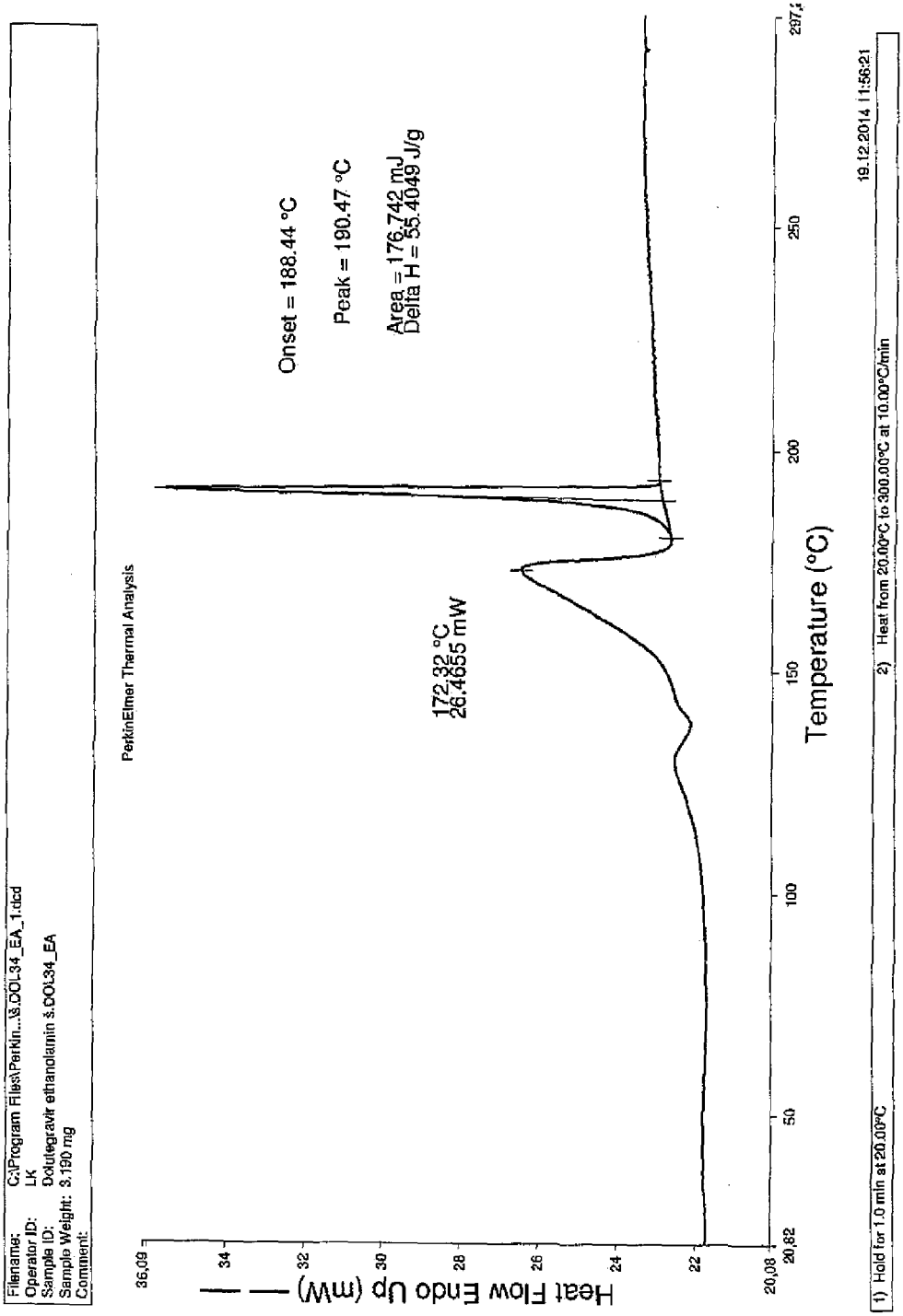
Filename: C:\Program Files\PerkIn...\8.DOL34_EA_1.dcd
Operator ID: LK
Sample ID: Dolutegravir ethanolamin s.DOL34_EA
Sample Weight: 8.190 mg
Comment:
PerkinElmer Thermal Analysis
Onset = 188.44 °C
Peak = 190.47 °C
Area = 176.742 mJ
Delta H = 55.4049 J/g
172.32 °C
28.4655 mW
Heat Flow Endo Up (mW)
Temperature (°C)
19.12.2014 11:56:21
1) Hold for 1.0 min at 20.00°C
2) Heat from 20.00°C to 300.00°C at 10.00°C/min

Fig. 12

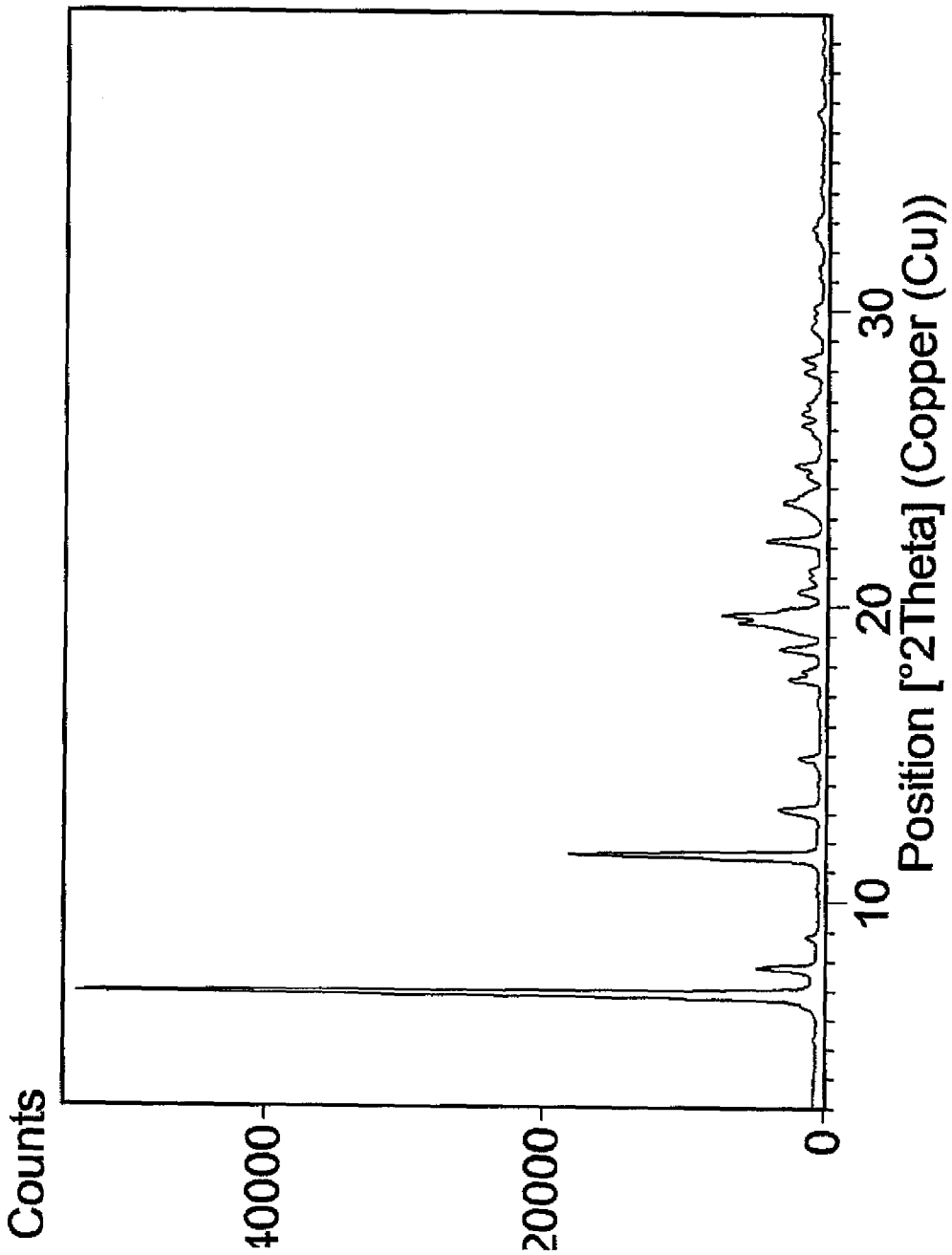

Fig. 13

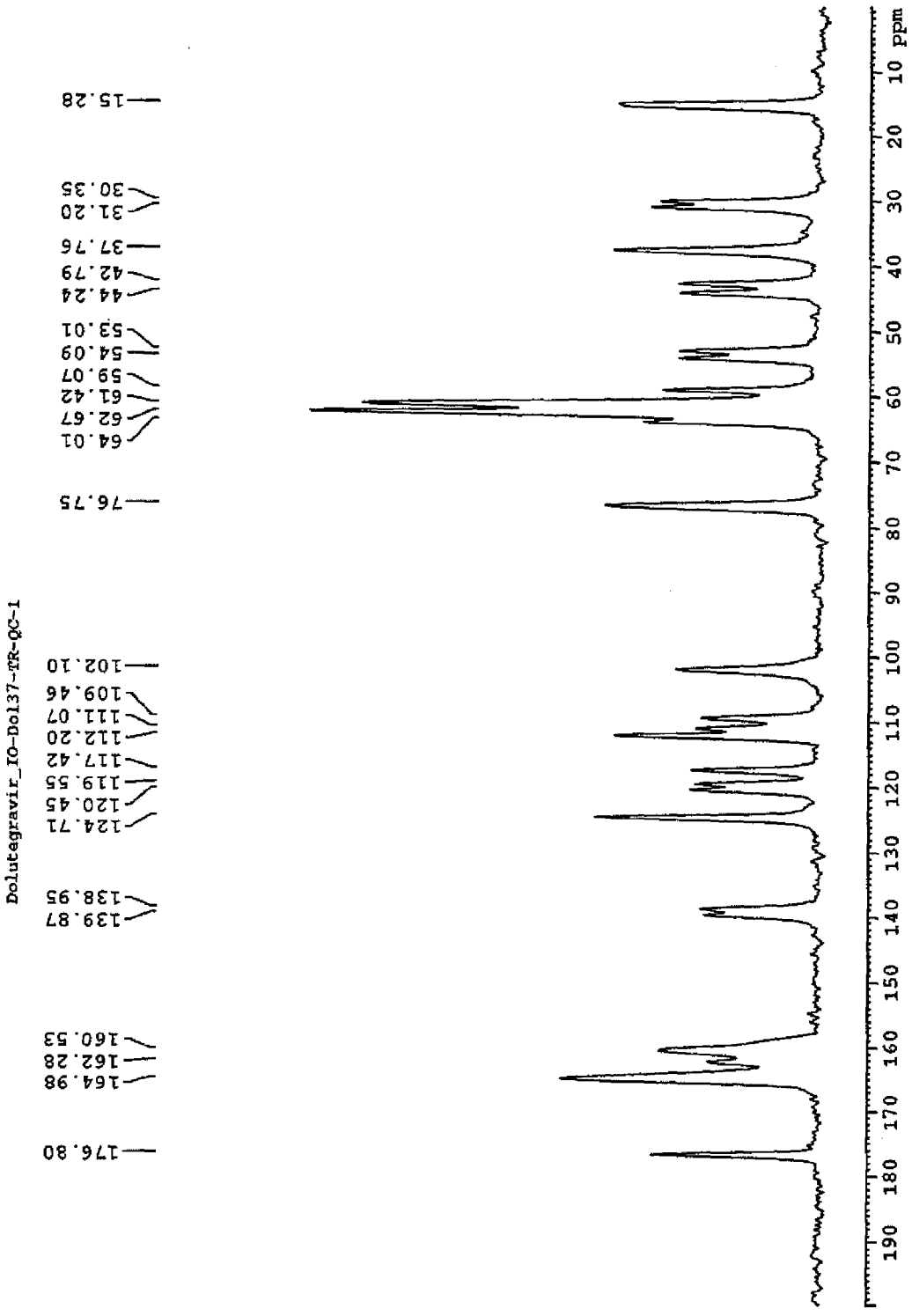
Dolutegravir_IO-Dol37-TR-QC-1
15.28
30.35
31.20
37.76
42.79
44.24
53.01
54.09
59.07
61.42
62.67
64.01
76.75
102.10
109.46
111.07
112.20
117.42
119.55
120.45
124.71
138.95
139.87
160.53
162.28
164.98
176.80
10 ppm

Fig. 14

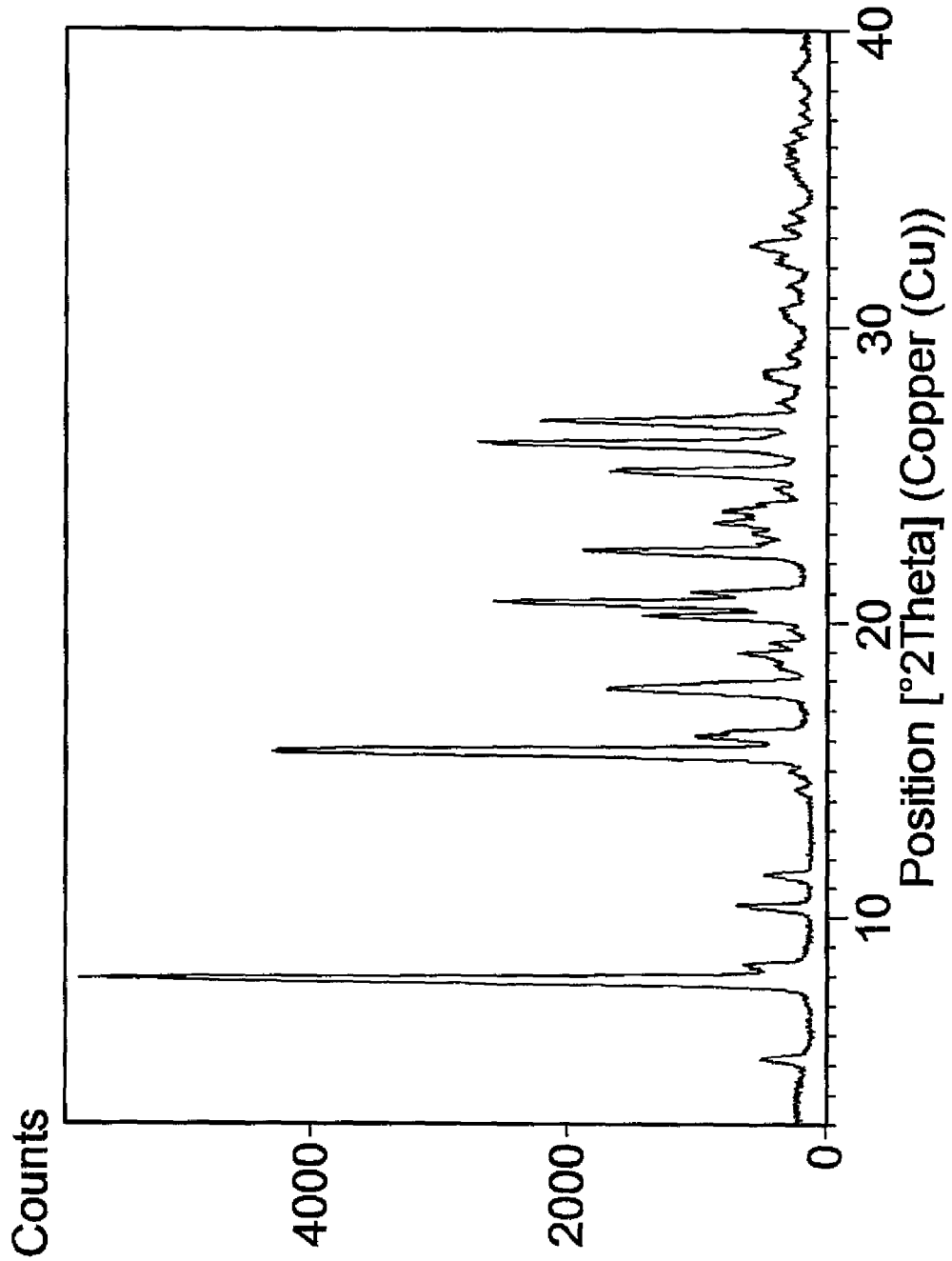

Fig. 15

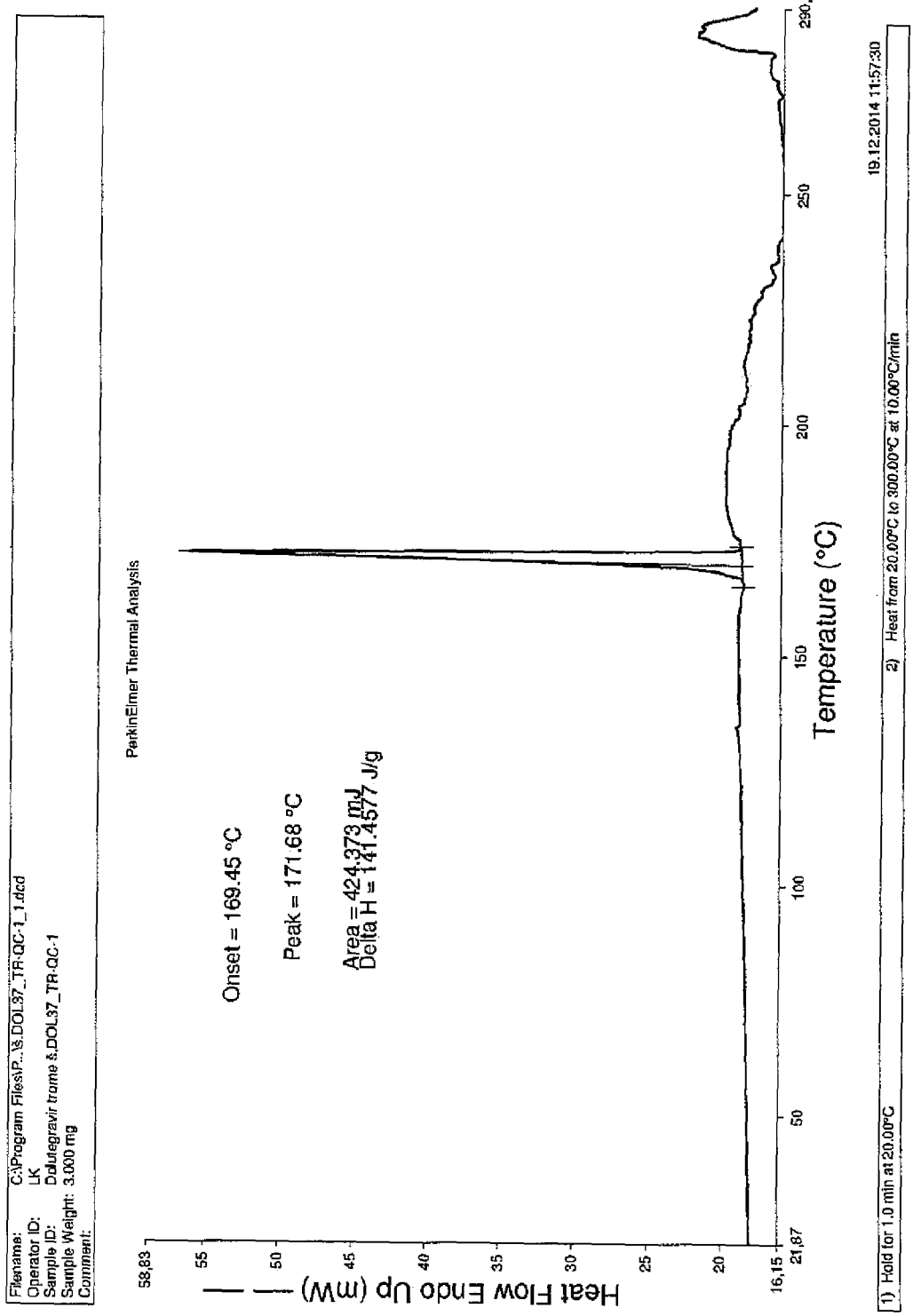
Filename: C:\Program Files\P...\S.DOL37_TR-QC-1_1.dcd
Operator ID: LK
Sample ID: Dolutegravir tramo 8.DOL37_TR-QC-1
Sample Weight: 3.000 mg
Comment:
PerkinElmer Thermal Analysis
Onset = 169.45 °C
Peak = 171.68 °C
Area = 424.373 mJ
Delta H = 141.4577 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
58,83
55
50
45
40
35
30
25
20
16,15
21,87
50
100
150
200
250
290,
19.12.2014 11:57:30
1) Hold for 1.0 min at 20.00°C
2) Heat from 20.00°C to 300.00°C at 10.00°C/min

Fig. 16

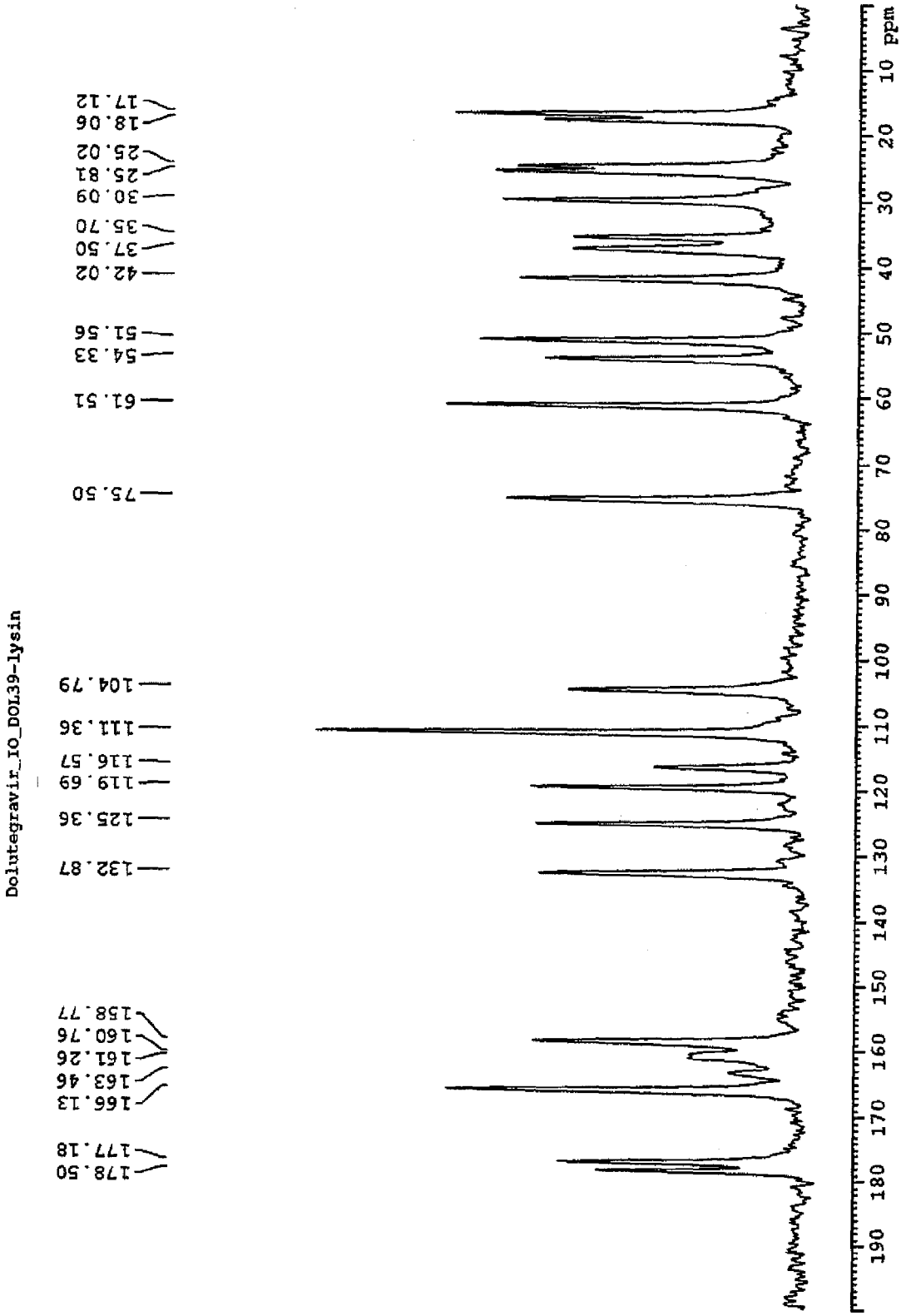
Dolutegravir_IO_DOL39-lysin
178.50
177.18
166.13
163.46
161.26
160.76
158.77
132.87
125.36
119.69
116.57
111.36
104.79
75.50
61.51
54.33
51.56
42.02
37.50
35.70
30.09
25.81
25.02
18.06
17.12
10 ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

Fig. 17

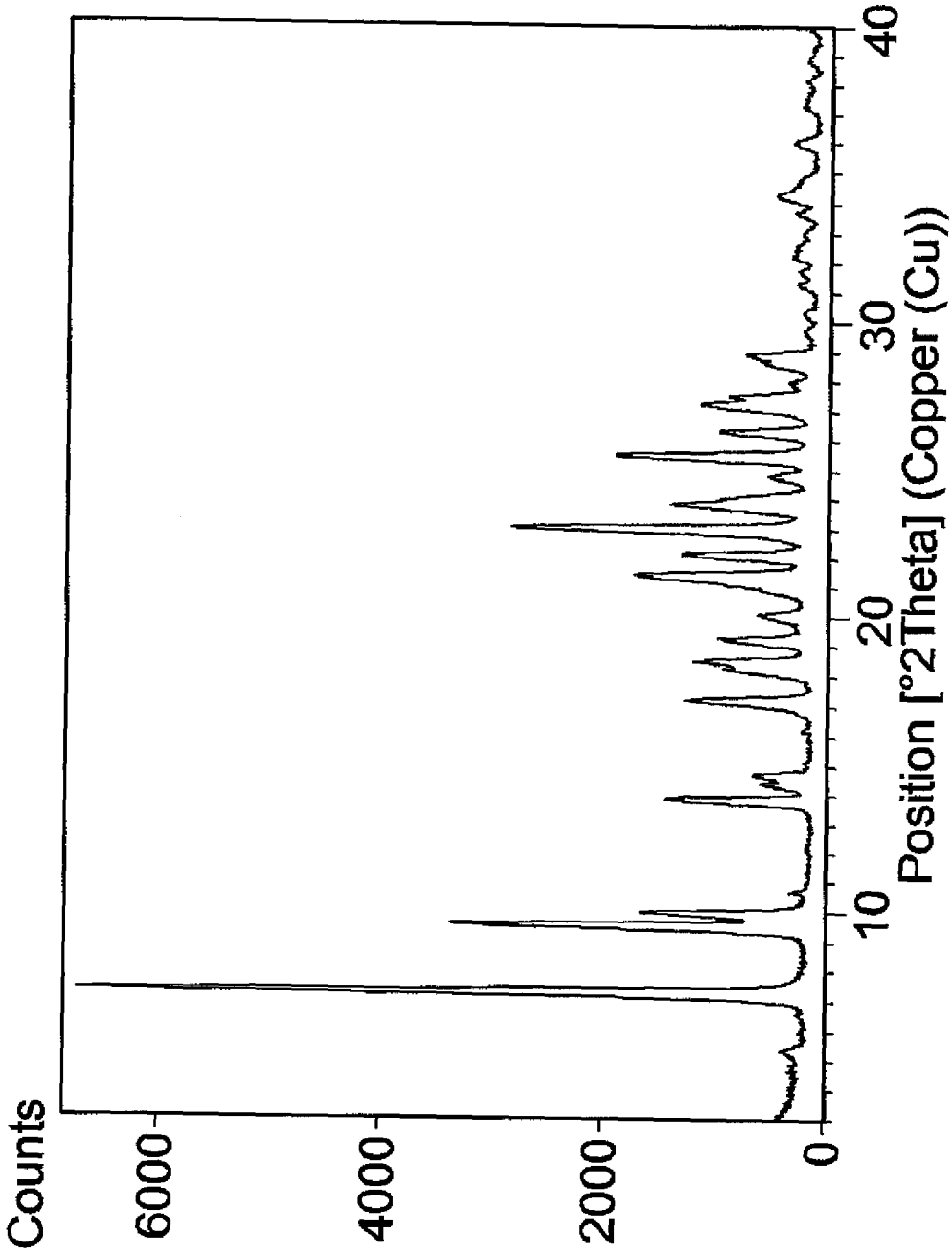

Fig. 18

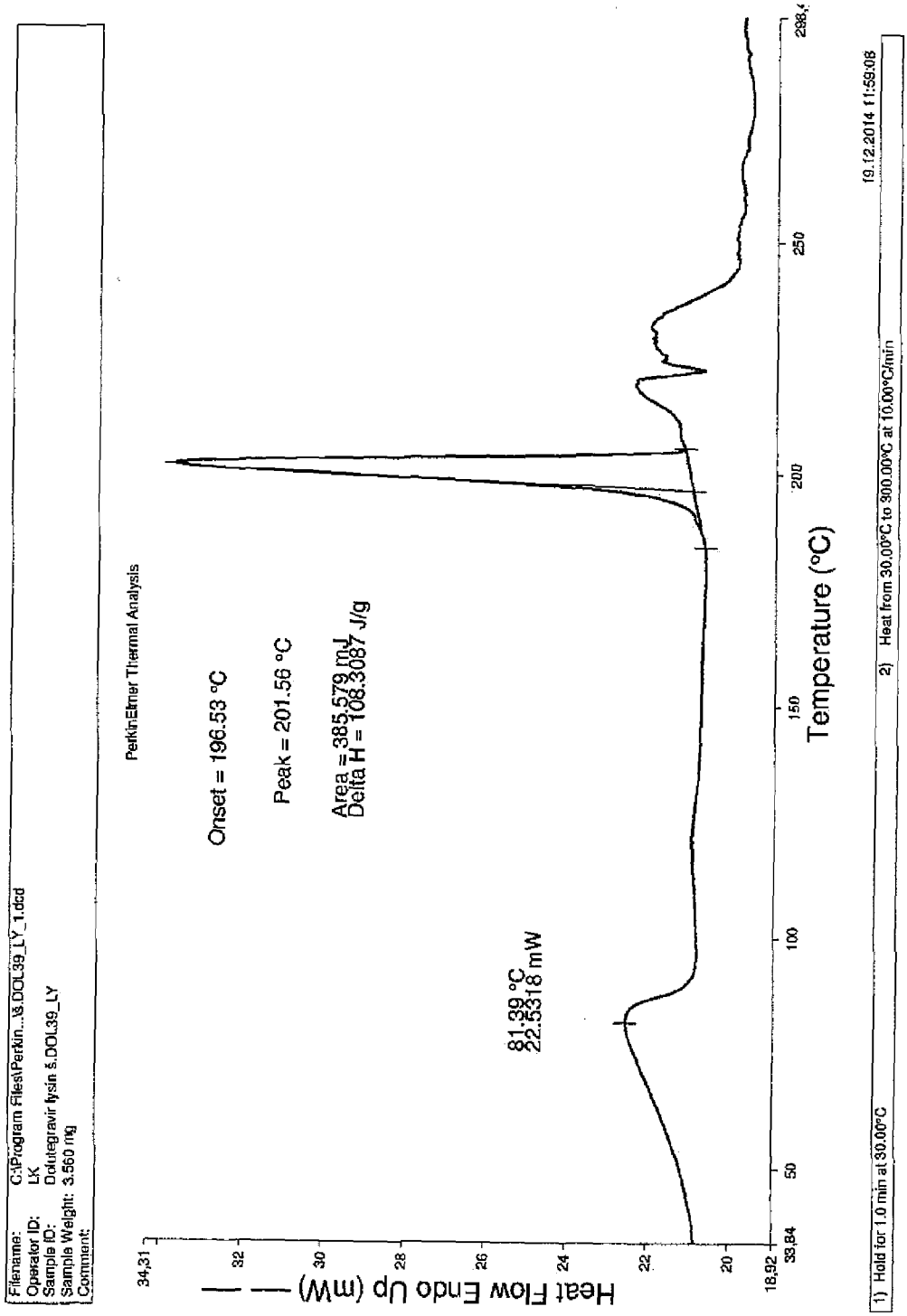
Filename: C:\Program Files\PerkinElmer\...\5.DOL39_LY_1.dcd
Operator ID: LK
Sample ID: Dolutegravir lysin 5.DOL39_LY
Sample Weight: 3.560 mg
Comment:
PerkinElmer Thermal Analysis
Onset = 196.53 °C
Peak = 201.56 °C
Area = 385.579 mJ
Delta H = 108.3087 J/g
81.39 °C
22.53318 mW
Heat Flow Endo Up (mW)
Temperature (°C)
34,31
32
30
28
26
24
22
20
18,92
33,84
50
100
150
200
250
298,4
19.12.2014 11:59:08
1) Hold for 1.0 min at 30.00°C
2) Heat from 30.00°C to 300.00°C at 10.00°C/min

Fig. 19

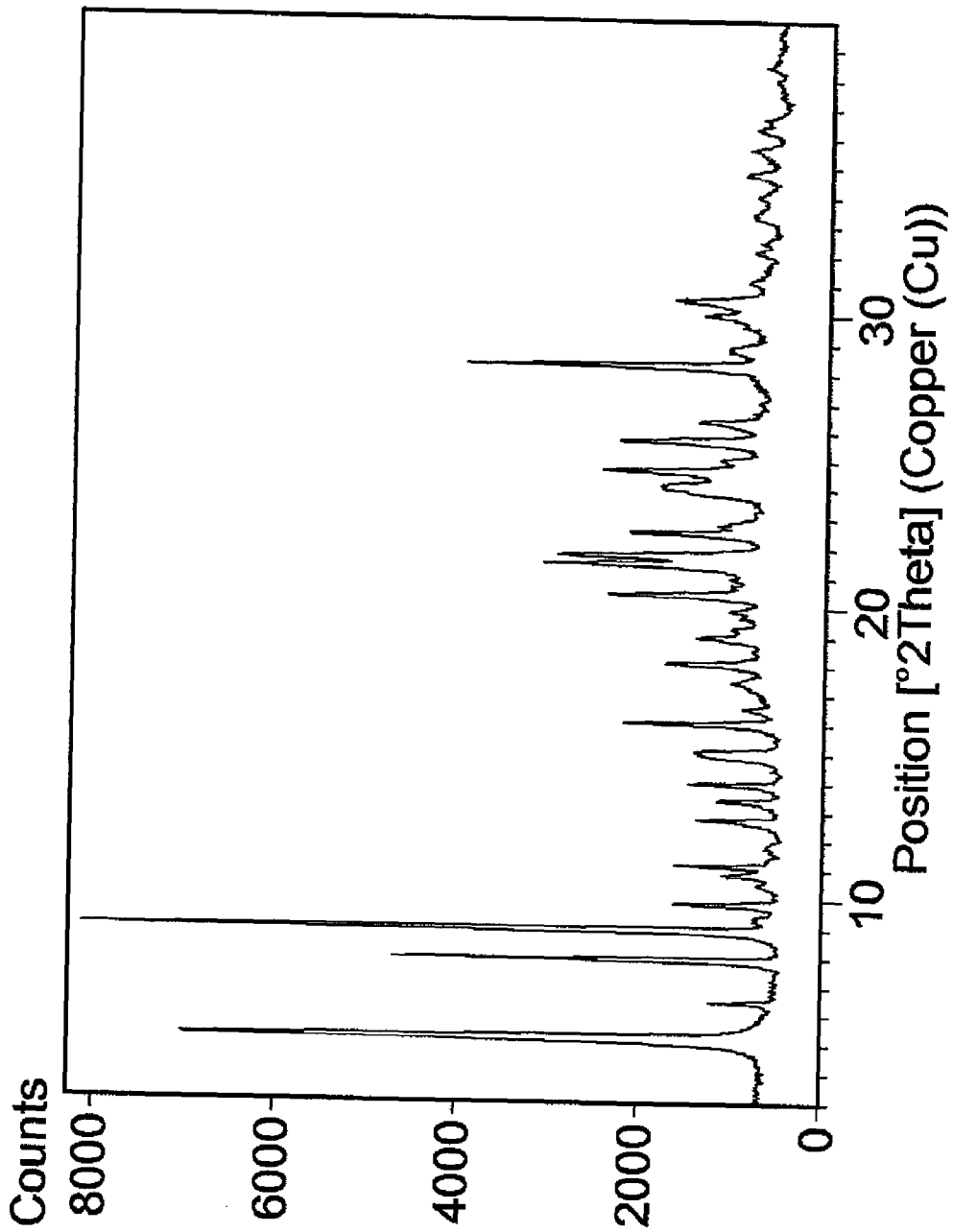
Counts
8000
6000
4000
2000
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig. 20

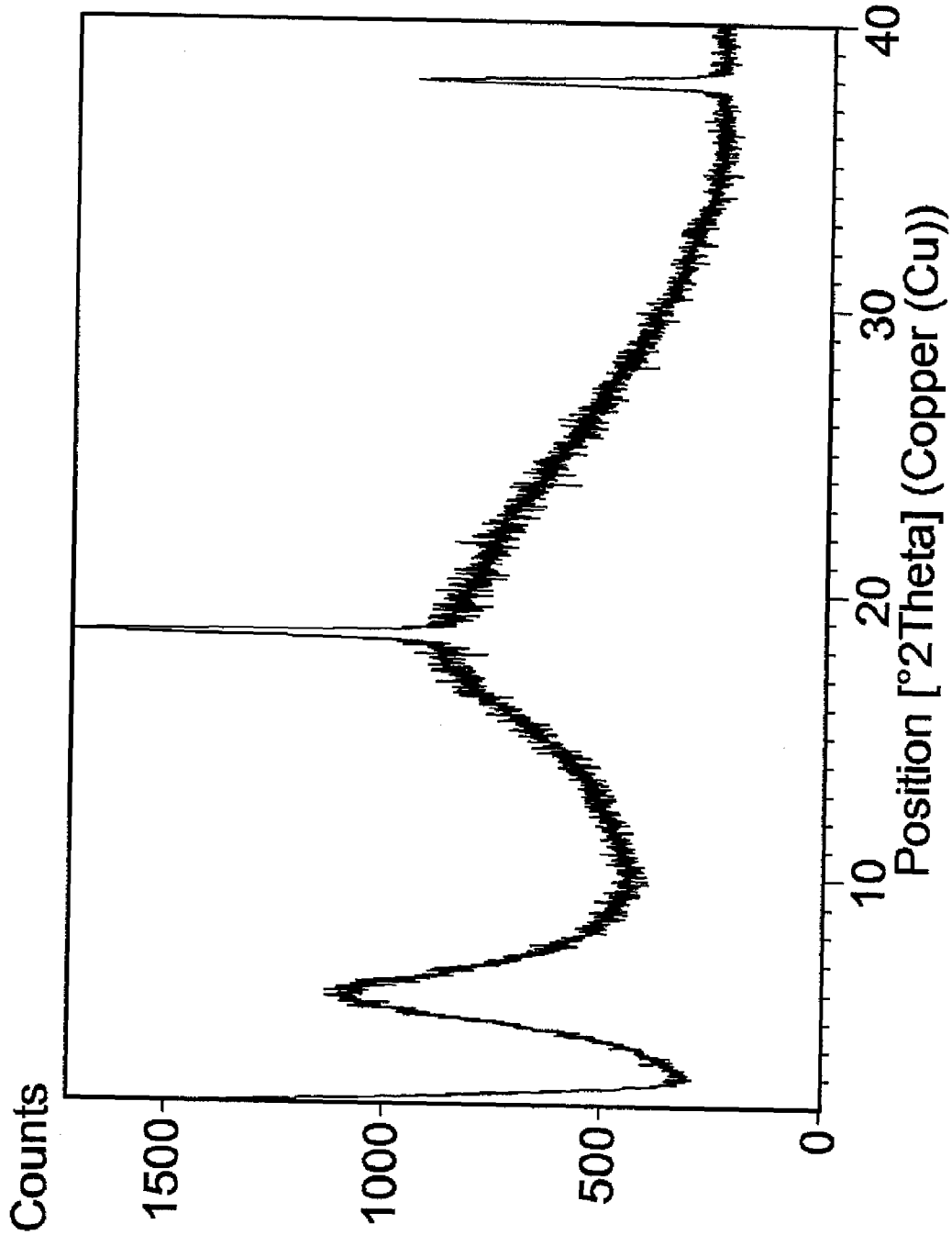

Fig. 21

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000019

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/04 A61K31/5365 A61P31/18
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 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 Y	WO 2010/068253 A1 (SHIONOGI & CO [JP]; GLAXOSMITHKLINE LLC [US]; YOSHIDA HIROSHI [JP]; TA) 17 June 2010 (2010-06-17) cited in the application Claims 14, 15, 28; page 1, lines 14-15; page 16, lines 3-7; page 17, reaction scheme: compound 13; page 22, examples 1l, 1m.	1,13-15, 24-29, 34-36, 40-45 1-12, 19-23, 28, 32-39, 42-45

X	WO 2013/038407 A1 (MAPI PHARMA LTD [IL]; MAROM EHUD [IL]; RUBNOV SHAI [IL]) 21 March 2013 (2013-03-21) cited in the application Abstract; page 2, lines 22-24; claims 1, 12, 18.	1,28,35, 43

	-/--	

[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
22 July 2016	02/08/2016

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	Weisbrod, Thomas

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CZ2016/000019

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:

see additional sheet

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.:

2-15, 19-23, 29, 32, 33, 37-39(completely); 1, 24-28, 34-36
40-45(partially)

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

International application No
PCT/CZ2016/000019

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 2015/009927 A1 (RATIOPHARM GMBH [DE]; TEVA PHARMA [US]) 22 January 2015 (2015-01-22) Abstract; claims 1, 20, 24-31; figures 4, 4A, 6, 6A, 8, 8A, 11, 12, 12A, 19, 19A; pages 25-27: examples 2A to 8; pages 30-31, example 10: dolutegravir potassium salt tablets. -----	1,13-15, 24-29, 34-36, 43-45
X,P	WO 2015/110897 A2 (LAURUS LABS PRIVATE LTD [IN]) 30 July 2015 (2015-07-30) Page 1, paragraph 0001; page 20, paragraphs 0037-0038; pages 37-38, paragraphs 00121-00127; page 60, paragraphs 00296-00303. -----	1,13,14, 24-29, 35,36, 43,44
Y	WO 2006/116764 A1 (SHIONOGI & CO [JP]; JOHNS BRIAN ALVIN [US]; KAWASUJI TAKASHI [JP]; TAI) 2 November 2006 (2006-11-02) cited in the application Title; claims; paragraph bridging pages 54 and 55. -----	1-12, 19-23, 28, 32-39, 42-45
X,P	WO 2015/177537 A1 (CIPLA LTD [IN]; KING LAWRENCE [GB]) 26 November 2015 (2015-11-26) Page 39, example 14 and page 65, claim 39: dolutegravir ethanolamine salt. -----	1-4,7,8, 19-23

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/000019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2744019 A1	17-06-2010
		CN 102245182 A	16-11-2011
		EP 2376080 A1	19-10-2011
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		RU 2011121785 A	20-01-2013
		SG 171308 A1	28-07-2011
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		US 2011282055 A1	17-11-2011
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		WO 2013038407 A1	21-03-2013
WO 2015009927 A1	22-01-2015	EP 3022209 A1	25-05-2016
		US 2016145269 A1	26-05-2016
		WO 2015009927 A1	22-01-2015
WO 2015110897 A2	30-07-2015	WO 2015110897 A2	30-07-2015
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WO 2006116764 A1	02-11-2006	AU 2006239177 A1	02-11-2006
		BR PI0610030 A2	11-10-2011
		CA 2606282 A1	02-11-2006
		CY 1115151 T1	09-12-2015
		DK 1874117 T3	23-09-2013
		DK 2465580 T3	10-03-2014
		EA 200702080 A1	28-04-2008
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		ES 2446324 T3	07-03-2014
		ES 2567197 T3	20-04-2016
		HK 1107227 A1	03-01-2014
		HK 1172282 A1	08-08-2014
		JP 4295353 B2	15-07-2009
		JP 2008540343 A	20-11-2008
		JP 2009079058 A	16-04-2009
		KR 20080009733 A	29-01-2008
		KR 20130133061 A	05-12-2013
		KR 20140097438 A	06-08-2014
		KR 20160003889 A	11-01-2016
		LU 92446 I2	29-10-2015
		MA 29460 B1	02-05-2008
		MX 302718 B	27-08-2012
		MX 312216 B	12-08-2013
		NZ 562339 A	28-01-2011

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/000019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		PT 1874117 E	17-10-2013
		PT 2465580 E	25-02-2014
		SI 1874117 T1	31-01-2014
		SI 2465580 T1	30-04-2014
		TW I378931 B	11-12-2012
		US 2009318421 A1	24-12-2009
		US 2012115875 A1	10-05-2012
		US 2013172559 A1	04-07-2013
		US 2014200209 A1	17-07-2014
		US 2015232479 A1	20-08-2015
		US 2016137666 A1	19-05-2016
		VN 34404 A1	25-07-2013
		WO 2006116764 A1	02-11-2006
WO 2015177537 A1	26-11-2015	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 13-15, 29(completely); 1, 24-28, 34-36, 40-45(partially)

   relating to the potassium salt of dolutegravir or its solvate.

   ---

2. claims: 16-18, 30, 31(completely); 1, 24-28, 34-36, 40-45(partially)

   relating to the magnesium or calcium salt of dolutegravir or their solvate.

   ---

3. claims: 2-12, 19-23, 32, 33, 37-39(completely); 1, 28, 34-36, 42-45(partially)

   relating to a salt of dolutegravir with an amine or their solvate.
