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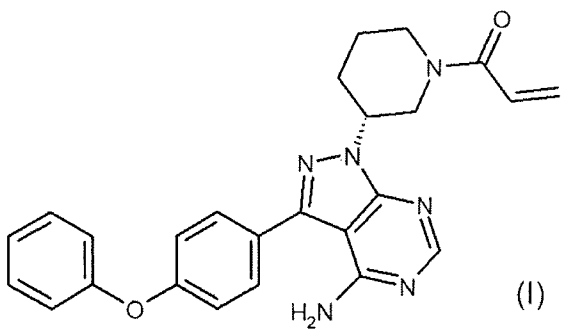
(54) Title: ACID ADDITION SALT OF IBRUTINIB

(57) Abstract: The present invention relates to acid addition salts of ibrutinib, a pharmaceutical composition comprising the same as well as a method of preparing the same.

Acid addition salt of ibrutinib

The present invention relates to acid addition salts of ibrutinib, a method of preparing the same as well as a pharmaceutical composition comprising the same.

Ibrutinib (1-[(3R)-3[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl] piperidin-1-yl]prop-2-en-1one) has the following chemical structure (I):



(I)

This pharmaceutically active ingredient is known from WO 2008/039218. Ibrutinib is an inhibitor of bruton's tyrosine kinase (BTK). BTK is a key mediator of at least three critical B-cell pro-survival mechanisms occurring in parallel regulating B-cell apoptosis, cell adhesion and lymphocyte migration and homing. By inhibiting BTK ibrutinib drives B-cells into apoptosis and/or disrupts cell immigration and adherence to tumor-protective microenvironments. Ibrunitib is therefore suitable for treating chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) which are B-cell non-hodgkin lymphomas (NHL). It is marketed in the US under the name Imbruvica.

Crystalline polymorphic forms of ibrutinib are disclosed in WO 2013/184572.

Pharmaceutical formulations comprising ibrutinib are disclosed in WO 2014/004707A1.

Ibrutinib has a very low solubility in water e.g. form A of ibrutinib shows according to WO 2013/184572, an observed aqueous solubility of only about 0.013mg/ml at about pH 8. The solubility strongly depends on the pH. This results in problems in the bioavailability of the active ingredient, first because of the low solubility, and second its solubility depends

on the pH value in the stomach of the patient. Particular problems arise from patients wherein the pH value is altered, e.g. due to physiological variability, diseases or premedication such as PP-inhibitors. Therefore, there is a need for oral pharmaceutical compositions that contain ibrutinib in a form which is highly soluble and thus provides a reliable bioavailability of the active ingredient.

As further forms of ibrutinib, both WO 2013/184572 and WO 2014/004707 generally disclose pharmaceutically acceptable salts of ibrutinib, including acid addition salts. However, none of these documents discloses any properties of specific salts. Further, none of these documents discloses methods how to obtain such salts, nor discloses that such salts have been obtained.

When one tries to prepare acid addition salts of ibrutinib following conventional procedures of the preparation of acid addition salts of pharmaceutical ingredients, high amounts of impurities are formed. That is, preparation of acid addition salts by a conventional method is not suitable for the preparation of pharmaceutical products comprising this active ingredient.

It has now surprisingly been found that the above-mentioned and further problems are solved by a specific method of preparing acid addition salts of ibrutinib, which comprises cooling the solution of ibrutinib when adding the acid to obtain the acid addition salt. This method allows for the first time preparation of acid addition salts of ibrutinib with high purity suitable for pharmaceutical preparations. Further it seems that only strong acids with a low pK_a (e.g. below about 2) are able to deprotonate ibrutinib to convert it into an acid addition salt.

Therefore the present invention relates to a method for preparing an acid addition salt of ibrutinib comprising the steps of a) dissolving ibrutinib in a suitable solvent, preferable an organic solvent, and b) contacting the obtained solution with the acid, wherein the solution of ibrutinib is cooled during addition of the acid. Preferably the method further comprises a step c) of precipitating the acid addition salt in a suitable antisolvent of the salt.

In the method of the present invention in step a) any suitable solvent for ibrutinib can be used which are known to the skilled person. Preferably, an organic solvent, more preferably a polar organic solvent, such as dichloromethane, chloroform, tetrahydrofurane

(THF) or methanol can be used. Most preferably ibrutinib is dissolved in dichloromethane. The solution of ibrutinib is cooled before adding the acid in step b), and preferably during addition of the acid in step b). The temperature of the solution of ibrutinib in step b) is below room temperature (22°C), preferably below 10°C, more preferably below 0°C, even more preferably below -5°C, in particular below -10°C, e.g. below -15°C, or even below -20°C.

In the method of the present invention in step b) the molar ratio of acid to ibrutinib is typically equal to or above 1, typically equal to or below 5, preferably in the range of 1 to 2, more preferably 1 to 1.5, even more preferred 1 to 1.3, in particular 1 to 1.2, e.g. about 1. In the method of the invention preferably the acid is added in step b) until these molar ratios are reached, preferably at the temperatures as defined above.

In step b) the solution of ibrutinib can be contacted with the acid following conventional procedures, preferably under stirring. Preferably the method of the invention is conducted under water-free conditions. Preferably, the acid is used in step b) is water-free in an organic solvent which may be the same or a different solvent as used for dissolving ibrutinib. The acids are typically commercially available in suitable organic solvents, e.g. hydrogen chloride in diethylether or isopropanol, which is preferably used according to the present invention to produce the preferred acid addition salt ibrutinib hydrochloride.

In a preferred embodiment the method of the present invention further comprises a step c) of precipitating the acid addition salt in a suitable antisolvent of the acid addition salt of ibrutinib. Suitable antisolvents of the acid addition salt are known to the skilled person. Preferably as antisolvent a weak polar or nonpolar organic solvent, such as methyl tert.-butylether (MTBE), diethylether, n-hexane or n-heptane is used. Also preferred as antisolvents are C_3 – C_6 alcohols, such as isopropanol. Most preferably the acid addition salt of ibrutinib is precipitated by addition of MTBE or isopropanol. The addition of the antisolvent is preferably performed under vigorous stirring. Preferably step c) is conducted at a temperature of below room temperature (22°C), preferably below 10°C, more preferably below 0°C, even more preferably below -5°C, in particular below -10°C, e.g. below -15°C, or even below -20°C. Most preferably the same temperature is used in step c), i.e. precipitating the acid addition salt, which is also used in step b), i.e. contacting the solution of ibrutinib with the acid. Cooling in step c) has been found to be advantageous for

the preparation of the precipitate of the acid addition salt of ibrutinib, as the precipitate can be easily removed from the solution and shows advantageous flowability characteristics.

The method of the present invention surprisingly allows preparing acid addition salts of ibrutinib with very high purity, in particular suitable for pharmaceutical compositions, which also have an improved solubility compared to ibrutinib free base.

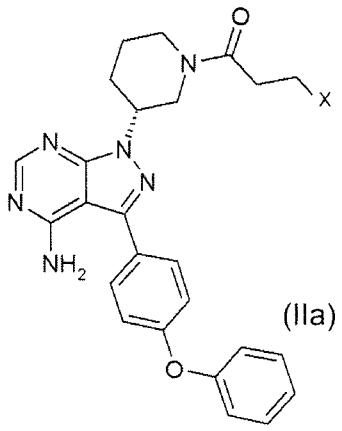
Therefore, the present invention also relates to acid addition salts of ibrutinib having a high purity, in particular suitable for pharmaceutical compositions, of at least 99.0%, preferably at least 99.5% more preferably at least 99.8%, in particular at least 99.9%. Purity can be determined by HPLC/UV (as defined below) and is expressed in [area-%] at the wavelength of the UV detection of λ=230 nm. Preferably the same purity, i.e. of at least 99.0%, preferably at least 99.5% more preferably at least 99.8%, in particular at least 99.9% is achieved in [area-%] at the wavelength of the UV detection of λ=254 nm.

The acid addition salts of ibrutinib can be prepared with known acids for the preparation of pharmaceutical acceptable salts. Preferably, inorganic acids are used such as hydrochloric acid or hydrobromic acid, most preferably hydrochloric acid is used. Preferably, the pK_a of the acid used is equal to or below 3, in particular below 1.

It has been found that when acid addition salts of ibrutinib are prepared according to known processes for the preparation of acid addition salts under conventional conditions, e.g. addition of acids to ibrutinib in a suitable solvent at room temperature, impurities are formed, which seem to be reaction products of an nucleophilic addition of the acid at the acrylic double bond of ibrutinib. It has further been found by the inventors that increasing the temperature during or after addition of the acid led to nearly quantitative preparation of the addition reaction product of the acid with the acrylic double bond of ibrutinib. On the other side, the inventors found that cooling the solution during the step of adding the acid to the solution of ibrutinib allows preparation of the acid addition salt with high purity, and in particular with very low content of the addition reaction product.

Therefore, the present invention also relates to acid addition salts of ibrutinib, in particular of the acids as defined in the above, wherein the content of the addition reaction product of the added acid with the acrylic double bond of ibrutinib is lower than 1% by weight, preferably lower than 0.5% by weight, more preferably by lower than 0.2% by weight, in

particular lower than 0.1% by weight. In general the addition reaction product of the added acid with the acrylic double bond of ibrutinib has the chemical formula (IIa):



(IIa)

wherein residue X corresponds to the deprotonated acid, such as Cl or Br, respectively, preferably residue X is Cl.

It has further surprisingly been found that it seems that only two selected salts, namely the hydrochloride and the hydrobromide salt of ibrutinib, can be obtained in crystalline and in excellent pure state. This allows the preparation of an active pharmaceutical ingredient in good crystalline quality with advantageous handling properties such as good flowability, in particular suitable for pharmaceutical compositions, which also has an improved solubility compared to ibrutinib free base.

In a preferred embodiment the present invention relates to ibrutinib hydrochloride. Ibrutinib hydrochloride is characterized by a ^{1}H-NMR spectrum showing the following signals: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 1 H); 1.86 - 1.98 (m, 1 H); 2.15 (m, 1 H); 2.23 (m, 1 H); 2.98 - 3.10 (m, 0.5 H); 3.22 (m, 1 H); 3.61 - 3.76 (m, 0.5 H); 4.05 (m, 0.5 H); 4.16 (m, 1 H); 4.54 (m, 0.5 H); 4.75 (m, 1 H); 5.53 - 5.73 (m, 1 H); 5.99 - 6.20 (m, 1 H); 6.60 - 6.93 (m, 1 H); 7.07 - 7.24 (m, 5 H); 7.37 - 7.49 (m, 2 H); 7.65 (d, J=8.21 Hz, 2 H); 8.57 (s, 1 H). A ^{1}H-NMR spectrum of ibrutinib hydrochloride is shown in figure 1.

Ibrutinib hydrochloride is further characterized by an IR-spectrum showing the following peaks: 3350; 3001; 1676; 1637; 1614; 1599; 1518; 1489; 1452; 1439; 1346; 1232; 1200;

1165; 1134; 1092; 987; 964; 868; 847; 789; 754; 723; 692; 629 cm^{-1}. A IR-spectrum of ibrutinib hydrochloride is shown in Figure 2.

It has been found that by the process of the invention ibrutinib hydrochloride can be prepared in excellent purity. Therefore, the present invention also relates to crystalline acid addition salts of ibrutinib, in particular, crystalline ibrutinib hydrochloride and crystalline ibrutinib hydrobromide. While ibrutinib base (Form A) is substantially insoluble at pH 4.5 and pH 6.8, ibrutinib hydrochloride has a solubility in water at 37°C of 0.02 mg/ml and 0.05 mg/ml at pH 4.5 and pH 6.8 respectively (after 1 hour) and 0.46 mg/ml and 0.41 mg/ml at pH 4.5 and pH 6.8 respectively (after 24 hours).

Moreover as expected, ibrutinib base (form A) has increased solubility at pH 1.2 (in 0.1M HCl) of 2.07 mg/ml. However, crystalline ibrutinib hydrochloride has an unexpectedly high solubility at pH 1.2 (in 0.1M HCl) of 7.37 mg/ml.

This may result in a significantly increased bioavailability of the active ingredient.

In a preferred embodiment the present invention provides crystalline ibrutinib hydrochloride in a certain polymorphic form which shows an XRPD pattern having peaks at 9.8, 13.6, 15.1, 17.0 and 21.1 degrees 2-theta ±0.2 degrees 2-theta or 9.8±0.1°2-θ, 15.3±0.1°2-θ, 21.1±0.1°2-θ, 22.6±0.1°2-θ and 24.3±0.1°2-θ. Further characteristic peaks are at 8.1, 8.2, 14.2, 19.9 and 28.9 degrees 2-theta ±0.2 degrees 2-theta or 13.5±0.1°2-θ, 16.5±0.1°2-θ, 17.0±0.1°2-θ, 25.5±0.1°2-θ and 28.9±0.1°2-θ.

In a particular preferred embodiment the polymorphic crystalline form of ibrutinib hydrochloride of the present invention shows substantially the XRPD pattern of figure 3.

Crystalline ibrutinib hydrochloride according to the present invention is further characterized by a DSC thermogram showing a broad endotherm with an onset temperature of approx. 150°C (± 5°C) and a peak temperature of 205° (± 1°C) followed by a broad exotherm with an onset temperature at 215°C (± 5°C) and a peak temperature at 217°C (± 2°C). A characteristic DSC thermogram is shown in Figure 4.

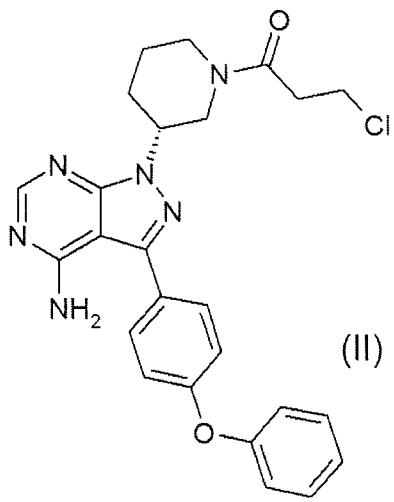
In a preferred embodiment the present invention relates to ibrutinib hydrobromide. Ibrutinib hydrobromide is characterized by a ^{1}H-NMR spectrum showing the following signals: ^{1}H

NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 1 H); 1.86 - 1.98 (m, 1 H); 2.15 (m, 1 H); 2.23 (m, 1 H); 2.98 - 3.10 (m, 0.5 H); 3.22 (m, 1 H); 3.61 - 3.76 (m, 0.5 H); 4.05 (m, 0.5 H); 4.16 (m, 1 H); 4.54 (m, 0.5 H); 4.75 (m, 1 H); 5.53 - 5.73 (m, 1 H); 5.99 - 6.20 (m, 1 H); 6.60 - 6.93 (m, 1 H); 7.07 - 7.24 (m, 5 H); 7.37 - 7.49 (m, 2 H); 7.65 (d, J=8.21 Hz, 2 H); 8.57 (s, 1 H). ^{1}H-NMR spectrum of ibrutinib hydrobromide is shown in figure 8.

In a preferred embodiment the present invention relates to ibrutinic hydrobromide, which is characterized by XRPD diffraction having peaks at 5.5, 18.1, 22.3, 24.5, and 26.9 degrees 2-theta ±0.2 degrees 2-theta. Ibrutinib hydrobromide is further characterized by XRPD diffraction peaks at 12.3, 15.6, 18.3, 20.2, 21.6 and 24.4 degrees 2-theta ±0.2 degrees 2-theta.

An XRPD diffraction pattern of ibrutinib hydrobromide is shwon in Figure 9.

As previously discussed inventors found that when acid addition salts of ibrutinib are prepared by processes under conventional conditions, impurities are formed. Not wishing to be bound by theory it seems that these impurities are generated by nucleophilic addition of the acid to the acrylic double-bond of ibrutinib. In order to confirm this theory, the chemical structure of an impurity was investigated, which is obtained when using hydrogen chloride as acid in order to prepare ibrutinib hydrochloride. The impurity was purified and investigated by mass spectrometry and ^{1}H-NMR spectroscopy. The proposed chemical structure of the impurity as nucleophilic addition product of HCl to ibrutinib, is shown as the following formula (II):



(II)

The ^{1}H-NMR spectrum of the compound formula (II), as shown in figure 5, comprises the following peaks ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.44 - 1.73 (m, 1 H); 1.90 (m, 1 H); 2.07 - 2.31 (m, 2 H); 2.65 - 2.78 (m, 0.5 H); 2.80 - 3.00 (m, 2 H); 3.15 (m, 1 H); 3.63 (m, 0.5 H); 3.69 - 3.80 (m, 2 H); 3.87 (m, 0.5 H); 4.05 (m, 0.5 H); 4.15 (m, 0.5 H); 4.52 (m, 0.5 H); 4.68 (m, 0.5 H); 4.77 - 4.91 (m, 0.5 H); 7.01 - 7.23 (m, 5 H); 7.42 (m, 2 H); 7.57 - 7.70 (m, 2 H); 8.54 - 8.64 (m, 1 H).

A compound of formula (II) can be obtained as impurity when preparing ibrutinib hydrochlorid. Therefore a compound of formula (IIa), in particular a compound of formula (II), is suitable for the determination of the purity of ibrutinib and pharmaceutical formulations comprising ibrutinib, in particular when ibrutinib is in the form of an acid addition salt, such as those described above. Further these compounds of formula (IIa) and (II) are suitable in a method for the preparation of ibrutinib with high purity, in particular in a purity as defined above. Preferably the ibrutinib is in the form of an acid addition salt, in particular the acid addition salts as defined above.

Therefore the present invention relates to the use of a compound of formula (IIa), wherein X is Cl or Br, for determination of the purity of ibrutinib in a pharmaceutical formulation comprising ibrutinib, wherein preferably the ibrutinib is in the form of an acid addition salt. Further the present invention relates to the use of a compound of formula (IIa), wherein X is Cl or Br, in a method for the preparation of ibrutinib or a pharmaceutical formulation comprising ibrutinib with high purity, wherein preferably the ibrutinib is in the form of an acid additional salt.

The present invention furthermore relates for pharmaceutical preparation comprising an acid addition salt of ibrutinib according to the present invention, preferably the acid addition salt of ibrutinib with hydrochloric acid, in particular crystallized ibrutinib, e.g. the polymorphic form as defined above. The parmaceutical preparation of the present invention preferably is an oral solid preparation, such as a capsule or tablet.

The pharmaceutical preparation can additionally contain one or more pharmaceutically acceptable excipients, such as fillers, binders, glidants, disintegrants, flow regulating

agents and release agents. Suitable excipients are for example disclosed in "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", published by H.P. Fielder, 4th Edition and "Handbook of Pharmaceutical Excipients", 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

Suitable fillers are for example lactose and calcium hydrogen phosphate. Fillers can be present in an amount of 0 – 80% by weight, preferably in an amount of 10 – 60% by weight of the total weight of the composition.

Suitable binders are for example polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose, sugars, dextran, or corn starch. Binders can be present in an amount of 0-80% by weight, preferably in an amount of 10-60% by weight of the total weight of the composition.

Suitable glidants are for example alkaline earth metal salts of fatty acids, like stearic acid. The glidant can be present for example in an amount of 0 – 2% by weight, preferably in an amount of 0.5 – 1.5% by weight of the total weight of the composition.

Suitable disintegrants are for example crosscarmelose sodium, sodium carboxymethyl starch, crosslinked polyvinylpyrrolidone (crosspovidone), sodium carboxymethylglycolate (such as Explotab) and sodium bicarbonate. The disintegrant can be present in an amount of 0 – 20% by weight, preferably in an amount of 1 – 15% by weight of the total weight of the composition.

A suitable flow regulating agent is for example colloidal silica. The flow regulating agent can be present in an amount of 0 – 8% by weight, preferably in an amount of 0.1 – 3% by weight of the total weight of this composition.

A suitable release agent is for example talcum. The release agent can be present in an amount of 0 – 5% by weight, preferably in an amount of 0.5 – 3% by weight of the total weight of the composition.

The pharmaceutical preparation of the present invention can be prepared by methods well known to a person skilled in the art.

Attached Figure 1a shows the ^{1}H-NMR spectrum of ibrutinib hydrochloride (upper graph) compared to the ^{1}H-NMR spectrum of ibrutinib free base (lower graph) (^{1}H-NMR in DMSO-d_6, 400 MHz).

Figure 1b shows a zoomed cutout of the ^{1}H-NMR spectrum of ibrutinib hydrochloride (upper graph) compared to the presumed ^{1}H-NMR spectrum of ibrutinib phosphate (lower graph) (^{1}H-NMR in DMSO-d_6, 400 MHz).

Figure 2 shows an IR-spectrum of ibrutinib hydrochloride.

Figure 3 shows an XRPD pattern of crystalline ibrutinib hydrochloride.

Figure 4 shows a DSD thermogram of ibrutinib hydrochloride.

Figure 5 shows an ^{1}H-NMR spectrum of compound (II).

Figure 6 shows a mass spectrum of compound (II).

Figure 7 shows the TGA spectrum of crystalline ibrutinib hydrochloride.

Figure 8 shows the ^{1}H-NMR spectrum of ibrutinib hydrobromide (^{1}H-NMR in DMSO-d_6, 400 MHz).

Figure 9 shows an XRPD pattern of crystalline ibrutinib hydrobromide.

Figure 10 shows an XRPD pattern of amorphous ibrutinib methylsulfonate.

Figure 11 shows an XRPD pattern of amorphous ibrutinib ethane disulfonate.

Figure 12 shows an XRPD pattern of amorphous ibrutinib sulfonate.

The invention will now be illustrated by the examples, which are not to be construed as limiting.

Analytical Methods

^{1}H-NMR Spectroscopy

Instrument: Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz.

HPLC/UV

Instrument:	Agilent 1200
Injection volume:	5 µl
Solvent A:	acetonitrile
Solvent B:	0.001M KH_2PO_4
Flow:	1.5 ml/min
Temperature:	RT
Column:	Discovery C18, 150 * 4.6 mm, 5 µm

time [min]	solvent B [%]
0.00	75
8.00	40
13.00	40
14.00	75
17.00	75

LCMS

Instrument:	Agilent 1260 Infinity
Injection volume:	2 µl
Solvent A:	acetonitrile
Solvent B:	water + 0.1% formic acid + 0.05% heptafluorobutyric acid
Flow:	1 ml/min
Temperature:	40°C
Column:	Phenomenex Kinetex 2.6 µm C18 100A 150 * 4.6mm 2.6 µm
Mass instrument:	Agilent 6110 Quadrupol LC/MS

time [min]	solvent B [%]
0.00	60
3.00	20
4.00	20
4.30	60
6.10	60

Differential Scanning Calorimetry (DSC)

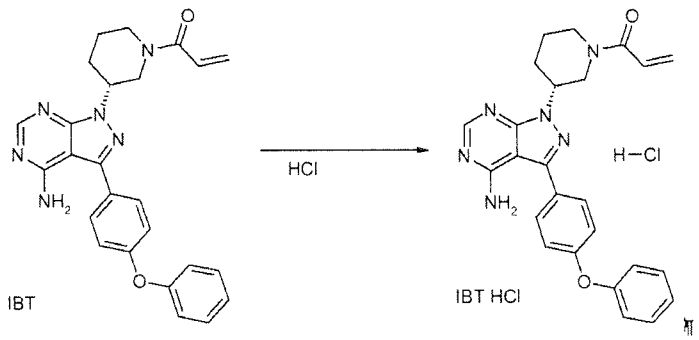
Instrument:	Mettler Toledo DSC 822E coupled with a Mettler Toledo Gas-Flow-Controller TS0800GC1 (Mettler-Toledo GmbH, Gießen, Germany)
Aluminium crucible:	40 µL
Lid:	Perforated
Temperature range:	30°C to 350°C
Heating rate:	10°C/ min
Nitrogen flush:	50 mL / min
Software:	STARe Version. 8.10
Interpretation:	Endothermic modus

X-Ray Powder Diffraction (XRPD)

The sample was analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS, Karlsruhe, Germany). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized in the table below. The raw data were analyzed with the program EVA (Bruker-AXS, Germany). The samples were layered onto a silicon specimen holder.

	standard measurement
radiation	Cu K_α ($\lambda = 1.5406$ Å)
source	38 kV / 40 mA
detector	Vantec
detector slit	Variable
divergence slit	v6
antiscattering slit	v6
2θ range / °	2 ≤ 2θ ≤ 55
step size / °	0.017

Example 1: Preparation of ibrutinib hydrochloride (IBT HCL) by conventional processes (Experiments 1 and 2) and by processes according to the present invention (Experiments 3 through 6)



Experiment 1:

2.0 g (4.54 mmol) ibrutinib (IBT) base were dissolved in 10 ml dichloromethane (DCM) followed by addition of 20 ml methyl tert.-butylmethylether (MTBE). While stirring at RT (22°C), 3.41 mL (6.8 mmol) 2 N HCl in diethylether (Et_2O) were added and stirring was continued for 30 min. After addition of another 20 ml MTBE, the formation of a fine white precipitate that shortly later converted into a sticky viscous semisolid. Solidification was induced by sonication and the resulting lumps were scraped off the glass wall using a spatula. The coarse suspension was stirred overnight at room temperature. The solids were filtered off, washed with 20 ml MTBE and dried 24 h at 40°C / 10 mbar.

Yield: 2.07 g (95.6%)

Chemical purity: 94 % (peak area at λ=230 nm and 254 nm).

Prominent impurity (IBT impurity compound of formula (II)): 5.1 / 4.7 % (peak area at λ=230 nm and 254 nm);

Experiment 2:

15.0 g (34.1 mmol) IBT base were dissolved in 75 ml DCM. While stirring at RT (22°C), 25.5 mL (51.1 mmol) 2 N HCl in Et_2O were added. After completion, the mixture was cooled to 0°C, followed by addition of 200 ml MTBE. Using a rotary evaporator, the volume was reduced to approx. 200 ml, another 150 ml MTBE was added and the mixture was stirred for 3 h at 50°C. The intermittently viscous semisolid converted into a solid, which was firmly attached to the inner glass wall of the flask. The solid was scraped off and the suspension was stirred for another 3 h. The solid was filtered off, washed with 100 ml MTBE and dried 24 h at 40°C / 10 mbar.

Yield: 16.1 g (99.1 %)

Chemical purity: 96 % (peak area at λ=230 nm and 254 nm).

IBT impurity (compound of formula (II)): 4.0/ 3.7 % (peak area at λ=230 nm and 254 nm);

Experiment 3:

5 g (11.4 mmol) IBT base was dissolved in 20 mL DCM. The solution was cooled to -10°C and 3.4 mL (13.6 mmol) 4 N HCl in dioxane was added. The clear solution was stirred for 10 min followed by dropwise addition of 200 ml MTBE over a period of 100 min, while keeping the temperature below 0°C. After completion, the fine white suspension was allowed to warm to RT and stirring was continued for 18h. The solid was filtered off, washed with 50 ml MTBE and dried 24 h at 40°C / 10 mbar.

Yield: 4.95 g (91.4 %)

Chemical purity: 99.4/>99.9 % (peak area at λ=230 nm and 254 nm).

IBT impurity (compound of formula (II)):: 0.4/ <0.1 % (peak area at λ=230 nm and 254 nm);

Experiment 4:

25 g (56.8 mmol) IBT base were dissolved in 100 ml DCM. The solution was cooled to -10°C and 17 ml (68.1 mmol) 4 N HCl in dioxane were added. The clear solution was stirred for 10 min followed by dropwise addition of 1 L MTBE over a period of 100 min, while keeping the temperature below +2°C. After completion, the fine white suspension

was allowed to warm to RT and stirring was continued for 18h. The solid was filtered off, washed with 200 ml MTBE and dried 24 h at 40°C / 10 mbar.

Yield: 26.2 g (96.8 %)

Chemical purity: 99.8 / 99.9 % (peak area at λ=230 nm and 254 nm).

IBT impurity (compound of formula (II)): 0.10/ <0.1 % (peak area at λ=230 nm and 254 nm);

Experiment 5:

30 g (68.1 mmol) IBT base were dissolved in 120 mL DCM. The solution was cooled to -20°C and 57 mL (71.5 mmol) 1.25 N HCl in isopropanol were added. The clear solution was stirred for 10 min followed by dropwise addition of 1500 ml MTBE over a period of 3 h, while keeping the temperature below -10°C. After completion, the mixture was allowed to warm to RT and stirring was continued for 40h. The resulting fine white solid was filtered off, washed with 300 ml MTBE and dried 24 h at 50°C / 10 mbar.

Yield: 30.1 g (92.4 %)

Chemical purity: 99.7/99.8 % (peak area at λ=230 nm and 254 nm).

IBT impurity (compound of formula (II)):: <0.1 % (peak area at λ=230 nm and 254 nm);

Experiment 6:

3 g (6.81 mmol) IBT base were dissolved in 4 mL DCM. The solution was cooled to -20°C and 5.7 mL (7.15 mmol) 1.25 N HCl in isopropanol (iPrOH) were added. The clear solution was stirred for 10 min followed by dropwise addition of 30 ml iPrOH, while keeping the temperature below -10°C. After completion, the mixture was allowed to warm to RT and stirring was continued for 18h. The resulting fine white solid was filtered off, washed with 10 ml iPrOH and dried 24 h at 50°C / 10 mbar.

Yield: 2.90 g (89.3 %)

Chemical purity: 99.9/99.9 % (peak area at λ=230 nm and 254 nm).

IBT impurity (compound of formula (II)):: <0.1 % (peak area at λ=230 nm and 254 nm);

The results of Experiments 1 through 6 are summarized below

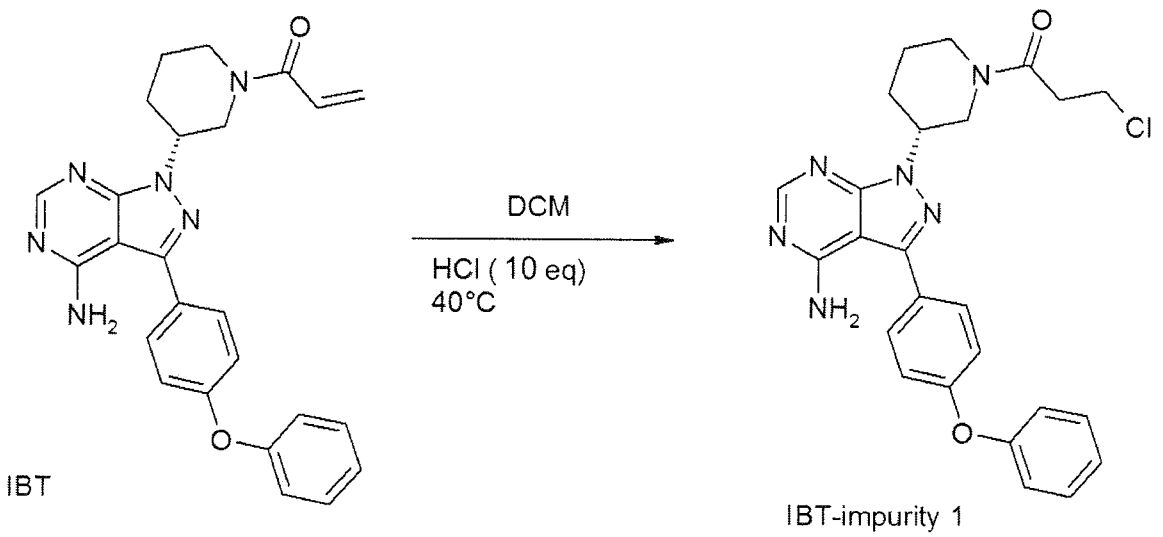
	Exp 1	Exp 2	Exp 3	Exp 4	Exp 5	Exp 6
Ibrutinib base in g	2.0	15.0	5.0	25.0	30.0	3.0
HCl, dissolved in	2N in diethylether	2N in diethylether	4N in dioxane	4N in dioxane	1.25N in isopropanol	1.25N in isopropanol
HCl excess in eq.	1.5	1.5	1.2	1.2	1.05	1.05
reaction temperature in °C	22	22	-10	-10	-20	-20
solvent	dichloro-methane	dichloro-methane	dichloro-methane	dichloro-methane	dichloro-methane	dichloro-methane
antisolvent	MTBE	MTBE	MTBE	MTBE	MTBE	isopropanol
yield in g	2.07	16.1	4.95	26.2	30.1	2.90
yield in %	95.6	99.1	91.4	96.8	92.4	89.3
purity in %	94.0	96.0	99.4	99.8	99.7	99.9

The quantitative conversion of ibrutinib into ibrutinib hydrochloride is verified by means of ^{1}H-NMR overlay indicating a complete shift of the pyrimidinium proton from 8.24 ppm to 8.57ppm (cf. Figure 1a) and thermogravimetric analysis (cf. Figure 7).

Comparison of solubilities of ibrutinib hydrochloride in pH values which are relevant for the gastrointestinal tract

solubility in mg/ml	pH 1.2 (0.1M HCl)			pH 4.5 (20mMol NaAc)			pH 6.8 (50 mMol KH_2PO_4)		
	15min	1h	24h	15min	1h	24h	15min	1h	24h
base	2.07	2.64	2.64	0.01	0.01	0.01	0.01	0.01	0.01
HCl	7.37	7.72	7.38	0.01	0.02	0.46	0.01	0.05	0.41

Example 2: Preparation of compound formula (II)



ibrutinib (II)

At RT, 50 mg (0.11 mmol) IBT base was dissolved in 1.0 ml DCM. After addition of 0.57 ml (1.1 mmol) 2N HCl in Et_2O, the mixture was briefly sonicated and warmed to 40°C. The formation of IBT impurity (compound of formula (II)) was monitored by HPLC/UV. After 26 h, IBT impurity 1 was isolated in 97% chemical purity ([area-%] at λ=230/254 nm).

Example 3: Comparison of ibrutinib acid addition salt preparations

Experiments were carried out with hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, ethanedisulfonic acid and phosphoric acid according to the following general methods:

Method I:

1 eq Ibrutinib (IBT) base was dissolved in 28 eq. dichloromethane (DCM). The clear solution was cooled to -20°C before 1.05 eq of the corresponding acid (1.25 M in iPrOH) was added. The solution was stirred for 5 min followed by addition of 190 eq. tert.-butylmethylether (MTBE). After completion the resulting slurry was allowed to reach room temperature and stirring was continued for 24 h. The obtained precipitate was filtered off, washed with MTBE and dried under reduced pressure to yield the corresponding acid addition salt.

Method II:

1 eq Ibrutinib (IBT) base was dissolved in 14 eq. dichloromethane (DCM). The clear solution was cooled to 6-10°C before 1.05 eq of the corresponding acid (1.25 M in iPrOH) was added. The solution was stirred for 5 min followed by addition of 150 eq. isopropanol (iPrOH). After completion the resulting mixture was allowed to reach room temperature and stirring was continued for 24 h. The obtained precipitate was filtered off, washed with isopropanol and dried under reduced pressure to yield the corresponding acid addition salt.

It was demonstrated that both procedures yield identical results regarding the chemical purity (≥99.8%) and the morphological state. An overview of the applied acids and the resulting solid state is given in the table below.

applied acid	**pKa(1)**	**pKa(2)**	**acid addition salt**	**morphology**
hydrobromic acid	-9.00		ibrutinib bromide	crystalline
hydrochloric acid	-6.00		ibrutinib chloride	crystalline
sulfuric acid	-3.00	1.99	ibrutinib hydrogensulfate	amorphous
ethanedisulfonic acid	-2.06	-1.50	ibrutinib hemi edisylate	amorphous
methanesulfonic acid	-1.90		ibrutinib mesylate	amorphous
phosphoric acid	2.15		ibrutinib base	----------

Figures 10 to 12 show that reacting ibrutinib with any of methanesulfonic acid, ethanedisulfonic acid or sulfuric acid leads to acid addition salts with amorphous morphology.

Further, not wishing to be bound to theory it seems that acid addition salts can be obtained when an acid with a pKa lower than approximately 2 is applied. Figure 1b illustrates that application of phosphoric acid does not convert ibrutinib into a salt, due to the missing shift of pyrimidinium proton at 8.24 ppm to 8.57 ppm in the ^{1}H-NMR spectrum as it is the case for example with hydrochloric acid (compare also with Figure 1a).

X-Ray Powder Diffraction results (XRPD)

The acid addition product ibrutinib HCl and ibrutinib HBr, as obtained by the above described procedures were characterized by means of x-ray powder diffraction. It is shown in Figures 3 and 9, respectively.

The x-ray powder diffractogram of ibrutinib HCl is characterized by the following peaks: 9.8, 13.6, 15.1, 17.0 and 21.1 degrees 2-theta ±0.2 degrees 2-theta or 9.8±0.1°2-θ, 15.3±0.1°2-θ, 21.1±0.1°2-θ, 22.6±0.1°2-θ and 24.3±0.1°2-θ. Further characteristic peaks are at 8.1, 8.2, 14.2, 19.9 and 28.9 degrees 2-theta ±0.2 degrees 2-theta or 13.6±0.1°2-θ, 16.5±0.1°2-θ, 17.0±0.1°2-θ, 25.5±0.1°2-θ and 28.9±0.1°2-θ.

The complete list of XRPD diffraction peaks of ibrutinib hydrochloride:

degrees 2-theta ±0.2 degrees 2-theta	**relative intensity**
8.1	6.9%
8.2	13.8%
9.1	1.9%
9.8	45.0%
10.7	3.0%
11.3	7.0%
11.5	13.7%
13.6	38.5%
14.1	11.2%
14.2	20.9%
15.1	32.9%
15.3	56.3%
15.6	24.7%
16.5	27.5%
17.0	44.0%
17.3	16.1%
18.5	23.2%
19.9	26.3%
20.9	16.4%
20.4	16.8%
20.6	28.1%
20.8	19.9%
21.1	100.0%
22.2	33.6%
22.6	76.3%
22.6	66.4%
23.1	30.4%
23.1	27.3%
23.6	12.2%
23.8	19.2%
24.3	97.0%
25.6	26.9%
25.5	59.1%
25.7	11.7%
28.6	34.9%
29.0	36.4%
28.9	40.2%
29.4	29.7%

29.7	11.1%
32.0	12.4%
32.2	14.2%
32.7	12.8%

The x-ray powder diffractogram of ibrutinib HBr is characterized by the following peaks: 5.5, 18.1, 22.3, 24.5 and 26.9 degrees 2-theta ±0.2 degrees 2-theta. Further characteristic peaks are at 12.3, 15.6, 18.3, 20.2, 21.6° and 24.4°. degrees 2-theta ±0.2 degrees 2-theta

The complete list of XRPD diffraction peaks of ibrutinib hydrobromide:

degrees 2-theta ±0.2 degrees 2-theta	**relative intensity**
5.5	18.6%
10.6	4.5%
11.1	3.3%
12.3	6.1%
12.7	2.0%
14.8	6.7%
15.6	16.5%
16.0	11.6%
16.6	15.7%
18.1	39.2%
18.3	15.1%
19.1	2.8%
20.2	23.2%
21.6	15.9%
22.3	100.0%
23.0	11.8%
24.4	18.0%
24.5	34.7%
24.7	8.7%
25.6	10.2%
26.9	22.3%
27.4	6.9%
29.3	6.1%
29.5	9.7%
29.6	8.6%
31.8	11.0%
33.6	7.0%
33.7	5.3%
36.0	6.1%
37.0	7.7%
38.7	6.9%
39.9	5.2%
41.2	10.3%
48.2	7.9%

Claims:

1. Crystalline acid addition salt of ibrutinib having a purity of at least 99.0 %.

2. Acid addition salt of claim 1, wherein the acid is hydrochloric acid or hydrobromic acid.

3. Acid addition salt of ibrutinib, wherein the content of an addition reaction product of the acid with the acrylic double bond of ibrutinib is lower than 1 % by weight.

4. Acid addition salt of ibrutinib according to claim 3, wherein the content of the addition reaction product is lower than 0.5 % by weight, preferably lower than 0.2 % by weight, more preferable lower than 0.1 % by weight.

5. Acid addition salt according to preceding claims, which is crystalline ibrutinib hydrochloride, which preferably shows an XRPD pattern having peaks at 9.8 ± 0.1°2- Theta, 15.3 ± 0.1°2- Theta, 21.1 ± 0.1°2- Theta, 22.6 ± 0.1°2- Theta and 24.3 ± 0.1°2- Theta.

6. Method of preparing an acid addition salt of ibrutinib comprising the steps of a) dissolving ibrutinib in a suitable solvent, preferably an organic solvent, and b) contacting the obtained solution with the acid, characterized in that during the step of adding the acid the solution is cooled below room temperature (22°C).

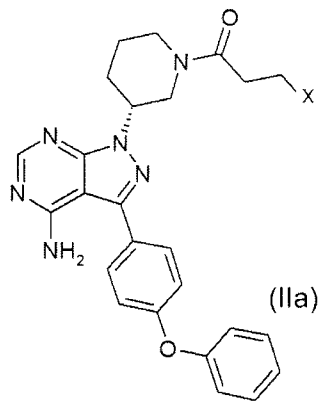
7. Method according to claim 6, which method further comprises the step of c) precipitating the acid addition salt in a suitable antisolvent.

8. Method according to claim 7 or 8, wherein the solution is cooled below below 10 °C, preferably below 0°C in steps b) and/or c).

9. Method according to claims 8 or 9, wherein the acid is hydrogen chloride.

10. Pharmaceutical composition comprising an acid addition salt of ibrutinib according to claim 1 to 5.

11. Use of a compound of formula (IIa),

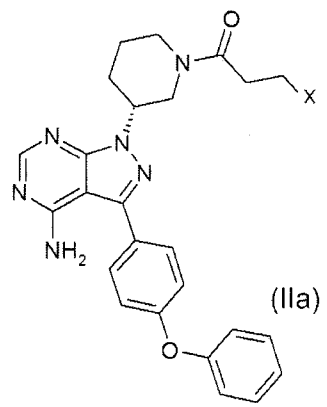


(IIa)

,

wherein X is Cl or Br, for determination of the purity of ibrutinib in a pharmaceutical formulation comprising ibrutinib, wherein preferably the ibrutinib is in the form of an acid addition salt.

12. Use of a compound of formula (IIa)



(IIa)

,

wherein X is Cl or Br, in a method for the preparation of ibrutinib or a pharmaceutical formulation comprising ibrutinib with high purity, wherein preferably the ibrutinib is in the form of an acid additional salt.

13. Crystalline acid addition salt of ibrutinib wherein the acid is hydrogen chloride or hydrogen bromide.

14. Pharmaceutical composition comprising an acid addition salt according to claim 13.

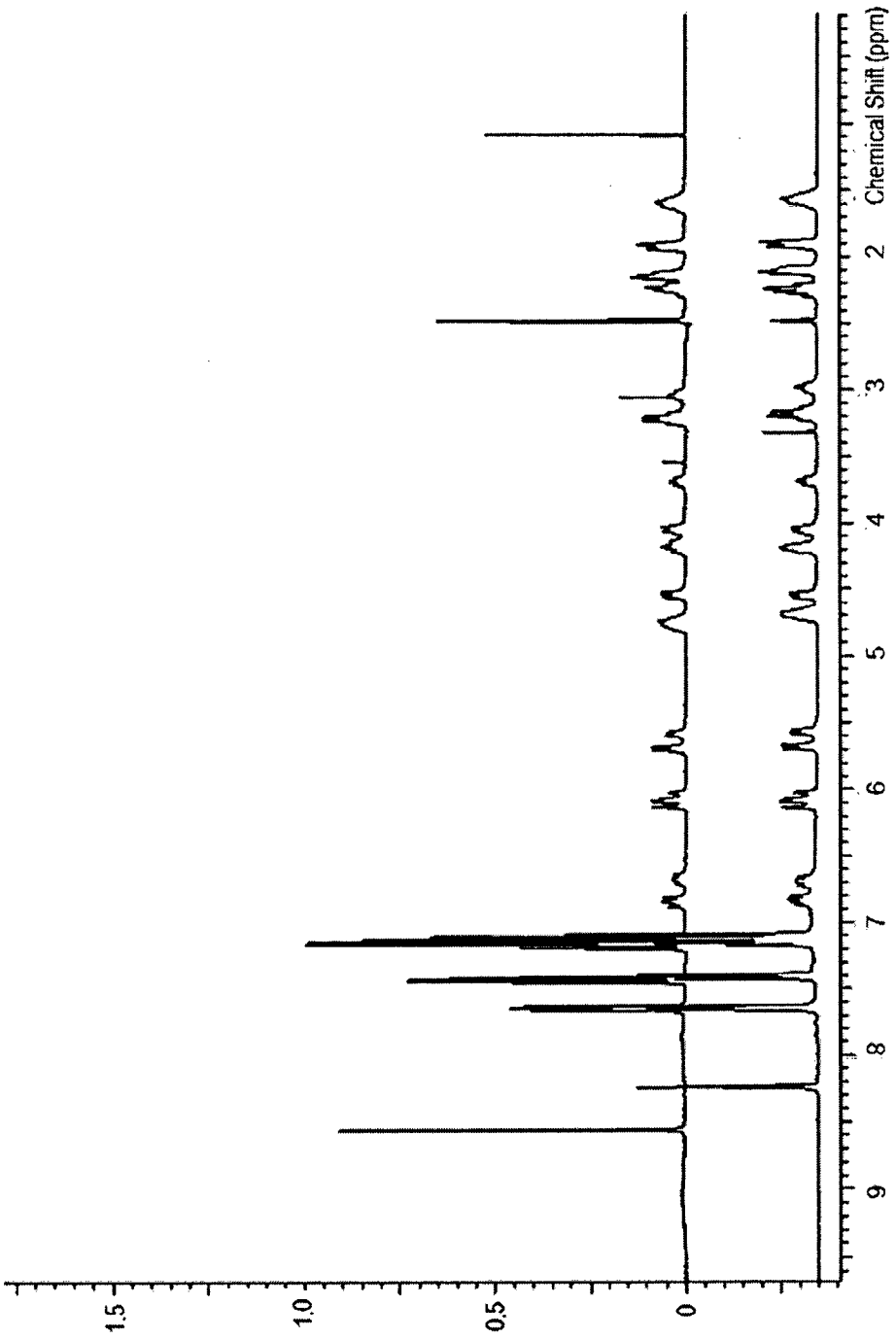


Figure 1a

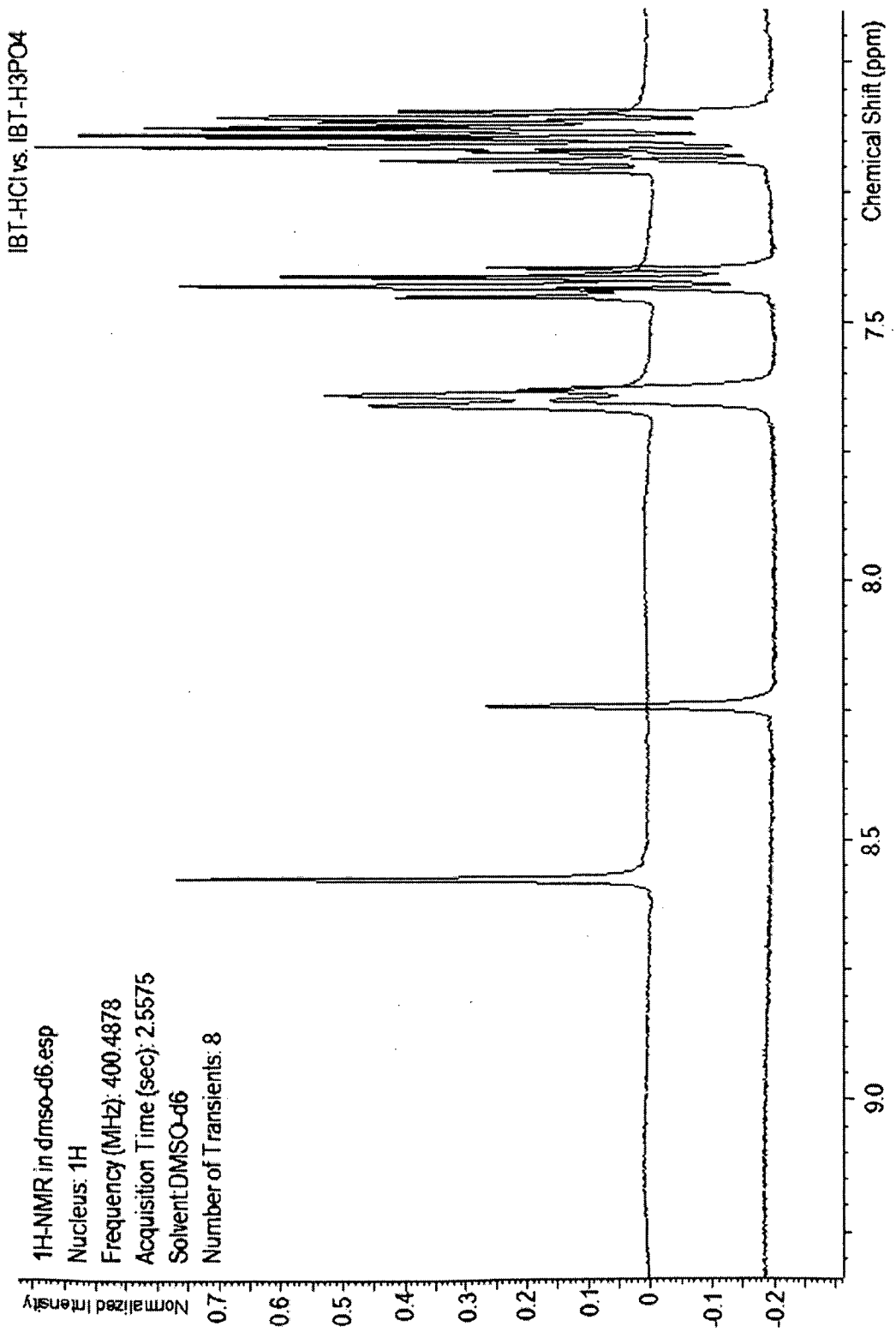

IBT-HCl vs. IBT-H3PO4
1H-NMR in dmso-d6.esp
Nucleus: 1H
Frequency (MHz): 400.4878
Acquisition Time (sec): 2.5575
Solvent:DMSO-d6
Number of Transients: 8
Normalized Intensity
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
9.0
8.5
8.0
7.5
Chemical Shift (ppm)

Figure 1b

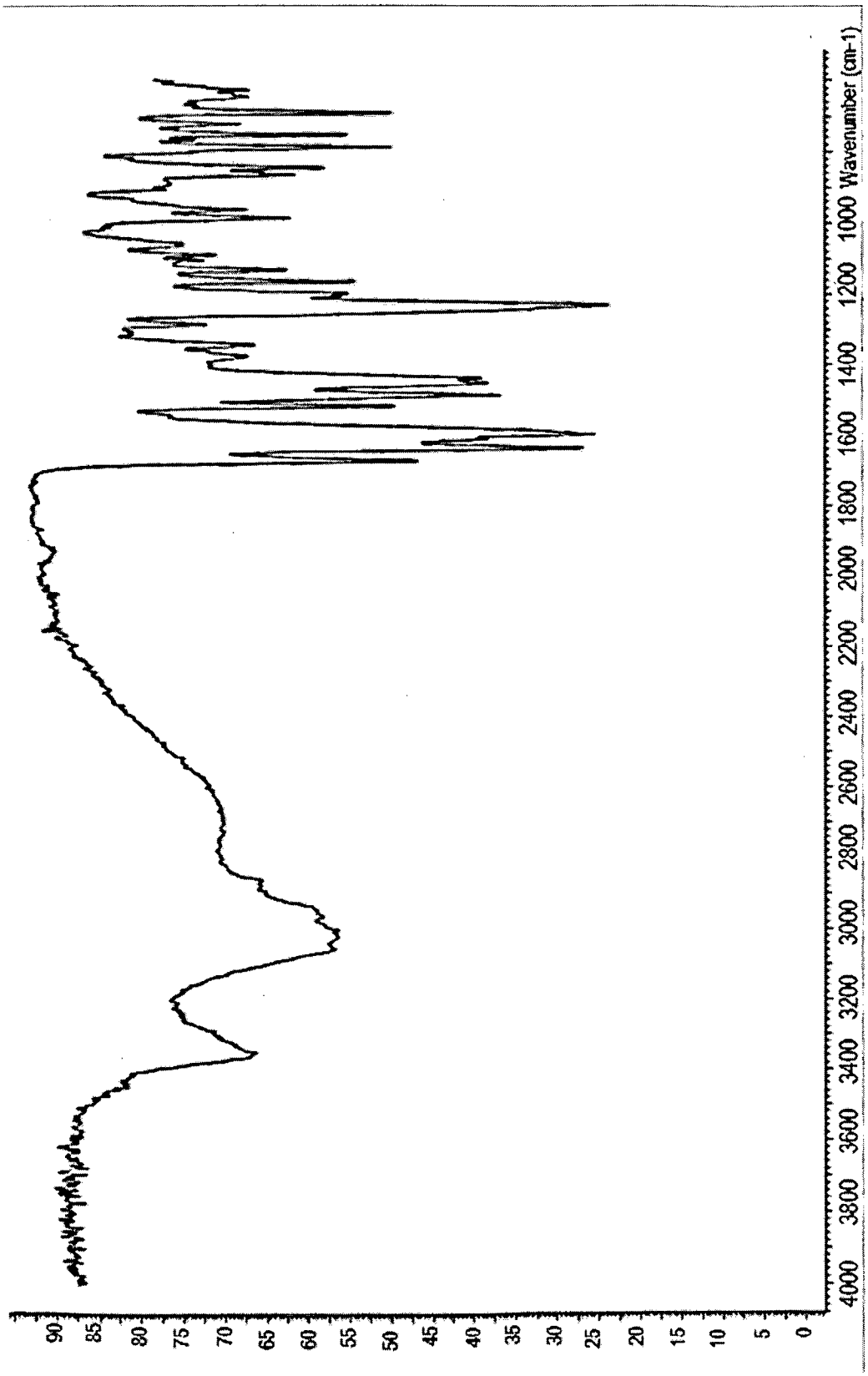

Wavenumber (cm-1)
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0

Figure 2

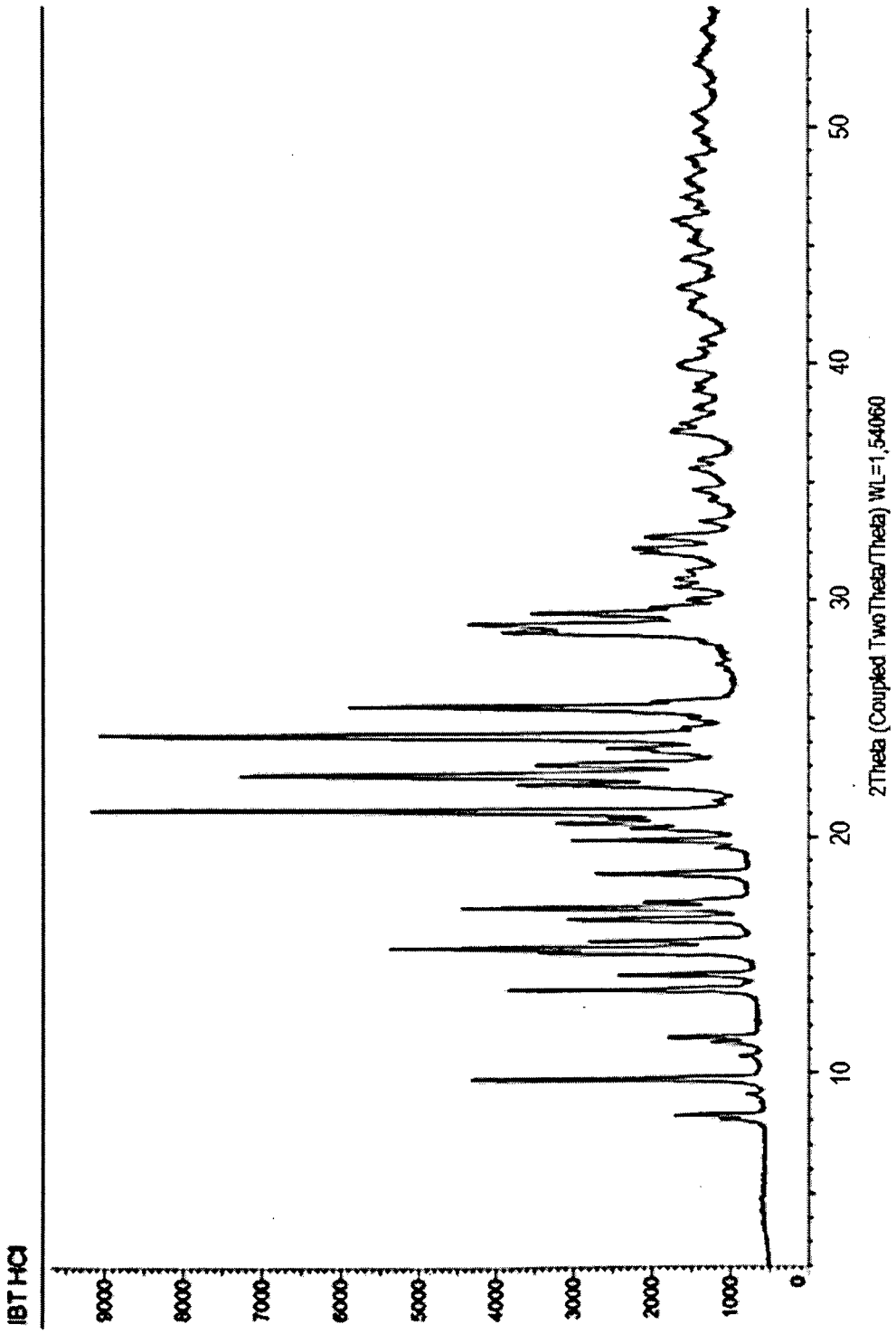

IBT HCl
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
2Theta (Coupled TwoTheta/Theta) WL=1,54060

Figure 3

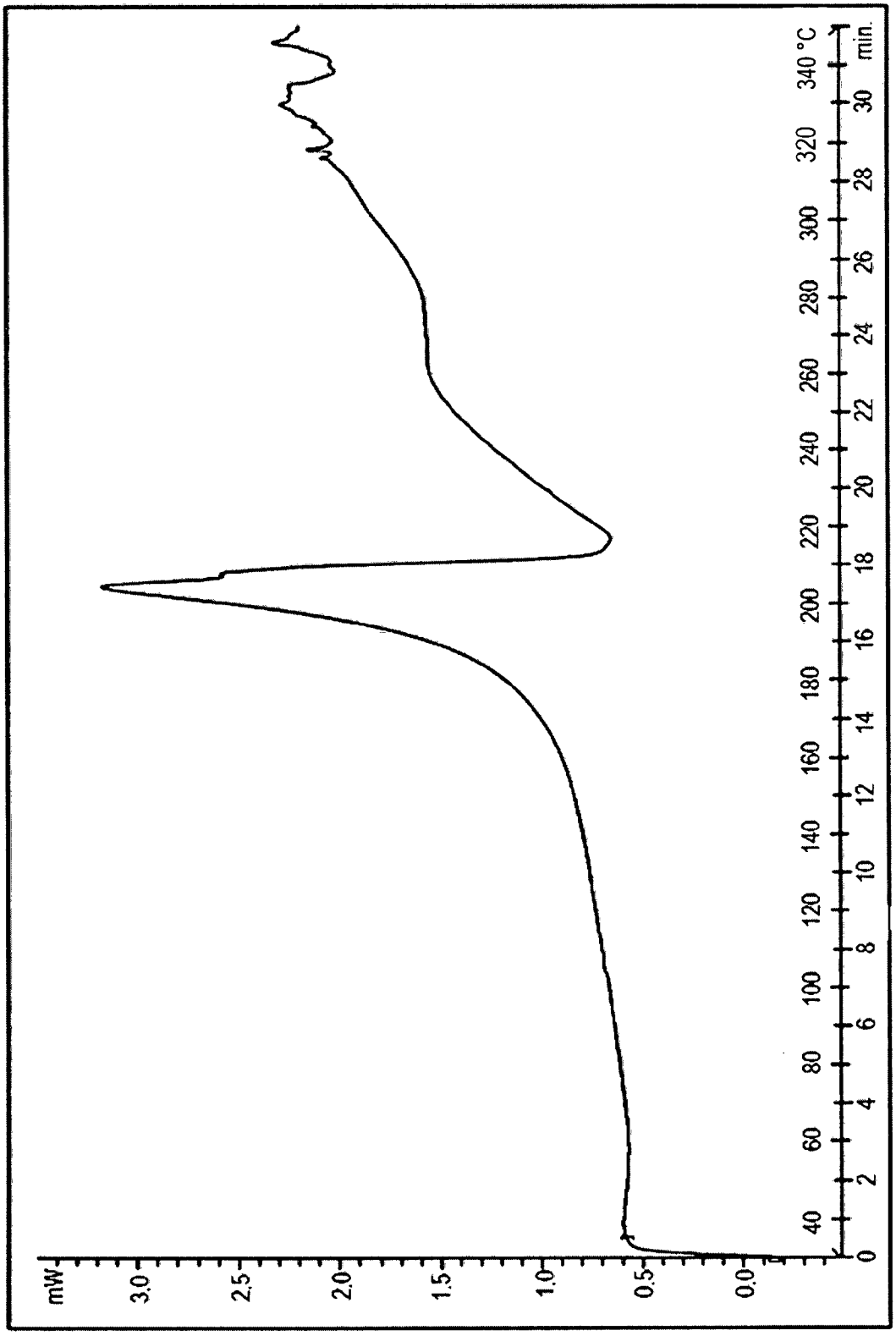

mW
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
min.
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340 °C

Figure 4

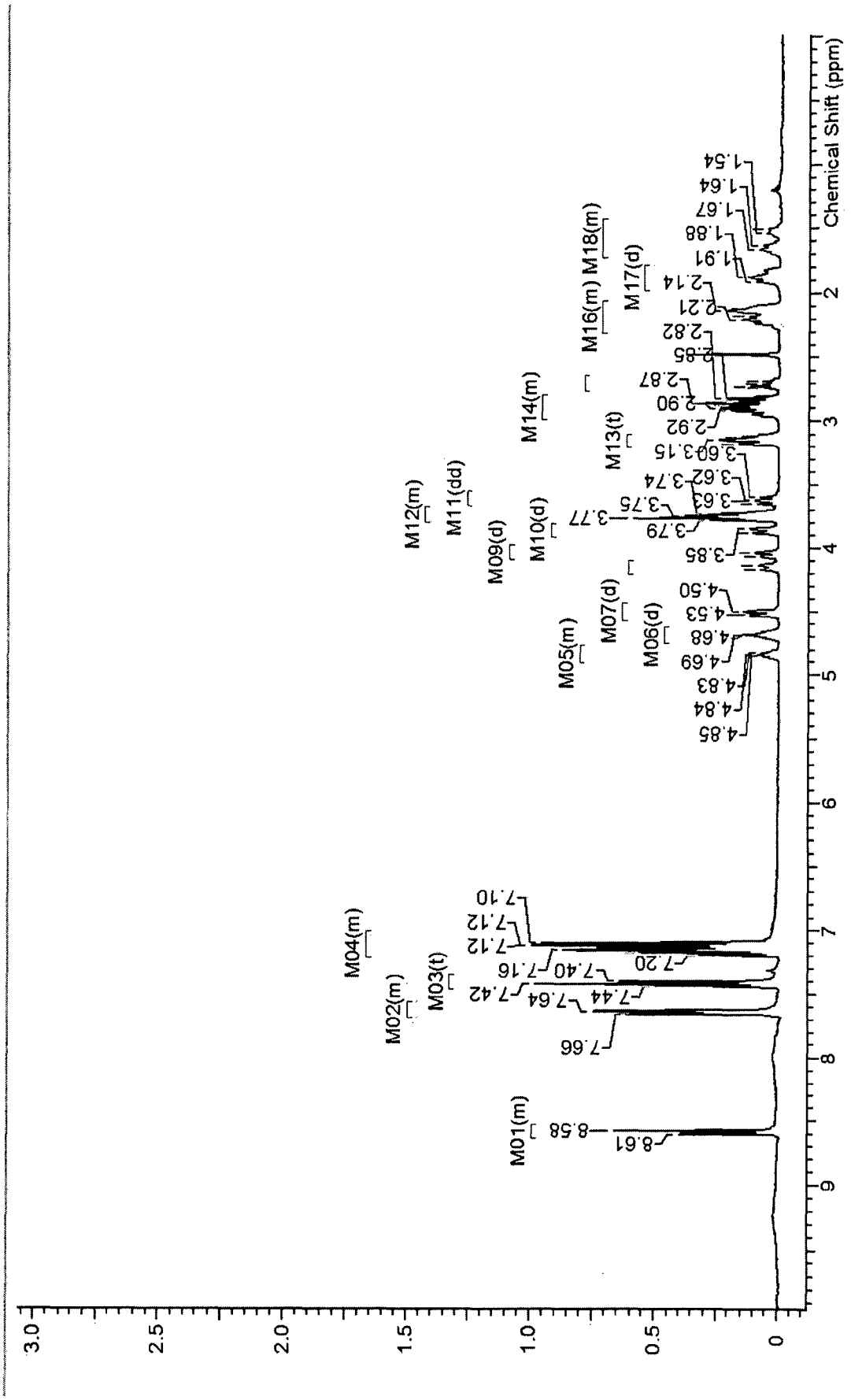

Chemical Shift (ppm)
M01(m)
M02(m)
M03(t)
M04(m)
M05(m)
M06(d)
M07(d)
M09(d)
M10(d)
M11(dd)
M12(m)
M13(t)
M14(m)
M16(m)
M17(d)
M18(m)
8.61
8.58
7.66
7.44
7.64
7.42
7.20
7.40
7.16
7.12
7.12
7.10
4.85
4.84
4.83
4.69
4.68
4.53
4.50
3.85
3.79
3.77
3.75
3.63
3.62
3.74
3.60
3.15
2.92
2.90
2.87
2.85
2.82
2.21
2.14
1.91
1.88
1.67
1.64
1.54

Figure 5

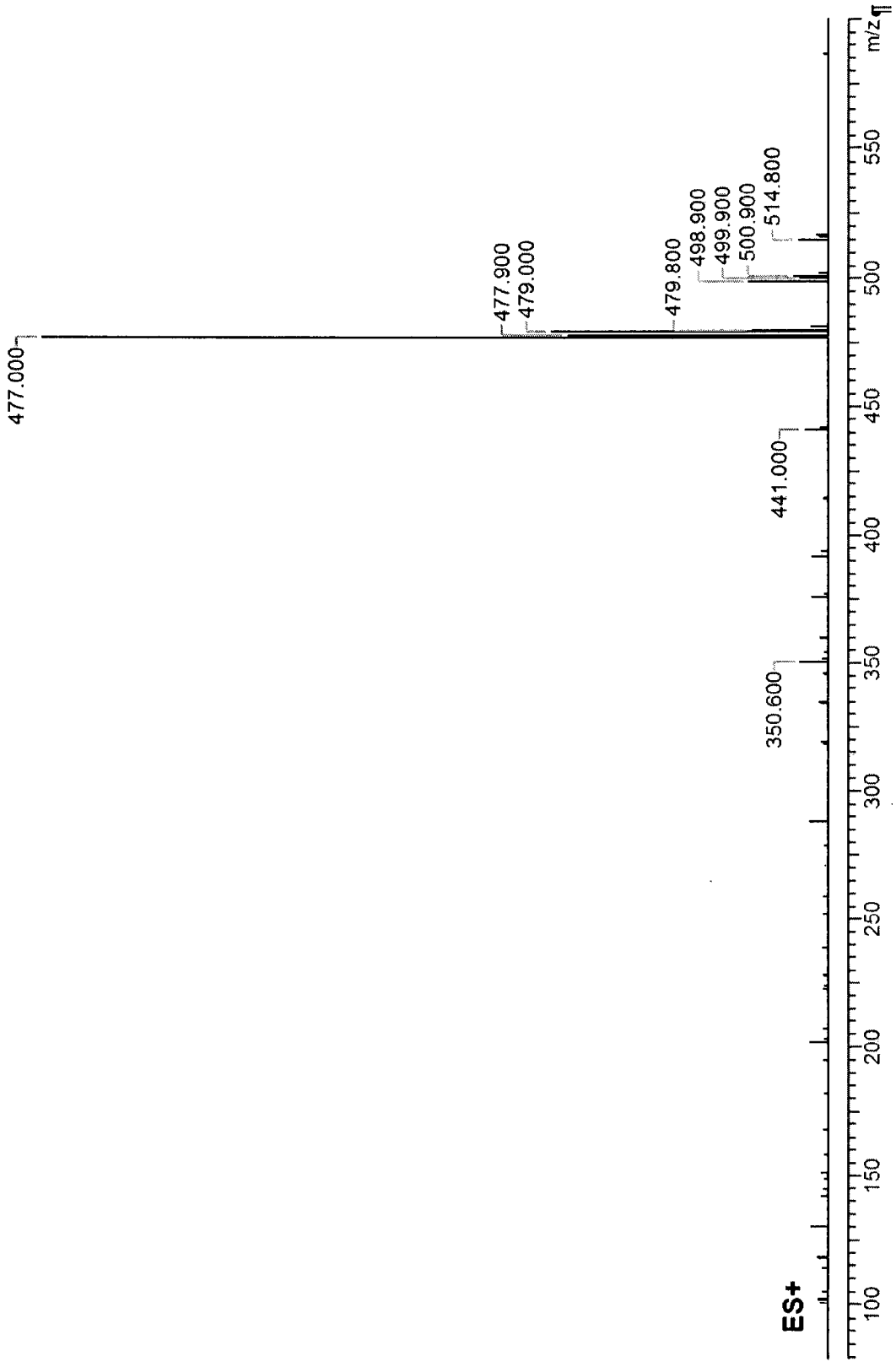

ES+
477.000
477.900
479.000
479.800
498.900
499.900
500.900
514.800
441.000
350.600
100
150
200
250
300
350
400
450
500
550
m/z

Figure 6

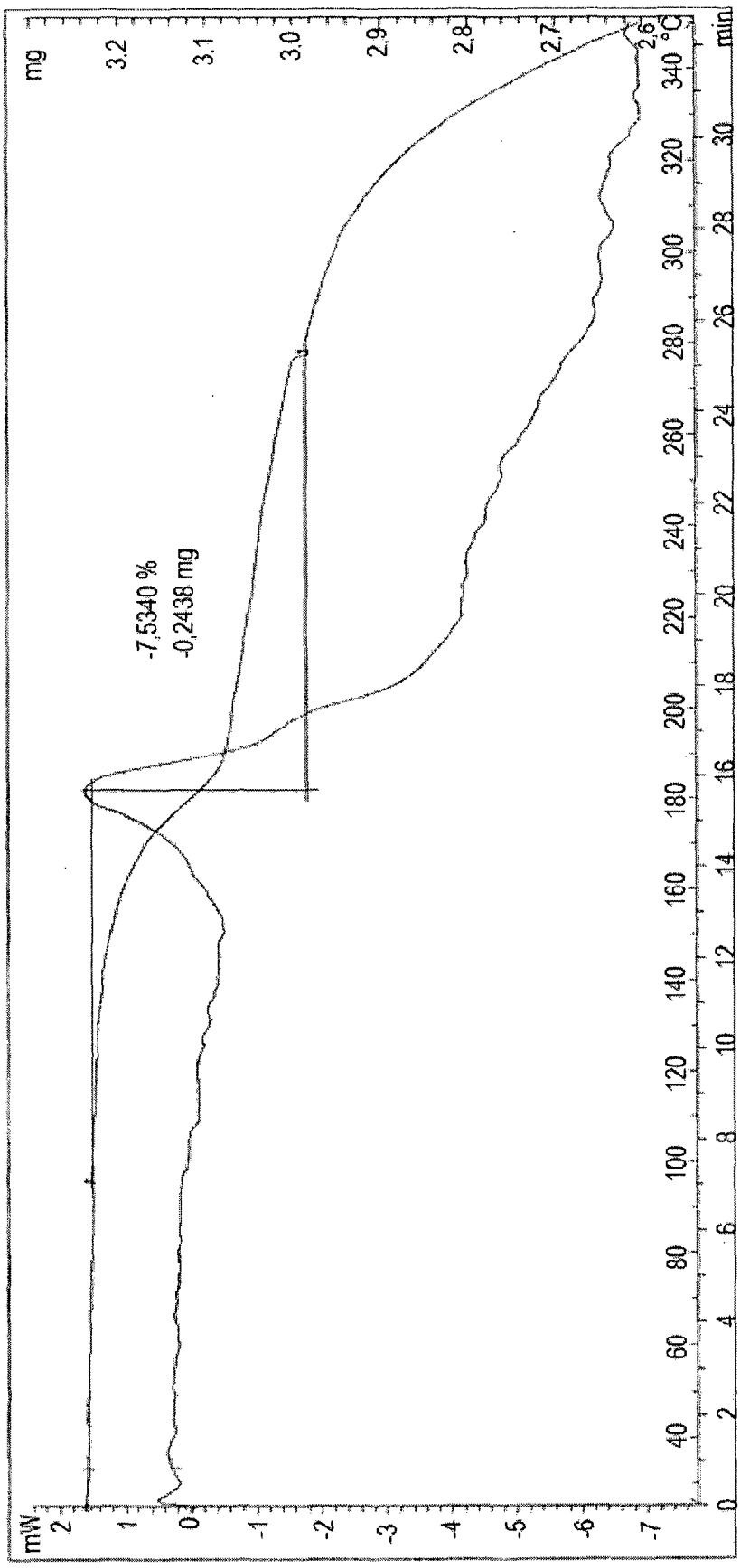

mg
3.2
3.1
3.0
2.9
2.8
2.7
2.6
°C
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
min
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
mW
2
1
0
-1
-2
-3
-4
-5
-6
-7
-7,5340 %
-0,2438 mg

Figure 7

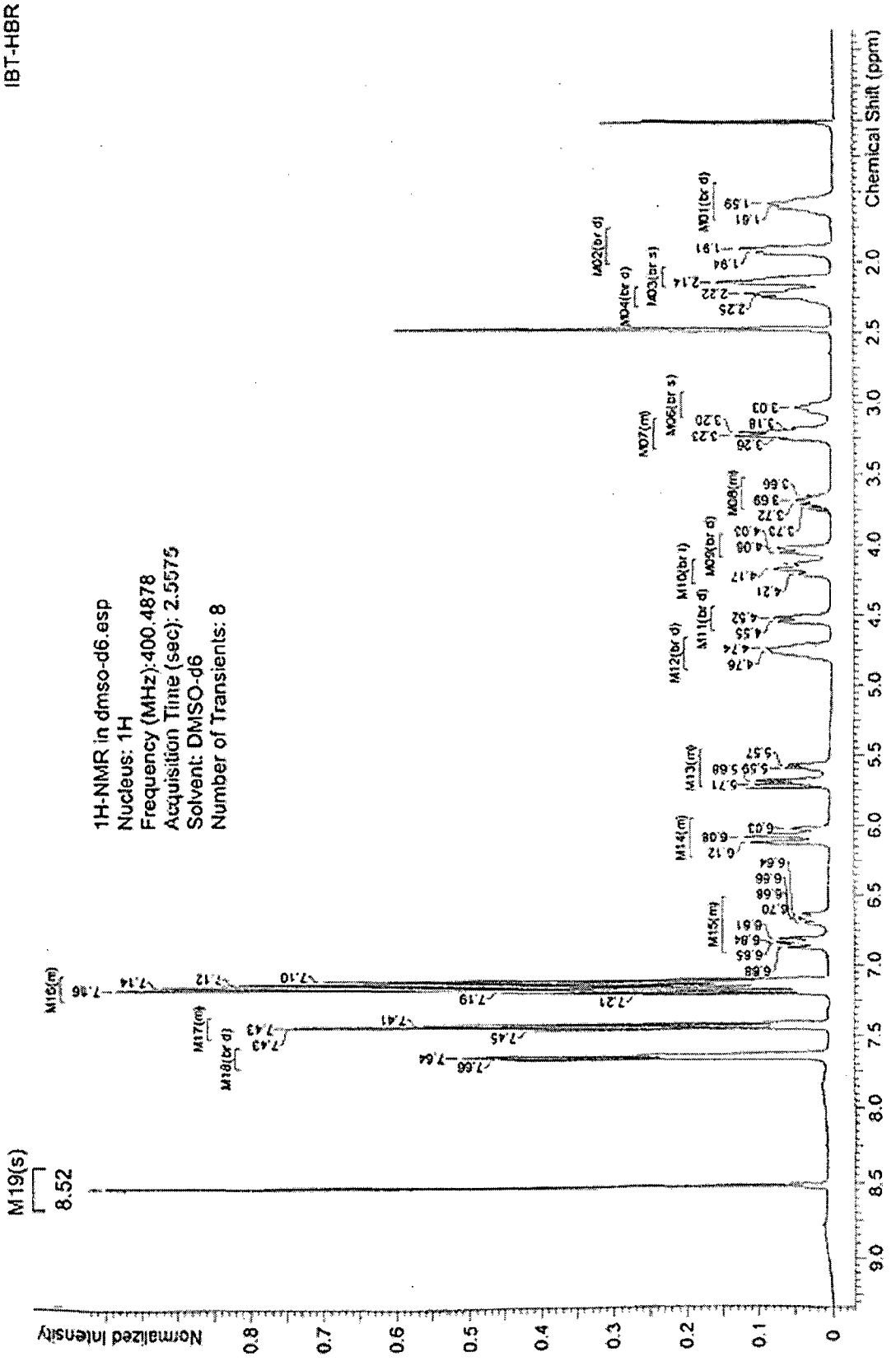

IBT-H8R
1H-NMR in dmso-d6.esp
Nucleus: 1H
Frequency (MHz):400.4878
Acquisition Time (sec): 2.5575
Solvent: DMSO-d6
Number of Transients: 8
M19(s)
8.52
Normalized Intensity
Chemical Shift (ppm)

Figure 8

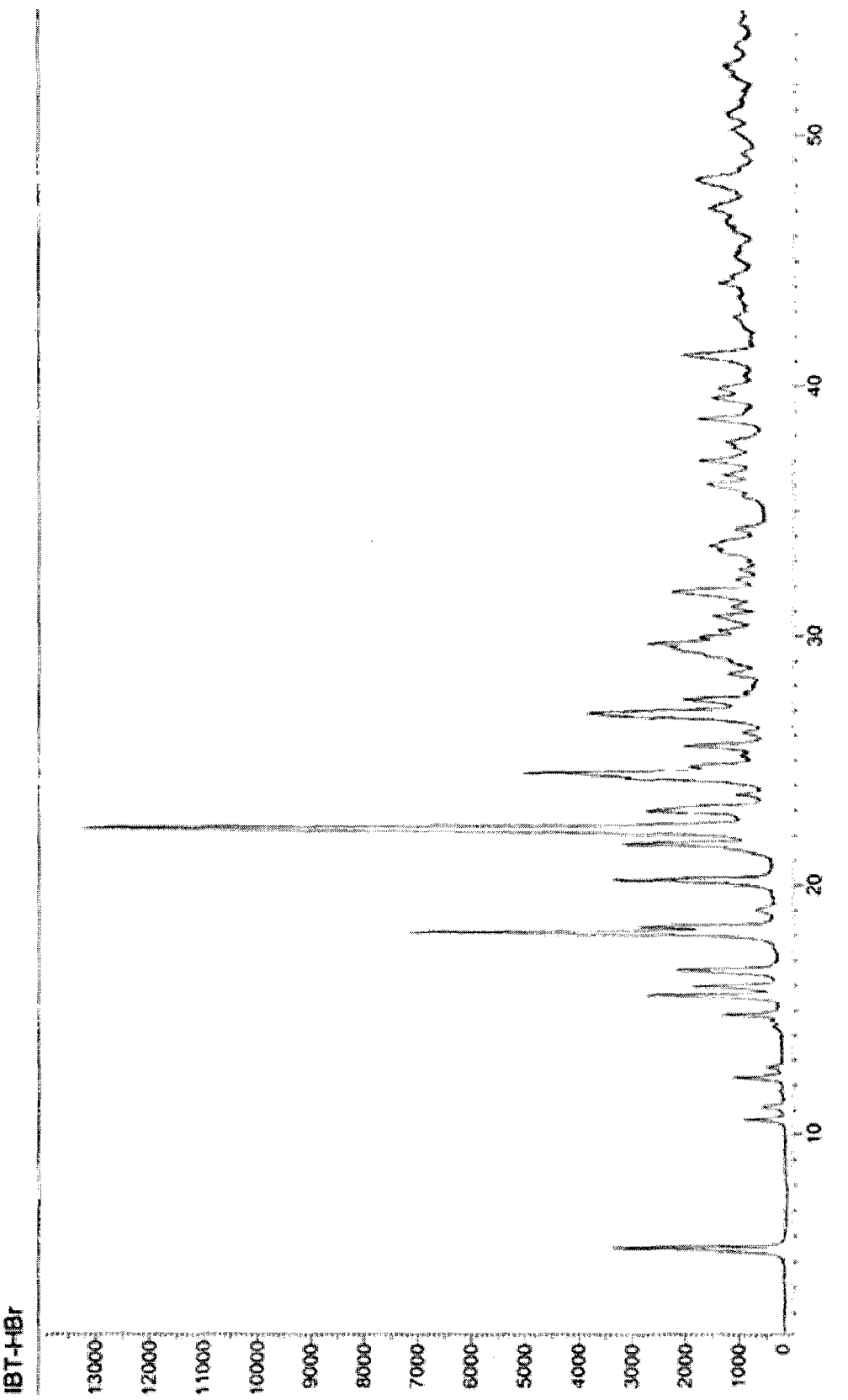

IBT-HBr
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
2Theta (Coupled Two Theta/Theta) WL= 1,54060

Figure 9

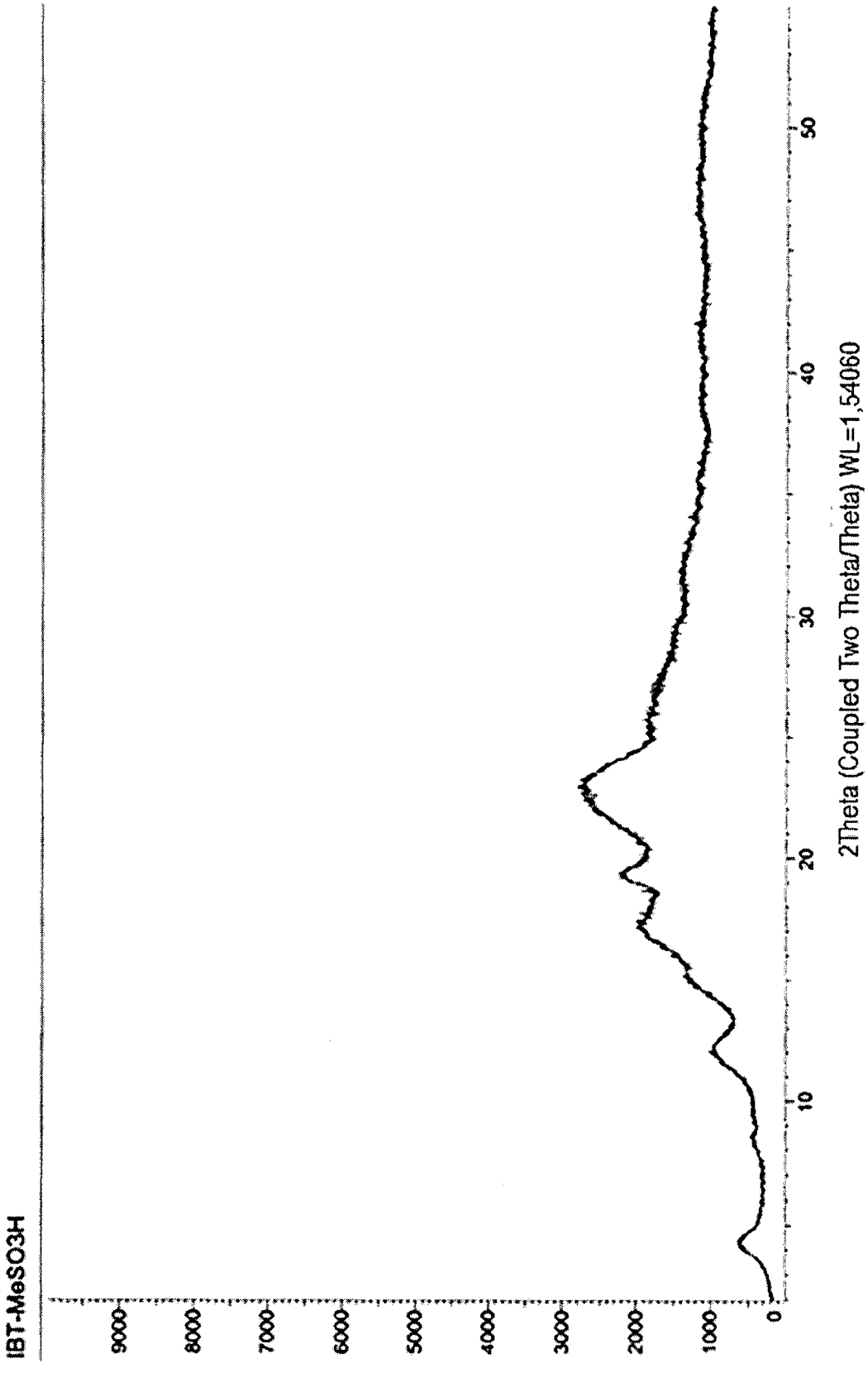

IBT-MeSO3H
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
2Theta (Coupled Two Theta/Theta) WL=1,54060

Figure 10

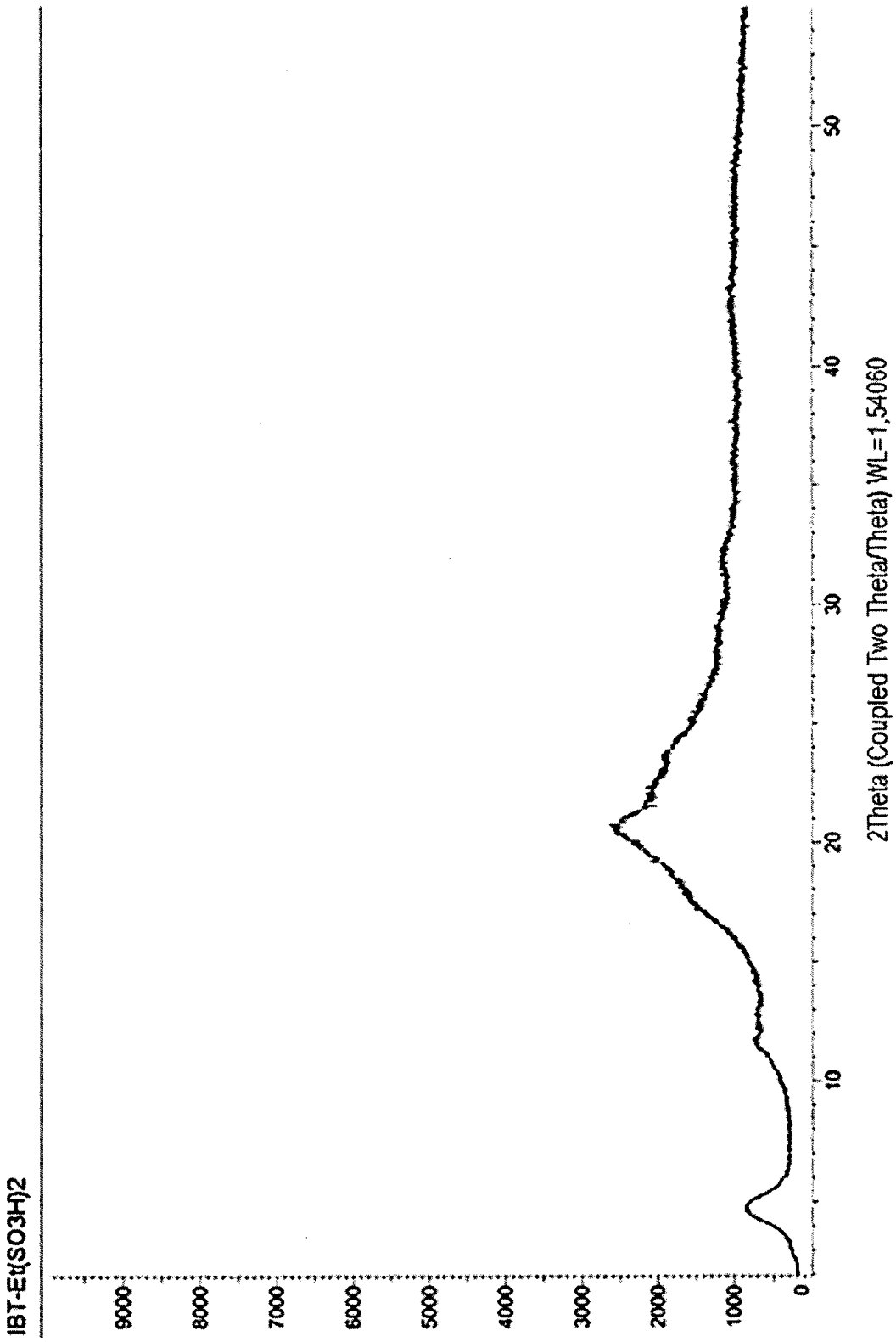

IBT-Et(SO3H)2
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
2Theta (Coupled Two Theta/Theta) WL=1,54060

Figure 11

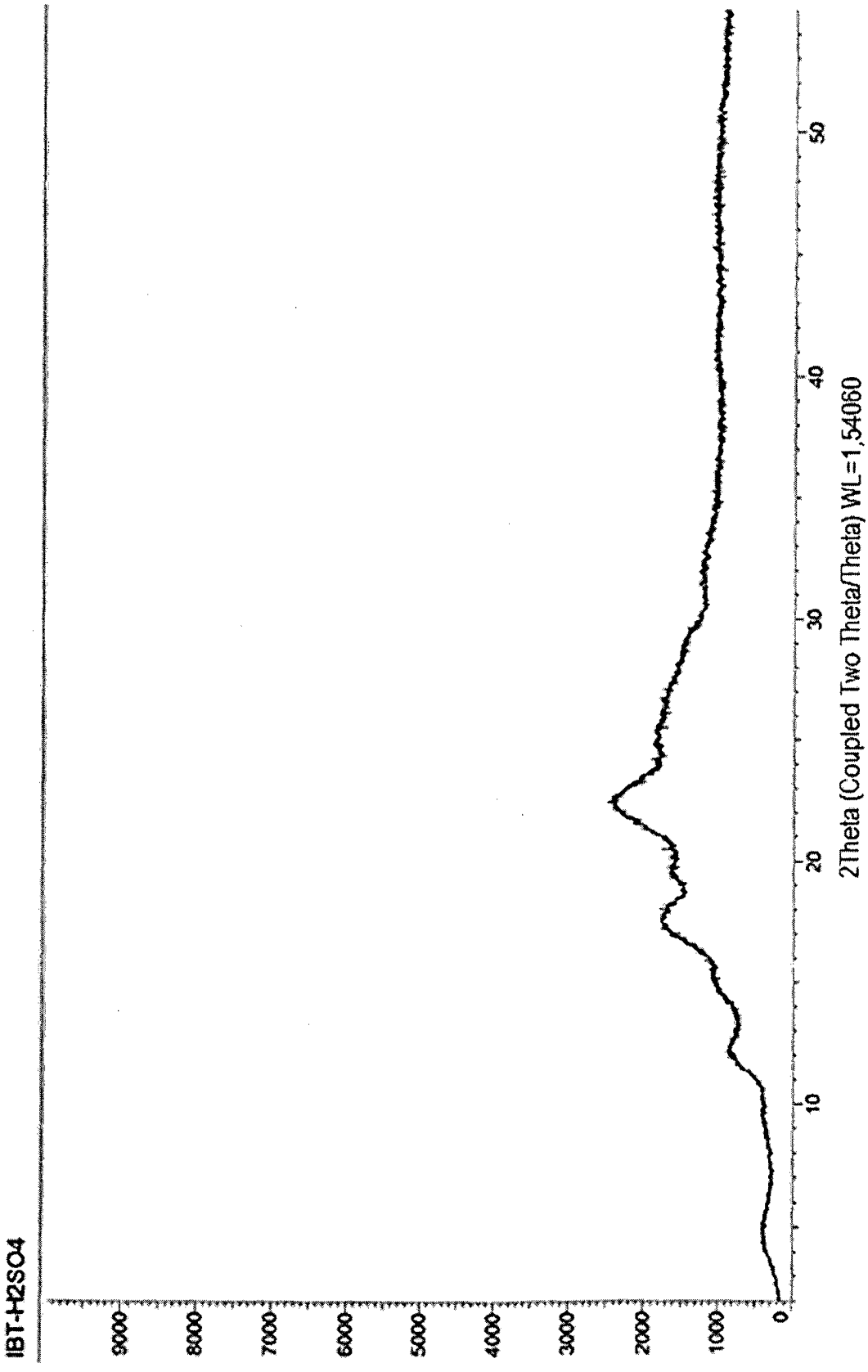

IBT-H2SO4
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
10
20
30
40
50
2Theta (Coupled Two Theta/Theta) WL=1,54060

Figure 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/069430

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/519 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, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/046964 A2 (PHARMACYCLICS INC [US]; CHEN WEI [US]; LOURY DAVID J [US]; MODY TARAK) 21 April 2011 (2011-04-21) page 47; example 4; compound 1	1-14
Y	WO 2014/004707 A1 (PRINCIPIA BIOPHARMA INC [US]) 3 January 2014 (2014-01-03) cited in the application page 26, lines 4-8	1-14
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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28 September 2015	16/10/2015

Name and mailing address of the ISA/	Authorized officer
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