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(54) Title: PROCESS FOR THE PREPARATION OF PAZOPANIP HCL AND CRYSTALLINE FORMS OF PAZOPANIB
HCL

(57) Abstract: Various crystalline forms of Pazopanib HCl were prepared. In preferred embodiments the obtained Pazopanib HCl
is essentially free from CPML.



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PROCESS FOR THE PREPARATION OF PAZOPANIB HCL AND CRYSTALLINE FORMS OF
PAZOPANIB HCL

Cross-Reference To Related Applications

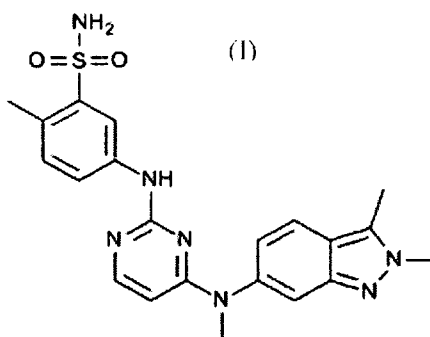
[0001] This application claims the benefit of U.S. Provisional Patent Application Serial Nos. 61/266,827, filed December 4, 2009; 61/290,165, filed December 24, 2009; 61/304,619, filed February 15, 2010; 61/346,016, filed May 18, 2010; 61/354,176, filed June 11, 2010; and 61/354,402, filed June 14, 2010, which are incorporated herein by reference.

Field of the Invention

[0002] The present invention encompasses crystalline forms of 5-[[4-[(2, 3-dimethyl-2H-indazol-6-yl) methylamino]-2-pyrimidinyl] amino]-2-methyl-benzolsulfonamide HCl, the preparation thereof and pharmaceutical compositions thereof.

Background of the Invention

[0003] Pazopanib, 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl] amino]-2-methyl-benzolsulfonamide, having the molecular formula $C_{21}H_{23}N_7O_2S$, a molecular weight of 437.52 g/mol and the following chemical structure:



is a tyrosine kinase inhibitor, indicated for the treatment of patients with advanced renal cell carcinoma. Pazopanib is administered as an HCl salt and is marketed by GSK in the US under the name Votrient®.

[0004] Pazopanib and its preparation are described in PCT Publication no. WO 2002/059110 (corresponding to US patent no. 7,105,530). The Journal of Pharmaceutical

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and Biomedical Analysis, 2009, Vol. 50, pp 144-150, also describes a process for the preparation of pazopanib HCl.

[0005] PCT Publication Nos. WO 2007/064753 (WO'753), WO 2007/143483 ("WO'483), WO 2003/106416 (WO'416), WO 2006/20564 (WO'564) and WO 2005/105094 (WO'094), as well as US publication Nos. US 2006/0252943 (US'943), US 2008/0293691 (US'691) and US 7,262,203 (US'203) describe anhydrous and hydrate forms of Pazopanib HCl and their preparation thereof.

[0006] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Pazopanib, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviours (e.g. measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), X-ray diffraction pattern, infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0007] Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound or salts thereof can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of Pazopanib.

Summary of the Invention

[0008] The present invention provides solid state forms of Pazopanib.

[0009] In yet another embodiment, the present invention further encompasses a pharmaceutical composition comprising the above described polymorphs of Pazopanib HCl crystalline forms, and at least one pharmaceutically acceptable excipient.

[00010] In another embodiment, the present invention encompasses the use of the above described crystalline forms of pazopanib HCl for the preparation of formulations.

Brief Description of the Drawings

- [00011] Figure 1 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib di-HCl Form I.
- [00012] Figure 2 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form II.
- [00013] Figure 3 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form III.
- [00014] Figure 4 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form IV.
- [00015] Figure 5 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form V.
- [00016] Figure 6 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form VI.
- [00017] Figure 7 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form VIII.
- [00018] Figure 8 provides DSC curve of crystalline Pazopanib HCl Form VIII.
- [00019] Figure 9 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form IX.
- [00020] Figure 10 provides DSC curve of crystalline Pazopanib HCl Form IX.
- [00021] Figure 11 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form X.
- [00022] Figure 12 provides DSC curve of crystalline Pazopanib HCl Form X.
- [00023] Figure 13 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form G.
- [00024] Figure 14 provides DSC curve of crystalline Pazopanib HCl Form G.
- [00025] Figure 15 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form A, prepared according to example 1.
- [00026] Figure 16 provides DSC and TGA curve of crystalline Pazopanib HCl Form A, prepared according to example 1.
- [00027] Figure 17 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form A, prepared according to example 2.

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[00028] Figure 18 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form XII.

[00029] Figure 19 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form XI.

[00030] Figure 20 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib HCl Form XIII.

[00031] Figure 21 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib di-HCl Form XIV.

[00032] Figure 22 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib di-HCl Form XV.

[00033] Figure 23 provides a characteristic X-ray powder diffractogram of crystalline Pazopanib base.

Detailed Description of the Invention

[00034] The present invention provides solid state physical properties of Pazopanib HCl.

[00035] A crystal form may be referred to herein as being characterized by graphical data "as shown in," or "as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. The skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form, and confirm whether the two sets of data are characterizing the same crystal form or two different crystal forms. A crystal form referred to herein as being characterized by graphical data "as shown in," or "as depicted in" a Figure includes the crystal form characterized by the data shown in the Figure or the data shown in the Figure with any of the small variations known to the skilled person.

[00036] Polymorphic forms according to the invention may be referred to herein as "pure" or "polymorphically pure." This terminology refers to the subject polymorph containing less than about 20% (w/w) of other polymorphic forms. Preferably, when a crystal form according to the invention is referred to as pure or polymorphically pure, it will contain less than 10%, less than 5%, less than 2%, less than 1% or even less than

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0.5% of other forms of the compound. In other embodiments, the polymorphs of Pazopanib according to the invention may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other polymorphic forms of Pazopanib.

[00037] As used herein, the term “substantially pure” refers to a compound, such as pazopanib HCl, having a purity of 99.0% area by HPLC or more. Preferably, the pazopanib HCl has a purity of about 99.5% area by HPLC or more, more preferably, about 99.9% area by HPLC or more.

[00038] The amount of solvent employed in a chemical process, e.g., a reaction or a crystallization may be referred to herein as a number of “volumes” or “vol” or “V.” For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression means milliliters per gram, such that suspending a 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent.

[00039] As used herein, the term “essentially free from CPMI” refers to pazopanib HCl containing less than about 0.05% area by HPLC of CPMI. In preferred embodiments, pazopanib HCl contains less than about 100 ppm of CPMI as measured by a suitable HPLC method as described herein, more preferably pazopanib HCl containing between 20 to 75 ppm of CPMI, less than 75 ppm of CPMI, or an undetectable amount of CPMI as measured by a suitable HPLC method.

[00040] As used herein, the term “essentially free from PZP-PDMI” refers to pazopanib HCl containing less than about 0.15% area by HPLC of PZP-PDMI. In preferred embodiments, pazopanib HCl contains less than about 0.1% area by HPLC of PZP-PDMI, more preferably pazopanib HCl containing less than about 0.05% area by HPLC of PZP-PDMI, most preferably, pazopanib HCl containing an undetectable amount of PZP-PDMI as measured by HPLC.

[00041] As used herein, the term “essentially free from AMBS” refers to pazopanib HCl containing less than about 0.15% area by HPLC of AMBS. In preferred embodiments, pazopanib HCl contains less than about 0.1% area by HPLC of AMBS, more preferably, pazopanib HCl containing less than about 0.05% area by HPLC of AMBS, most preferably, pazopanib HCl containing an undetectable amount of AMBS as measured by HPLC.

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[00042] As used herein, the term "pazopanib di-HCl salt" refers to pazopanib HCl having about 1.7 to about 2.3 moles equivalent of HCl per 1 mole of pazopanib. More preferably, having about 2 moles equivalent of HCl per 1 mole of pazopanib.

[00043] As used herein, the terms "room temperature", or "ambient temperature" refers to a temperature of about 15°C to about 30°C, more preferably, to a temperature of about 20°C to about 25°C.

[00044] As used herein, the terms "vacuum" or "reduced pressure" refers to a pressure of about 2 mmHg to about 100 mmHg.

[00045] In one embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form II. Form II can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.5, 16.9, 19.0, 19.6 and 24.1 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 2; and combinations thereof. Pazopanib HCl Form II can be further characterized by additional X-ray powder diffraction peaks at 13.0, 15.0, 23.6 and 30.1 ± 0.2 degrees 2-Theta.

[00046] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form III. Form III can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 9.8, 14.7, 18.8, 19.8 and 24.0 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 3; and combinations thereof. Pazopanib HCl Form III can be further characterized by additional X-ray powder diffraction peaks at 16.7, 18.3, 26.1 and 30.1 ± 0.2 degrees 2-Theta.

[00047] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form V. Form V can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at: 6.6, 17.4, 19.0, 19.9, 21.3 and 27.1 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 5; and combinations thereof. Pazopanib HCl Form V can be further characterized by additional X-ray powder diffraction peaks at 9.4, 12.9, 16.3, 1.8 and 25.9 ± 0.2 degrees 2-Theta.

[00048] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form VI. Form VI can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at: 10.1, 14.7, 19.0, 19.5, 22.3 and 24.3 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as

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depicted in figure 6; and combinations thereof. Pazopanib HCl Form VI can be further characterized by additional X-ray powder diffraction peaks at 12.7, 16.8, 18.2, 20.0 and 25.9 ± 0.2 degrees 2-Theta.

[00049] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form VII. Form VII can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 10.7, 15.4, 16.6, 23.4 and 23.9 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 7; and combinations thereof. Pazopanib HCl Form VIII can be further characterized by additional X-ray powder diffraction peaks at 13.9, 14.6, 19.7 and 27.6 ± 0.2 degrees 2-Theta and by the differential scanning calorimetry ("DSC") thermogram substantially as depicted in Figure 8.

[00050] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form IX. Form IX can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.2, 12.3, 16.7, 21.3 and 24.0 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 9; and combinations thereof. Pazopanib HCl Form IX can be further characterized by additional X-ray powder diffraction peaks at 13.7, 14.6, 17.4, 18.3, 19.2 and 25.1 ± 0.2 degrees 2-Theta and by the DSC thermogram substantially as depicted in Figure 10.

[00051] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form X. Form X can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 7.2, 14.5, 17.1 and 23.0 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in Figure 11; and combinations thereof. Pazopanib HCl Form X can be further characterized by additional X-ray powder diffraction peaks at 19.0, 20.9 and 26.8 ± 0.2 degrees 2-Theta and by the DSC thermogram substantially as depicted in Figure 12.

[00052] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form XII. Form XII can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 8.9, 9.8, 17.0, 18.9, 19.3 and 21.5 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in Figure 18; and combinations thereof. Pazopanib HCl Form XII can be further characterized by additional X-ray powder diffraction peaks at 14.0, 14.4, 17.8, 20.5 and 26.9 ± 0.2 degrees 2-Theta.

[00053] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form G. Form G can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 9.6, 16.8, 19.6, 24.7 and 26.2 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 13; and combinations thereof. Pazopanib HCl Form G can be further characterized by additional X-ray powder diffraction peaks at 11.8, 14.6, 15.3, 18.4, 20.3 and 23.6 ± 0.2 degrees 2-Theta and by the DSC thermogram substantially as depicted in figure 14.

[00054] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form XI. Form XI can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.7, 11.9, 15.1, 15.6 and 24.3 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 19; and combinations thereof. Pazopanib HCl Form XI can be further characterized by additional X-ray powder diffraction peaks at 19.7, 20.9, 25.1 and 27.3 ± 0.2 degrees 2-Theta.

[00055] In another embodiment, the present invention encompasses crystalline Pazopanib HCl, designated herein as Form XIII. Form XIII can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 15.1, 16.6, 19.9 and 23.8 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 20; and combinations thereof. Pazopanib HCl Form XIII can be further characterized by additional X-ray powder diffraction peaks at 10.4, 14.4, 15.4 and 24.5 ± 0.2 degrees 2-Theta. Typically form XIII is an acetic acid solvate.

[00056] In another embodiment, the present invention encompasses crystalline Pazopanib di-HCl, designated herein as Form XIV. Form XIV can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 7.8, 12.4, 22.9, 23.6 and 26.9 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 21; and combinations thereof. Pazopanib di-HCl Form XIV can be further characterized by additional X-ray powder diffraction peaks at 14.8, 17.5, 19.0, 25.3 and 27.4 ± 0.2 degrees 2-Theta.

[00057] In another embodiment, the present invention encompasses crystalline Pazopanib di-HCl, designated herein as Form XV. Form XV can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.9, 12.1, 23.6, 26.8 and 27.4 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as

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depicted in figure 22; and combinations thereof. Pazopanib di-HCl Form XV can be further characterized by additional X-ray powder diffraction peaks at 15.7, 19.4, 23.3 and 25.7 ± 0.2 degrees 2-Theta.

[00058] In another embodiment, the present invention encompasses crystalline Pazopanib base, characterized by data selected from: an X-ray powder diffraction pattern having peaks at 7.3, 13.2, 14.7, 18.6 and 21.7 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 23; and combinations thereof. Pazopanib base can be further characterized by additional X-ray powder diffraction peaks at 12.3, 13.7, 16.1, 24.7 and 26.7 ± 0.2 degrees 2-Theta.

[00059] The present invention further provides crystalline Pazopanib di-HCl, designated herein as Form I. Form I can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 6.7, 7.4, 12.0, 14.8 and 23.6 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 1; and combinations thereof. Pazopanib di-HCl Form I can be further characterized by additional X-ray powder diffraction peaks at 13.3, 14.8, 19.0 and 26.6 ± 0.2 degrees 2-Theta.

[00060] The present invention further provides crystalline Pazopanib HCl, designated herein as Form IV. Form IV can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 11.5, 11.9, 15.5, 17.2 and 20.9 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 4; and combinations thereof. Pazopanib HCl Form IV can be further characterized by additional X-ray powder diffraction peaks at 18.2, 18.7, 25.7 and 27.1 ± 0.2 degrees 2-Theta. Typically form IV is a hydrate.

[00061] The present invention further provides crystalline Pazopanib HCl, designated herein as form A. Form A can be characterized by data selected from: an X-ray powder diffraction pattern having peaks at 5.6, 15.5, 16.4, 24.0 and 24.3 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 15, 17 or 18; and combinations thereof. Pazopanib HCl form A can be further characterized by data selected from: additional X-ray powder diffraction peaks at 10.5, 16.8, 17.9, 26.4 and 32.9 ± 0.2 degrees 2-Theta; a DSC thermogram substantially as depicted in figure 16; and thermogravimetric analysis ("TGA") substantially as depicted in figure 16. Form A is an anhydrous form containing less than about 1% water as measured by the Karl-Fisher method.

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[00062] In another embodiment, the present invention encompasses a process for preparing Pazopanib HCl comprising reacting N-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2H-indazol-6-amine (CPMI) and 5-amino-2-methylbenzenesulfonamide (AMBS) with acetic acid or alternatively in a mixture of water and acetic acid.

[00063] Typically, the CPMI and AMBS are combined with acetic acid or with a mixture of water and acetic acid to provide a solution. The solution is then cooled to obtain a suspension comprising Pazopanib HCl.

[00064] When the reaction is done with acetic acid, the reaction can be carried out at a temperature of about 80°C to about 120°C, or at a temperature of about 90°C to about 100°C, for example at a temperature of about 95°C. When the reaction is complete, the reaction mixture may be cooled, for example to about ambient temperature. The reaction mixture can be further maintained following the cooling, for a period of about 1 hour to provide a suspension comprising Pazopanib HCl form XIII.

[00065] The obtained pazopanib HCl may be recovered from the suspension by any suitable technique, for example by precipitation, filtering and washing the precipitate and drying. Washing can be done with acetic acid. Drying can be done for example, by heating at a temperature of about 50-70°C, for a period of about 48-72 hours, e.g., about 62 hours.

[00066] When the reaction is done with a mixture of acetic acid and water, the reaction can be carried out at a temperature of about 65°C. The solution can be further heated to a temperature of about 100°C for a period of about 1 hour. When the reaction is complete, the reaction mixture may be cooled, for example to about 0°C. The cooling can be accompanied by addition of ethanol to form a suspension comprising Pazopanib HCl form A.

[00067] The obtained pazopanib HCl may be recovered from the suspension by any suitable technique, for example by precipitation, filtering and washing the precipitate and drying. Washing can be done with ethanol. Drying can be done for example, under vacuum e.g., at less than about 200 mbar, at a temperature of about 50-60°C for a period of about 12-17 hours.

[00068] The pazopanib HCl obtained according to the above process using acetic acid or a mixture of acetic acid and water is substantially pure.

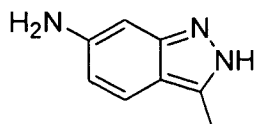
[00069] Accordingly, the above described process for preparing Pazopanib HCl can be used to purify Pazopanib HCl and thus produce chemically pure Pazopanib HCl.

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Further, the process provides pazopanib HCl essentially free of the starting material CPMI.

[00070] CPMI can be prepared according to example 52 or 54. During its preparation several impurities, described herein, can be formed.

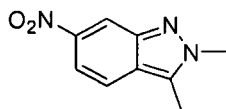
[00071] One impurity that has been observed is 3-methyl-2H-indazol-6-amine ("Des-Me-DMAD"), having the following formula:



which is characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 147.18.

[00072] Des-Me-DMAD can be prepared for example according to the procedure described in example 49. Preferably, the obtained Des-Me-DMAD is crystalline.

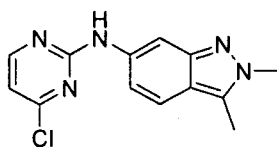
[00073] Another impurity that has been observed is 2,3-dimethyl-6-nitro-2H-indazole ("DMND"), having the following formula:



and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 191.19.

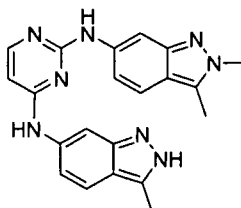
[00074] DMND can be prepared for example according to the procedure described in example 50. Preferably, the obtained DMND is crystalline.

[00075] Another impurity that has been observed is N-(4-chloropyrimidin-2-yl)-2,3-dimethyl-2H-indazol-6-amine ("4-CPDMI"), having the following formula:



and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 273.72.

[00076] Still another impurity that has been observed is N2,N4-bis(2,3-dimethyl-2H-indazol-6-yl)pyrimidine-2,4-diamine ("bis-PDMI"), having the following formula:

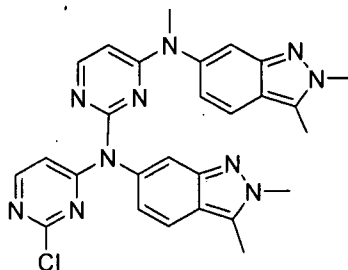


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and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 398.46.

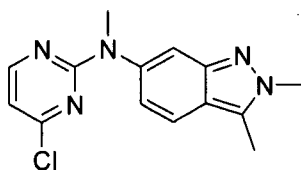
[00077] Bis-PDMI can be prepared for example according to the procedure described in example 48. Preferably, the obtained bis-PDMI is crystalline.

[00078] Yet another impurity that has been observed is N2-(2-chloropyrimidin-4-yl)-N2,N4-bis(2,3-dimethyl-2H-indazol-6-yl)-N4-methylpyrimidine-2,4-diamine ("PMI-CPDMI"), having the following formula:



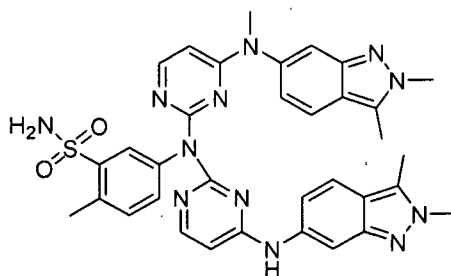
and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 525.01.

[00079] Another impurity that has been observed is N-(4-chloropyrimidin-2-yl)-N,2,3-trimethyl-2H-indazol-6-amine ("4-CPMI"), having the following formula:



and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 287.75.

[00080] The above described process further provides pazopanib HCl which is essentially free of 5-((4-((2,3-dimethyl-2H-indazol-6-yl)(methyl)amino)pyrimidin-2-yl)(4-(2,3-dimethyl-2H-indazol-6-ylamino)pyrimidin-2-yl)amino)-2-methylbenzene-sulfonamide ("PZP-PDMI"), an impurity which is formed during the preparation of pazopanib HCl, which has the following formula:



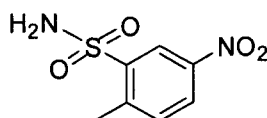
and which is characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 674.78.

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[00081] PZP-PDMI can be isolated from the reaction mixture, where it is formed. For example the separation can be done by filtering the precipitated PZP-PDMI or by isolating it from the reaction mixture using column chromatography on silica.

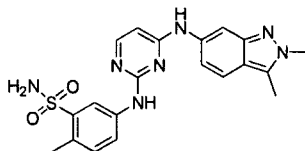
[00082] In addition to the above described impurity PZP-PDMI several different impurities, described herein, can be formed either during the preparation of pazopanib HCl or as a byproduct or degradant of one of the reactants.

[00083] One impurity that has been observed is 2-methyl-5-benzenesulfonamide ("NMBS"), having the following formula:



and characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 216.21.

[00084] Another impurity that has been observed is 5-(4-(2,3-dimethyl-2H-indazol-6-ylamino)pyrimidin-2-ylamino)-2-methylbenzenesulfonamide ("Des-Me-PZP"), that has the following formula:



and is characterized by a mass spectrum of MS-ESI $[M+H]^+ = m/z$ 423.49.

[00085] Des-Me-PZP can be prepared for example according to the procedure described in example 43. Preferably, the obtained Des-Me-PZP is crystalline.

[00086] Pazopanib HCl can be also prepared by a process comprising: reacting N-(2-chloropyrimidin-4-yl)-2, 3-dimethyl-2H-indazol-6-amine ("CPMI") and 5-amino-2-methylbenzenesulfonamide ("AMBS") in water; and then adding HCl.

[00087] Typically, CPMI and AMBS are combined with water to form a reaction mixture, and HCl is then added to the reaction mixture to form a suspension comprising the crystalline form.

[00088] The reaction mixture may be heated before the HCl addition or after it. Preferably, this heating is to about the reflux temperature. The heating step may be followed by a maintaining step. Preferably, the heated mixture is maintained at the temperature achieved in the heating step. Preferably, the heated mixture is maintained at that temperature until the amount of CPMI of less than about 1%, more preferably, less

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than about 0.5%, most preferably, less than about 0.1%, as measured by HPLC. The process may further comprise a cooling step, e.g., to about ambient temperature, such as about 25°C.

[00089] When the reaction is done in water form IV is obtained. Pazopanib HCl form IV is a hydrate, having a water content of about 5% as measured by the Karl-Fisher method.

[00090] Crystalline pazopanib HCl form IV may further be recovered from the suspension, for example, by filtering the suspension comprising pazopanib HCl form IV, washing the filtered mater, e.g., with water, and then drying it. Drying may be done by heating, e.g., in a vacuum oven at a temperature of about 40-60°C, preferably, for a period of about 8-24 hours.

[00091] The above crystalline forms can be prepared by a process comprising crystallizing pazopanib HCl from a polar aprotic solvent selected from: dimethylformamide (DMF), dimethylamide (DMA), N-methylpyrrolidone (NMP), dimethylsulfoxide (DMSO), and mixtures thereof, or a protic solvent selected from: a C₁-C₄ alcohol, such as methanol or ethanol; a C₁-C₄ halogenated alcohol, such as trifluoroethanol (TFE), formic acid, acetic acid, trifluoroacetic acid and mixtures thereof, to form a precipitate.

[00092] When a polar aprotic solvent is used, the crystallization comprises providing a solution of pazopanib HCl in the polar aprotic solvent and cooling the solution, e.g., to a temperature from about 0°C to about 10° C, to obtain a suspension comprising the above crystalline forms. When the solvent is DMSO, the process is preferably done at about ambient temperature, more preferably, at about 25°C to about 20°C. Also, when the solvent is DMSO, a maintaining step is performed. Preferably, the cooled DMSO suspension is maintained at the reduced temperature for about 12 to about 24 hours, more preferably, for about 15 hours to about 17 hours.

[00093] When the solvent is methanol, the heating is to a temperature of about 50°C to about 75°C, more preferably, to about 60°C to about 65°C. Preferably, the heating is for about 5 minutes to about 30 minutes, more preferably, for about 15 minutes. Also, when the solvent is methanol, the cooling is preferably to about ambient temperature, more preferably, from about 25°C to about 20°C. . When the solvent is methanol, the process may further comprise a maintaining step. Preferably, the cooled mixture is maintained for about 10 minutes to about 3 hours, more preferably, for about 2

hours to obtain form A. When the cooled mixture is further maintained for about 1 to about 3 days, form XII is obtained.

[00094] When the solvent is MeOH, the obtained Pazopanib HCl may further be recovered, *e.g.*, by filtering; and then drying. Drying is preferably done at reduced pressure, preferably, at a temperature of about 40°C to about 60°C, more preferably, at about 35 mbar and about 45°C. Preferably, the drying is done for about 12 hours to about 90 hours, more preferably, for about 24 hours to about 72 hours.

[00095] When the solvent is NMP, DMF or DMA the process preferably comprises heating to a temperature of about 120°C to about 140°C, more preferably, to about 125°C to about 130°C. When the solvent is TFE, the heating is preferably to reflux temperature. When the solvent is TFE, NMP, DMF or DMA, the cooling is preferably to about ambient temperature, more preferably, to about 25°C to about 20°C.

[00096] Optionally, when the solvent is TFE, DMF or DMA, prior to the cooling step, a maintaining step is performed. Preferably for these solvents, the heated mixture is maintained at the heated temperature for about 10 minutes to about 3 hours, more preferably, for about 15 minutes to about 2 hours. Preferably, when the solvent is NMP, the maintaining step is done for about 1 day to about 5 days, more preferably, for about 3 days.

[00097] The obtained Pazopanib HCl may further be recovered, *e.g.*, by techniques such as filtering, centrifugation or solvent decantation; and then drying. When the solvent is NMP, the recovery is preferably done by centrifugation or solvent decantation, and then drying. When the solvent is DMF, pazopanib HCl form II is obtained, and when the solvent is DMA or NMP, form III is obtained.

[00098] When the solvent is acetic acid, the heating is preferably to a temperature of about 110°C to about 120°C, more preferably, to about 117°C to about 118°C, and the cooling is preferably to about ambient temperature, more preferably, to about 25°C to about 20°C. Optionally, prior to the cooling step, additional acetic acid is added. Preferably, the addition is done dropwise until complete dissolution is obtained.

[00099] The process when acetic acid is the solvent may further comprise a maintaining step. Preferably, the acetic acid mixture is maintained at the cooled temperature for an interval of about 30 minutes to about 2 hours, more preferably, for about 1 hour. The obtained Pazopanib HCl may further be recovered, for example, by filtering; washing; and drying. Preferably, the drying is done at reduced pressure, *e.g.*, from about

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25mbar to about 35 mbar, at a temperature of about 60°C to about 80°C, more preferably, at about 75°C, for about 10 hours to about 20 hours, more preferably, for about 17 hours. Washing is preferably done with acetic acid.

[000100] The invention further encompasses a precipitation process for preparing pazopanib HCl comprising: dissolving pazopanib HCl in formic acid, DMSO or TFE and adding an anti-solvent selected from: acetone, acetonitrile, methyl tert-butyl ether (MTBE), ethyl-acetate (EtOAc), toluene, and ethanol. Preferably, the anti-solvent is added over a period of about 5 minutes to about 10 minutes.

[000101] The solvent are used in suitable amounts. For example, DMSO is preferably used in about 10 vol. to about 15 vol, and formic acid is used in about 2.0 vol. to about 3 vol. The anti-solvent is preferably used in about 30 vol. to about 35 vol. Preferably, when the solvent is DMSO or formic acid, the process is done at about room temperature. Formic acid, suitable for this process contains less than about 5%, preferably, less than about 3% water.

[000102] Preferably, when the solvent is TFE, prior to the addition of anti solvent a heating step is performed. Preferably, the heating is to a temperature of about 40°C to about 60°C, more preferably about 40°C, most preferably, until dissolution is obtained. Preferably, following the heating step a cooling step is performed. Preferably cooling is to about ambient temperature, more preferably, from about 25°C to about 20°C.

[000103] The product may further be recovered, e.g., by filtration. The filtered product may further be dried. Drying is preferably done under vacuum at a temperature of about 45°C to about 80°C, more preferably, at about 60°C, and for about 20 hours to about 30 hours. Optionally, a washing step is performed, preferably, using the anti-solvent used in the process. Washing may be repeated.

[000104] Typically, when the solvent is TFE, form VIII is obtained; when DMSO is used as the solvent, pazopanib HCl form G is obtained; when the solvent is formic acid and the anti solvent is MTBE form XI is obtained, when the solvent is formic acid and the antisolvent is EtOAc, form X is obtained, and, when the solvent is formic acid and the antisolvent is toluene, form I is obtained.

[000105] The invention further encompasses a process for preparing pazopanib HCl comprising: slurring pazopanib HCl in acetone or DMF. This slurry process is preferably done at about ambient temperature, more preferably, at about 25°C to about 20°C. The slurry process is also preferably done with stirring, e.g., for about 10 hours to

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about 27 hours, more preferably, for about 10 to about 17 hours. The slurry process may further comprise a recovery step, e.g., by filtering.

[000106] When the solvent is acetone, the recovery step further comprises drying, preferably, at a temperature of about 55°C to about 85°C, more preferably from about 65°C to about 75°C, most preferably, at 70°C. When the solvent is acetone, washing is preferably done, e.g., with acetone, and optionally may be repeated.

[000107] Typically, when the slurry solvent is DMF, form V is obtained, and, when the slurry solvent is acetone, form VI is obtained.

[000108] The invention further encompasses a process for preparing pazopanib HCl comprising: dissolving pazopanib HCl in TFE and rapidly evaporating the TFE.

[000109] Preferably, prior to the evaporation, a heating step is performed, e.g., to about 80°C to about 120°C, more preferably, about 100°C to about 110°C, most preferably, about 110°C. Preferably, following the heating a purging step is performed. Preferably, the purge is done in the presence of nitrogen, and under vacuum, preferably, at a pressure of about 6 mbar to about 10 mbar. Preferably, this process comprises rapidly evaporating the solvent while adding solution of Pazopanib HCl and TFE under reduced pressure. Preferably, the addition is done in portions, more preferably, drop-wise. Typically, the Pazopanib HCl obtained using this process is amorphous.

[000110] The above process may further comprise a recovery step. The recovery step may comprise drying; and cooling. Preferably, drying is done under vacuum, more preferably, at the same pressure used in the process. Cooling is preferably to about ambient temperature, more preferably, to about 25°C to about 20°C. Preferably, said cooling is done under nitrogen.

[000111] The present invention further encompasses 1) a pharmaceutical composition comprising at least one of the solid state forms of Pazopanib as described above, and at least one pharmaceutically acceptable excipient; 2) the use of any one or combination of the above-described solid state forms of Pazopanib in the manufacture of a pharmaceutical composition, and 3) a method of treating advanced renal cell carcinoma comprising administering a pharmaceutically effective amount of at least one of the solid state forms of Pazopanib as described above to a subject in need of the treatment. The pharmaceutical composition can be useful for preparing a medicament. The present invention also provides at least one of the solid state forms of Pazopanib as described above for use as a medicament.

[000112] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

HPLC Analyses

[000113] The compounds may be characterized by high performance liquid chromatography (HPLC) using Agilent 1200 HPLC system equipped with a diode array detector or Waters Acquity UPLC system with a photo diode array (PDA) detector. One analytical column used here is the Zorbax Eclipse XDB-C8 150x 4.6mm (3.5 μ m particle size) from Agilent Technology. In addition, some analyses were done using a Acquity UPLC BEH C18, 2.1x100mm (1.7 μ m particle size) from Waters Corp. These two HPLC methods are provided below. Of the two methods, the one employing the Acquity UPLC (Ultra high performance liquid chromatography) column, with its smaller particle size affords the lower detection limit. The two methods used herein are provided below.

HPLC method 1:

Column: Zorbax Eclipse XDB-C8 150x 4.6mm 3.5 μ m

Mobile phase: A: 90% 0.01M NH₄OAc (spontaneous pH ~6.3) : 10% ACN

B: ACN

Column temp.: 40°C

Detection: 254nm

Flow rate: 1.0 ml/min

Sample conc.: 0.5mg/mL

Inj. Vol.: 10 μ L

Diluent: Eluent A

Gradient:

%B	%A	Time
10	90	0

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20	80	10
20	80	19
35	65	34

HPLC method 2: determination of CPMI by UPLC

Column: Acquity UPLC BEH C18, 2.1x100mm, 1.7 μ m

Mobile phase: A: 90% 0.01M NH₄HCO₃: 10% ACN

B: ACN

Column temp.: 50°C

Detection: 254nm

Flow rate: 0.5 ml/min

Sample conc.: 4.0mg/mL

Inj. Vol.: 2 μ L

Diluent: MeOH

Gradient:

<u>B, %</u>	<u>A, %</u>	<u>Time, min</u>
10	90	0
20	80	1.9
20	80	7.2
30	70	11.8
30	70	14.6

For the UPLC method the detection limit for CPMI is 20 ppm and the quantification limit is 40 ppm.

X-ray powder diffraction:

[000114] The X-ray powder diffractions of Pazopanib HCl forms I-IV and of the anhydrous form (form A) were performed on an ARL X-ray powder diffractometer model X'TRA-019, with a Peltier detector. Copper K α_1 radiation ($\lambda=1.5418$ Å) was used. The sample holder was a round standard aluminum sample holder with round zero background plate (quartz or silicon). The scanning parameters were: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05°; and scan rate: 3 degrees/minute. The peak

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positions were determined by using silicon powder as internal standard in an admixture with the sample measured. The position of the silicon (111) peak was corrected to be 28.45 degrees two theta. The positions of the peaks were corrected respectively (no corrections were performed on the presented diffractograms in the figures).

[000115] The X-ray powder diffractions of Pazopanib HCl forms V-XV, G and the amorphous form, and of Pazopanib base form were performed on a Philips X'Pert PRO powder diffractometer with the following parameters:

Sample is applied directly on silicon PW1817/32 "zero background" holder	Sample holder preparation
Philips X'Pert PRO	Instrument
PW3050/60	Goniometer
PW3040; 45 kV, 40 mA	Generator
PW3373/00; Cu anode LFF	X-ray tube
$\lambda(\text{CuK}\alpha_1) = 1.540598 \text{ \AA}$	X-ray radiation
295±5K	Temperature

[000116] The scanning parameters were: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.0167°; and scan rate: 0.05 degrees/sec. The silicon powder as internal standard was present as an admixture within the samples. The position of the silicon (111) peak was 28.45 degrees two theta. No corrections were performed on the presented diffractograms in the figures and peak list.

DSC/TGA

[000117] DSC measurements were performed on Differential Scanning Calorimeter Mettler Toledo, Star SW 9.20. Aluminium sample pan was used. Program: heating rate: 10°C/min; Nitrogen flow 40ml/min. Temperature range: 20 °C - 250 °C for forms I-VI, 20 °C - 300 °C for form A.

Example 1: Preparation of Pazopanib HCl form A

[000118] A 1000 mL reactor was charged with CPMI (48 g, 167 mmol), AMBS (32 g, 170 mmol, 1.02 eq) EtOH abs. (480 mL, 10V) and HCl (1.2 mL, 2.7M in dioxane, 3.2 mmol, 0.02 eq) and the resulting mixture was stirred with an impeller and heated to 70-

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74°C for 10 h. Subsequently, the reaction mixture was cooled to 20 °C and kept at this temperature whilst stirring for 1 h. The mixture was filtered and the filter cake was washed with EtOH (2 x 160 mL) and dried under reduced pressure (30 mbar) at 45 °C for 16 h to give Pazopanib HCl form A (73.5 g, 93% yield, 98.6% purity, 0.17% AMBS, 0.9% CPMI, 0.21% PZP-PDMI) as an off-white solid.

Example 2: Preparation of substantially pure Pazopanib HCl

[000119] To a 250 mL round bottom flask, equipped with a magnetic stirrer and a reflux condenser was added CPMI (5.00 g, 17.4 mmol), AMBS (3.33 g, 17.9 mmol, 1.03 eq) and EtOH abs. (50 mL, 10V). The resulting suspension was stirred and heated to 78 °C leading to dissolution for 1 h, and then maintained at 70-73°C for 2 h. HCl (0.13 g, 2.7M in dioxane, 0.35 mmol, 0.02 eq) was added, gradually leading to precipitation. Stirring was continued for 11 h and the reaction mixture was then cooled to 20 °C. The mixture was stirred at 20 °C for another 40 min and then the contents of the flask were filtered and the filter cake was washed with EtOH (2 x 16 mL). The cake was dried at 45 °C in a vacuum oven (25-35 mbar) for 16 h to give crude Pazopanib HCl as an off-white solid (7.43 g, 90.6% yield, 99.0% purity, 0.09% AMBS, 0.67% CPMI, 0.18% PZP-PDMI).

Example 3: Preparation of substantially pure Pazopanib HCl

[000120] A 250 mL reactor equipped with an impeller was charged with CPMI (10.00 g, 34.8 mmol), EtOH abs. (100 mL, 10V) and AMBS (7.12 g, 38.2 mmol, 1.1 eq) and the resulting mixture was stirred and heated to reflux (70 °C) under N₂. To the mixture was added portion-wise HCl (0.25 mL, 2.7M in dioxane, 0.67 mmol, 0.02 eq). Stirring was continued at the same temperature for 11 h until there was no more consumption of CPMI according to HPLC. The reaction mixture was diluted with EtOH abs. (33.0 mL, 3.3V) and cooled to 20-25 °C. Stirring was continued at this temperature for 40 min, and then the mixture was filtered and the filter cake was washed with EtOH abs. at room temperature. The solid was dried at 45 °C under vacuum (25 mbar) to give crude Pazopanib HCl (15.95 g, 96.8% yield, 99.3% purity, 0.11% AMBS, 0.61% CPMI, PZP-PDMI not detected).

Example 4: Preparation of Pazopanib HCl

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[000121] CPMI (1 g, 3.48 mmol), AMBS (0.67 g, 3.58 mmol, 1.03 eq), and acetic acid (10 mL, 10V) were stirred at room temperature and heated to 95 °C over 20 min leading to a clear solution. Heating was continued for 2 h and then another portion of AMBS (0.04 g) was added and the reaction was monitored by HPLC until all CPMI had been consumed (less than the detection limit). The reaction was cooled to ambient temperature and stirring was continued for 1 h leading to precipitation. The resulting solid was isolated by vacuum filtration and the filter cake was washed with acetic acid and dried in a vacuum oven (25 mbar), 60 °C for 62 h to yield PZP.HCl (1.45 g, 88%) as a white solid (>98.9% purity, 0.08%AMBS, CPMI and PZP-PDMI not detected by HPLC method 1). Form XIII was obtained.

Example 5: Preparation of substantially pure Pazopanib HCl

[000122] CPMI (1 g, 3.48 mmol), AMBS (0.67 g, 3.58 mmol, 1.03 eq), and water (10 mL, 10V) were stirred at room temperature and then heated to reflux. Heating was continued for 2 h after which time HPLC analysis indicated that the reaction had not started. In order to initiate reaction, HCl 1N (3 drops) was added at 100 °C gradually leading to precipitation after ca. 15 min, and the reaction progress was monitored by HPLC until <0.6% CPMI remained. The reaction was cooled to ambient temperature and stirring was continued for 16 h. The resulting solid was isolated through vacuum filtration and the filter cake was washed with water and dried in a vacuum oven (25 mbar), 60 °C for about 16 h to give PZP.HCl (1.5 g, 91% yield, 99.0% purity, 0.02% AMBS, 0.62% CPMI, 0.21% PZP-PDMI) as a white solid. Form IV was obtained.

Example 6: Preparation of substantially pure Pazopanib HCl

[000123] A 100 mL round bottom flask was charged with Pazopanib HCl (form A 1.97 g; 98.6% purity and containing 0.92% CPMI) and DMF (35V). The mixture was stirred and heated to 125°C for 10 min resulting in dissolution. The solution was then cooled to ambient temperature over 50 min and stirring was continued at the same temperature for another 60 min leading to precipitation. The solid was filtered and dried in vacuum at 70°C for 66 h to give Pazopanib HCl >99.9% purity and essentially free from CPMI and PZP-PDMI according to HPLC method 1 (1.69 g, 86% yield, >99.9% purity). (form II when wet/dry).

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Example 7: Preparation of Pazopanib HCl Form II

[000124] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 130 mg) and DMF (2.0 mL) and the resulting mixture was heated to 130°C leading to dissolution. After 12 minutes, the solution was cooled to ambient temperature resulting in precipitation. The solids were filtered, dried at 60°C for 5 days (26 mbar) and analyzed by XRD analysis, which indicated polymorphic form II.

Example 8: Preparation of substantially pure Pazopanib HCl Form V

[000125] A 20 mL vial equipped with a magnetic stirrer was charged with anhydrous Pazopanib HCl (form A 100 mg; 98.6% purity and containing 0.92% CPMI) and DMF (2 mL, 20V). The resulting slurry was stirred 17 h at rt and then filtered. The solid was analyzed by XRD, which indicated form V. (>99.6% purity, AMBS, CPMI and PZP-PDMI not detected according to HPLC method 1). Drying of this at 45°C, 25 mbar overnight gave form II.

Example 9: Preparation of Pazopanib HCl Form III

[000126] A 20 mL vial equipped with a magnetic stirrer was charged with anhydrous Pazopanib HCl (form A, 135 mg) and DMA (11.3 mL) and the resulting mixture was heated to 130°C leading to dissolution. Stirring was continued for 10 minutes and then, the solution was cooled to ambient temperature resulting in precipitation. The solids were filtered, dried at 60 °C for about 6 days and analyzed by XRD analysis, which indicated polymorphic form III.

Example 10: Preparation of Pazopanib HCl Form III

[000127] PZP.HCl (form A, 0.154 g) was suspended in NMP (30V) and heated to 130°C for 30 min until dissolution, and subsequently cooled to ambient temperature. Stirring was continued for 3 days leading to precipitation. The resulting precipitate was separated by centrifugation, the solvent was decanted and the solid (form III) was dried at 70 °C (25 mbar) for 66 h to give polymorphic form III.

Example 11: Preparation of substantially pure Pazopanib HCl

[000128] A 250 mL flask was charged with Pazopanib HCl (form A, 1.16 g ; 98.6% purity and containing 0.92% CPMI) and MeOH (75V). The mixture was stirred and

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heated to reflux for 10 mins resulting in dissolution. The solution was then gradually cooled to ambient temperature over 40 min and stirring was continued at the same temperature for 2 h leading to precipitation. The solid was filtered and dried under vacuum (25 mbar) at 60°C for 18 h to give Pazopanib HCl. (>99.99% purity, AMBS, CPMI and PZP-PDMI not detected by HPLC method 1)

Example 12: Preparation of substantially pure Pazopanib HCl

[000129] Crude Pazopanib HCl (form A, 1.04 g ; 98.6% purity and containing 0.92% CPMI) was mixed with glacial acetic acid (2 mL, 2V) at room temperature and then heated to reflux (117-118° C) whilst stirring. Another 4V glacial acetic acid was added dropwise, leading to complete dissolution. The resulting solution was cooled to room temperature for 1.5 h leading to precipitation, and the stirring was continued for another 1 h. The solid was isolated by vacuum filtration and the filter cake was washed with glacial acetic acid (0.5 mL, 0.5V) and dried in a vacuum oven (25 mbar) at 60°C for 17 h to give Pazopanib HCl as a white solid. (98% yield, >99.9% purity, AMBS not detected, CPMI 0.02%, PZP-PDMI 0.01%). Form XIII was obtained.

Example 13: Preparation of Pazopanib HCl

[000130] To a 250 mL round bottom flask, equipped with a magnetic stirrer and reflux condenser was added CPMI (2.13 g, 7.4 mmol, 98.7% purity), AMBS (1.37 g, 7.4 mmol) and IPA (64 mL). The resulting suspension was stirred and HCl (40 drops, 32%) was added and the mixture was heated to 80°C, leading to complete dissolution. After 10 minutes at 80°C, precipitation commenced. Stirring was continued for 3.5 h and the reaction mixture was then cooled to ambient temperature and diethylether (60 mL) was added. The contents of the flask were filtered and filter cake was washed with diethylether (2 x 20 mL). The solid was dried 35°C (35 mmHg) for 24 h to give a hydrate of Pazopanib HCl as an off-white solid (3.46 g, 96.5% yield, 98.3% purity, ca 2% water by KF). XRD analysis of the material indicated a mixture of polymorphic forms I and A.

Example 14: Preparation of substantially pure Pazopanib HCl Form IV

[000131] 1 g Pazopanib HCl, obtained according to example 2, was stirred with IPA (15mL). The mixture was heated to 80°C, then 0.05N HCl (5.4 ml) was added and the particles dissolved to give a clear solution. The resulting solution was cooled to 62°C, and

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then seeded with Pazopanib HCl obtained by the process of example 12. Turbidity was observed and the mixture was cooled to ambient temperature for 0.5 h. The resulting white crystals were filtered, washed with IPA and dried in a vacuum oven at 45°C overnight to obtain Pazopanib HCl form IV (0.92 g, yield: 92%; purity: 99.95%, CPMI: 0.03%, AMBS and PZP-PDMI not detected by HPLC method 1) TGA = 3.5%.

Example 15: Preparation of Pazopanib HCl Form VI

[000132] A 20 mL vial equipped with a magnetic stirrer was charged with anhydrous Pazopanib HCl (form A); 180 mg and acetone (2 mL). The resulting slurry was stirred at ambient temperature for ca. 27 h and then filtered and the filter cake was washed with acetone. The solid was dried in a vacuum oven (25 mbar) at 70°C for 72 h to give form VI. (99.4% purity, AMBS not detected, CPMI 0.1%, PZP-PDMI 0.24%)

Example 16: Preparation of Pazopanib di-HCl Form I

[000133] A 20 mL vial equipped with a magnetic stirrer was charged with PZP.HCl (200 mg) (form A). Formic acid (0.5 mL) was added at ambient temperature with stirring, leading to dissolution. Toluene (3 mL) was added drop-wise and stirring was continued at ambient temperature for 1.5 h. The resulting precipitate was filtered and the solid was analyzed by XRD, which indicated form I.

Example 17: Preparation of Pazopanib HCl Form IX

[000134] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A) (200 mg) and formic acid 98% (0.5 mL, 2.5V). The mixture was stirred at ambient temperature leading to dissolution. To the solution was added water (2 mL, 8V) leading to precipitation. Stirring was continued for 3 h at ambient temperature and then the solid was isolated by vacuum filtration to give form IX, which was dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form IX.

Example 18: Preparation of Pazopanib HCl Form IX

[000135] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A) (200 mg) and formic acid 98% (0.5 mL, 2.5V). The mixture was stirred at ambient temperature leading to dissolution. To the solution was added MTBE

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(1 mL, 4V) leading to precipitation. Stirring was continued for 3 h at ambient temperature and then the solid was isolated by vacuum filtration to give form IX, which was dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form IX.

Example 19: Preparation of Pazopanib HCl Form X

[000136] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and formic acid 98% (0.5 mL, 2.5V). The mixture was stirred at ambient temperature leading to dissolution. To the solution was added EtOAc (1 mL, 5V) leading to precipitation. Stirring was continued for 3h at ambient temperature and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form X.

Example 20: Preparation of substantially pure Pazopanib HCl form G

[000137] A 20 mL vial was charged with Pazopanib HCl (form A, 171 mg; 98.6% purity and containing 0.92% CPMI) and DMSO (2 mL). The mixture was stirred at room temperature for about 10 min, resulting in dissolution. To the solution was added acetone (4.8 mL) drop-wise over 5 min leading to precipitation. Stirring was continued at room temperature for 17 h. The solid was filtered, washed with acetone (2x1.7 mL) and dried under vacuum (25mbar) at 60°C for 24 h to give Pazopanib HCl form G (46% yield, >99.9% purity, AMBS, CPMI and PZP-PDMI not detected by HPLC method 1)

Example 21: Preparation of substantially pure Pazopanib HCl form G

[000138] A 20 mL vial was charged with Pazopanib HCl (form A, 333 mg; 98.6% purity and containing 0.92% CPMI) and DMSO (3.2 mL). The mixture was stirred at room temperature for 10 min resulting in dissolution. To the solution was added acetonitrile (10.4 mL) drop-wise over 5 min leading to precipitation. Stirring was continued at room temperature for 17 h. The solid was filtered, washed with acetonitrile (2x3 mL) and dried under vacuum (25mbar) at 60°C for 24 h to give Pazopanib HCl form G (93% yield, >99.9%, AMBS, CPMI and PZP-PDMI not detected).

Example 22: Preparation of substantially pure Pazopanib HCl form G

[000139] A 20 mL vial was charged with Pazopanib HCl (form A, 171 mg; 98.6% purity and containing 0.92% CPMI) and DMSO (1.7 mL). The mixture was stirred at

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room temperature for 10 min resulting in dissolution. To the solution was added ethyl acetate (5.6 mL) drop-wise over 5 min leading to precipitation. Stirring was continued at room temperature for 17 h. The solid was filtered, washed with ethyl-acetate (2x1.7 mL) and dried under vacuum (25mbar) at 60°C for 24 h to give Pazopanib HCl form G (86% yield, >99.9% purity, AMBS, CPMI and PZP-PDMI not detected by HPLC method 1)

Example 23: Preparation of Pazopanib HCl form G

[000140] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (229 mg, form A) and DMSO (2.5 mL, 11V). The mixture was stirred at ambient temperature for about 10 min resulting in dissolution. To the solution was added ethanol (4.8 mL, 30V) drop-wise over 5 min leading to precipitation. Stirring was continued at ambient temperature for 17 h. The solid was filtered, washed with ethanol (2x2 mL) (polymorph G) and dried under vacuum (26 mbar) at 60°C for 22 h to give Pazopanib HCl form G.

Example 24: Preparation of Pazopanib HCl form G

[000141] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (98.6% purity and containing 0.92% CPMI) (210 mg, form A) and DMSO (2.3 mL, 11V). The mixture was stirred at ambient temperature for about 10 min resulting in dissolution. To the solution was added MTBE (6.1 mL, 29V) dropwise over 5 min leading to precipitation. Stirring was continued at ambient temperature for 20 h. The solid was filtered, washed with MTBE (2x2 mL) (polymorph G) and dried under vacuum (25 mbar) at 60 °C for 39 h to give Pazopanib HCl (59% yield, >99.9% purity, AMBS not detected, CPMI 0.04%, PZP-PDMI 0.03%) form G.

Example 25: Preparation of Pazopanib HCl form G

[000142] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (214 mg, form A) and DMSO (2.6 mL, 12V). The mixture was stirred at ambient temperature for about 10 min resulting in dissolution. Stirring was continued at ambient temperature for 17 h leading to precipitation. The pasty solid was filtered and dried under vacuum (26 mbar) at 70°C for 66 h to give Pazopanib HCl form G (67% yield).

Example 26: Preparation of Pazopanib HCl form VIII

[000143] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and 2,2,2-trifluoroethanol (1.5 mL, 6V). The mixture was heated to 40 °C leading to dissolution. The reaction vessel was removed from the heat source to allow cooling to ambient temperature and then ethanol (3 mL, 12V) was added, leading to precipitation. Stirring was continued for 1.5 h at ambient temperature and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form VIII.

Example 27: Preparation of Pazopanib HCl form VIII

[000144] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and 2,2,2-trifluoroethanol (1 mL, 5V). The mixture was heated to 40 °C leading to dissolution. The reaction vessel was removed from the heat source to allow cooling to ambient temperature and then EtOAc (1 mL, 5V) was added, leading to precipitation. Stirring was continued for 1.5 h at ambient temperature and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form VIII.

Example 28: Preparation of Pazopanib HCl form VIII

[000145] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and 2,2,2-trifluoroethanol (1 mL, 5V). The mixture was heated to 40 °C leading to dissolution. The reaction vessel was removed from the heat source to allow cooling to ambient temperature and then acetone (1 mL, 5V) was added, leading to precipitation. Stirring was continued for 1.5 h at ambient temperature and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form VIII.

Example 29: Preparation of Pazopanib HCl form VIII

[000146] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and 2,2,2-trifluoroethanol (1 mL, 5V). The mixture was heated to 40 °C leading to dissolution. The reaction vessel was removed from the heat source to allow cooling to ambient temperature and then acetonitrile (1 mL, 5V) was added, leading to precipitation. Stirring was continued for 1.5 h at ambient temperature

and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form VIII.

Example 30: Preparation of Pazopanib HCl form X

[000147] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib HCl (form A, 200 mg) and 2,2,2-trifluoroethanol (1 mL, 5V). The mixture was heated to 40 °C leading to dissolution. The reaction vessel was removed from the heat source to allow cooling to ambient temperature and then toluene (3 mL, 15V) was added, leading to precipitation. Stirring was continued for 1.5 h at ambient temperature and then the solid was isolated by vacuum filtration and dried in a vacuum oven (25 mbar) at 70°C for about 16 h to give form X.

Example 31: Preparation of Pazopanib HCl form X

[000148] PZP.HCl (form A, 100 mg) was suspended in 2,2,2-trifluoroethanol (3 mL, 3V). The mixture was heated to reflux resulting in dissolution with mixing. The resulting clear solution was cooled to ambient temperature and stirred over night leading to precipitation. The precipitate was filtered and dried at 70 °C (25 mbar) for 72 h to give polymorphic form X. The wet form was a mixture of form IX and X.

Example 32: Preparation of amorphous Pazopanib HCl

[000149] A three-necked flask equipped with a magnetic stirrer and connected to a vacuum pump was immersed into an oil bath, heated to 110 °C and the system was purged with nitrogen. A solution of Pazopanib HCl (form A, 250 mg) in 2,2,2-trifluoroethanol (1.5 mL, 6V) was added drop-wise by syringe through a septum into the flask under vacuum (6-10 mbar), which led to rapid evaporation of the solvent. Drying of the concomitant amorphous solid was continued under vacuum at about 6 mbar and then the contents of the flask were cooled to ambient temperature under nitrogen.

Example 33: Process for preparation of form XI

[000150] PZP.HCl (ca 100 mg) (form A) and acetic acid (ca 0.3 mL) was stirred and the mixture was heated to dissolution. The resulting clear solution was cooled to ambient temperature by removal of the heat source and stirring was continued over night. The

resulting solid was filtered and dried at 70 °C (25 mbar) for 72 h to give polymorphic form XI.

Example 34: Process for preparation of form XI

[000151] PZP.HCl (200 mg, form A) and formic acid (0.5 mL) was stirred at ambient temperature leading to dissolution. To the resulting solution was added acetone (1 mL) and stirring was continued for 3 h at ambient temperature leading to precipitation. The resulting solid was filtered and dried at 70 °C (25 mbar) for 72 h to give polymorphic form XI.

Example 35: Process for preparation of form XI

[000152] PZP.HCl (100 mg, form A) and formic acid (0.5 mL) was stirred at ambient temperature leading to dissolution. The resulting solution was added dropwise to acetone (3 mL), previously cooled to -18 °C with stirring, and the resulting slurry was then stirred for 1.5 h at ambient temperature. The resulting solid was isolated by vacuum filtration and analyzed by XRD, which indicated polymorphic form XI.

Example 36: Process for preparation of form XI

[000153] PZP.HCl (200 mg, form A) and formic acid (0.5 mL) was stirred at ambient temperature leading to dissolution. To the resulting solution was added acetonitrile (1 mL) and stirring was continued for 3 h at ambient temperature leading to precipitation. The resulting solid was filtered and dried at 70 °C (25 mbar) for 72 h to give polymorphic form XI.

Example 37: Process for preparation of form XI

[000154] PZP.HCl (200 mg, form A) and formic acid (0.5 mL) was stirred at ambient temperature leading to dissolution. To the resulting solution was added cyclohexane (2 mL) and stirring was continued for 3 h at ambient temperature leading to precipitation. The resulting solid was filtered and dried at 70 °C (25 mbar) for 72 h to give polymorphic form XI.

Example 38: Process for preparation of forms XIV and XV (di-HCl salt from PZP free base)

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[000155] A 20 mL vial equipped with a magnetic stirrer was charged with Pazopanib free base (100 mg) followed by DMF (1 mL) at ambient temperature. The resulting solution was stirred and HCl (0.5 mL, 4M in dioxane) was added dropwise. Stirring was continued over 2 days and turbidity gradually increased leading to precipitation at ambient temperature. The resulting solid was isolated through filtration to give form XIV. Drying of this material in a vacuum oven gave form XV.

Example 39: Process for preparation of forms XIV (di-HCl salt from PZP free base)

[000156] PZP base (SF1661/2, 0.6 g) was slurried with methylethylketone (12 mL, 20V) containing 21% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. XRD indicated form XIV. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 15.3%) form XIV (0.72 g, 99.5% purity).

Example 40: Process for preparation of forms XIV and XV (di-HCl salt from PZP free base)

[000157] PZP base (SF1661/2, 0.6 g) was slurried with acetonitrile (12 mL, 20V) containing 13.6% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 16.8%) form XIV (0.78 g, 99.7% purity).

Example 41: Process for preparation of forms XV (di-HCl salt from PZP free base)

[000158] PZP base (SF1661/2) (0.6 g) was slurried with ethyl acetate (12 mL, 20V) containing 8.7% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 13.9%) form XV (0.73 g, 99.2% purity).

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Example 42: Process for preparation of forms XIV (di-HCl salt from PZP free base)
[000159] PZP base (SF1661/2) (0.6 g) was slurried with acetone (12 mL, 20V) containing 11.1% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. XRD indicated form XIV. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 13.5%) form XIV (0.72 g, 99.5% purity).

Example 43: Process for preparation of forms XIV (di-HCl salt from PZP free base)
[000160] PZP base (SF1661/2, 0.6 g) was slurried with methyl isobutylketone (12 mL, 20V) containing 16.9% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. XRD indicated form XIV. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 13.1%) form XIV (0.61 g, 99.4% purity).

Example 44: Process for preparation of forms XIV (di-HCl salt from PZP free base)
[000161] PZP base (SF1661/2, 0.6 g) was slurried with methyl tertbutylether (12 mL, 20V) containing 8.8% HCl (previously prepared by bubbling HCl gas through the solvent) at 5 °C. Stirring was continued for 17 h and then the slurry was warmed to room temperature. After 2 h additional stirring the solid was isolated through filtration. XRD indicated form XIV. Drying of the solid in a vacuum oven (25 mbar) at 60 °C for 17 h afforded Pazopanib.2HCl (Cl content = 13.2%) form XIV (0.66 g, 99.4% purity).

Example 45: Process for preparation of Pazopanib free base (PZP)
[000162] PZP.HCl (500 mg, form A) was slurried with a 10% aqueous solution of sodium carbonate (10 mL) at ambient temperature. To the slurry was added chloroform (15 mL) with stirring. Stirring was continued and then the slurry was filtered and the filter cake was washed with water and dried in a vacuum oven at 35°C. Titration of the material indicated that all HCl had been removed to below detection limit.

Example 46: Process for preparation of Pazopanib free base (PZP)

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[000163] PZP.HCl (14.6 g, form A) was slurried with a 5% aq solution of sodium carbonate (125 mL) at ambient temperature with stirring. After 30 min the solid was filtered and slurried again a 5% aq solution of sodium carbonate (125 mL) at ambient temperature. This operation was repeated again and the resulting solid was isolated by filtration. Cl titration indicated a small presence of HCl so the material was slurried in sodium carbonate (10% aq. soln) over night at room temperature. The solid was filtered, washed with water (120 mL) and dried at room temperature under nitrogen stream for 16 h to give PZP free base (13.2 g, 97.1% assay, chloride content not detectable).

Example 47: Process for preparation of Pazopanib free base (PZP)

[000164] PZP.HCl (1 g, form A) was slurried with sodium carbonate (10% aq. soln) (9.0 g, 8 eq) and MeOH (9.0 g) at ambient temperature. Stirring was continued for 5 h before the solid was filtered and dried in a vacuum oven (35mbar) at 40 °C for 17 h to give PZP free base (0.92 g, 97% yield, chloride content not detectable)

Example 48: Process for preparation of bis-PDMI

[000165] DMAD (2 g, 12.4 mmol) and DCP (0.93 g, 6.2 mmol, 0.5 eq) were dissolved in MeOH (16 mL, 8V) and a few drops of HCl (4M in dioxane) were added. The reaction mixture was stirred at 30 °C for 48 h leading to precipitation. The solids were isolated by filtration and the filter cake was washed with methanol (10+5 mL) and dried in a vacuum oven at 50 °C for 24 h to give the title compound as a off-white solid (1.88 g, 75.8%).

Example 49: Process for preparation of des-Me-DMAD

[000166] A 250 mL reactor was charged with 3-methyl-6-nitro-2H-indazole (5.00 g, 28.2 mmol) in 2-methoxyethyl ether (52.5 mL, 10.5V) and the resulting solution was cooled to 0 °C. To the stirred solution of was added a solution of tin (II) chloride (21.41 g, 113 mmol, 4 eq) in 32% HCl (22 mL) dropwise over 5 min. After the addition was complete, the system was heated to 20 °C over 10 min and stirring was continued for an additional 40 min until the reaction was deemed complete by TLC. Diethyl ether (180 mL, 36V) was added to the reaction, and stirring was continued for 1 h resulting in the formation of a precipitate. The solid was isolated by filtration and the filter cake was washed with diethyl ether (20 mL). The resulting solid (6.67 g) was triturated with

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diethylether (5V), filtered and dried on the filter under a nitrogen stream to afford a hydrochloride salt of 3-methyl-2H-indazole-6-amine (des-Me-DMAD), as a yellow solid (5.23 g, 99.9%).

Example 50: Process for preparation of DMND

[000167] To a stirred solution of 3-methyl-6-nitro-1H-indazole (MNID) (5.0 g, 28.2 mmol) in acetone (95 mL, 19V) at ambient temperature was added trimethyloxonium tetrafluoroborate (5.3 g, 35.8 mmol, 1.27 eq). Stirring was continued under nitrogen and the reaction was monitored by TLC. After 5.5 h another 1 g of trimethyloxonium tetrafluoroborate was added to the reaction in an attempt to push it to completion. After 7.5 h total reaction time the solvent was removed and saturated sodium bicarbonate (162 mL) was added to the residue, followed by a 4:1 mixture of CHCl_3 : IPA (54 mL). The resulting mixture was agitated and the layers were separated. The aqueous phase was washed with additional CHCl_3 : IPA 4:1 (4x54 mL) and the combined organic phases were dried (Na_2SO_4), filtered and evaporated to dryness. The resulting brown solid was washed with diethylether (about 160 mL) and dried on the filter under nitrogen/vacuum to afford crude DMND (3.2 g, 87.5% purity). The crude material (2.9 g) was then dissolved in EtOH (50 mL) at reflux and the solution was gradually cooled to ambient temperature and then to 5 °C, and was kept at this temperature for 1 h. The resulting precipitate was isolated by filtration and the filter cake was washed with cold EtOH (10 mL) and dried in a vacuum oven (35 mbar) at 55°C for 4 h to give 2,3-dimethyl-6-nitro-2H-indazole (1.57g, ca 32%) as a yellow solid.

Example 51: Process for preparation of des-Me-PZP

[000168] A 100 mL reactor was charged with CPDMI (98.0% purity, 98.8% assay) (5.0 g; 18.3 mmol), AMBS (3.57 g, 19.2 mmol, 1.05 eq) and EtOH (50 mL). The stirred reaction mixture was heated to 72 °C and then HCl (0.1 mL, 4M in dioxane) was added to initiate the reaction. Stirring was continued for 8 h and then the mixture was allowed to cool to RT. After 4 days of standing at RT, DMF (50 mL) was added and stirring of the reaction mixture was continued at 100 °C for 6 h. The reaction mixture was cooled to ambient temperature and then the solids were filtered and washed with cold (5°C) EtOH (20 mL) and dried on the filter under vacuum over night to give 5-(4-(2,3-dimethyl-2H-

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indazol-6-ylamino)pyrimidin-2-ylamino)-2-methylbenzenesulfonamide (7.73 g, 99%) as a yellow solid.

Example 52: Process for preparation of CPDMI

[000169] A 1L reactor equipped with a mechanical stirrer was charged with CPDMI (80 g, 0.29 mol), dimethylcarbonate (131.6 g, 1.46 mol, 5 eq), potassium carbonate (10.1 g, 0.073 mol, 0.25 mol eq) and DMF (266 mL, 3.3V) and the resulting mixture was stirred and heated to 118°C. Stirring was continued at this temperature for 7.5 h and then the reaction mixture was cooled to 65°C and subsequently water (800 mL, 10V) was added over a period of 20 min, keeping the temperature at 54-56°C during this time. Stirring was continued at the same temperature for 30 min and then the reaction mixture was cooled to 20°C. After 2 h additional stirring at 20°C, the suspension was cooled to 9°C and stirring was continued for 3 h. The solids were isolated by filtration at 9°C and the resulting filter cake was washed with water (320 mL, 4V) at 20°C. The filter cake was then washed with a 2:3 mixture of EtOH:water (200 mL). The solid was dried in a vacuum oven to constant weight at 60°C for 20 h to give the title compound (72 g, 85.1% yield, 99.4% assay, 98.7% purity).

Example 53: Process for preparation of CPDMI

[000170] A 3L reactor equipped with a mechanical stirrer was charged with DMAD (283.54 g, 1.69 mol, 96.4% assay), DCP (377.3 g, 2.53 mol, 1.5 eq, 96% purity), sodium bicarbonate (283.7 g, 3.38 mol, 2.0 eq) and methanol (2175 mL, 8V). The reaction was stirred at 25 °C for 23 h under nitrogen (until it was deemed complete by HPLC) leading to precipitation and then cooled to 10°C. Stirring was continued at this temperature for 30 min and then the reaction mixture was filtered at 10°C. The filter cake was added to the reactor and slurried with ethyl acetate twice (2x850 mL, 2x3V) at 10°C. The solid was filtered and the filter cake was slurried with tap water twice (2x4083 mL, 2x15V) at 25°C. The slurry was filtered and the filter cake was washed with ethyl acetate (300 mL, 1V), dried in a vacuum oven (30 mbar, 60°C) for 24 h to constant weight to give the title compound as an off-white solid (404.5 g, 86.8% yield, 99.1% assay, 98.0 % purity, KF=0.11%, ash=0.06%).

Example 54: Process for preparation of CPDMI

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[000171] A 3L reactor equipped with a mechanical stirrer was charged with CPDMI (150 g, 0.55 mol), dimethylcarbonate (246.8 g, 2.74 mol, 5.0 eq), potassium carbonate (18.9 g, 0.14 mol, 0.25 mol/mol CPDMI) and DMF (500 mL, 3.3V) and the resulting mixture was stirred and heated to 118 °C. Stirring was continued at this temperature for 9 h during which the reaction was monitored by HPLC. The reaction mixture was then cooled to 60°C and subsequently water (1500 mL, 10V) was added drop-wise over a period of 60 min, keeping the temperature at 55-60°C during this time. Stirring was continued at the same temperature for 30 min and then the reaction mixture was cooled to 20°C. After 2 h additional stirring at 20°C, the suspension was cooled to 10°C and stirring was continued for 3 h. The solids were isolated by filtration at 10-20°C and the resulting filter cake was slurried with water (2x300 mL, 2x2V) at 20°C. The resulting suspension was filtered and the filter cake was then washed by portion-wise addition of a 2:3 mixture of EtOH:water (375 mL, 2.5V). The solid was dried in a vacuum oven (30 mbar) to constant weight at 60 °C for 21 h to give the title compound (129.2 g, 81.9% yield, 97.7% assay, 99.0% purity, KF=0.06%, ash=0.03%).

Example 55: Process for the preparation of PZP.HCl

[000172] A 3L reactor equipped with a mechanical impeller and a reflux condenser was charged with CPMI (121.7 g, 0.41 mol, 97.7% assay) and AMBS (81.0 g, 0.44 mol, 1.05 eq). A 90:10 mixture of acetic acid/water (600 mL, 5V) was added and the reactor was heated to 65°C under nitrogen ($T_{int} = 58-67^{\circ}\text{C}$). Complete dissolution was observed followed by an exotherm ($T_{int} = 67^{\circ}\text{C}$) after ca 30 min heating. Stirring was continued for 18 h, leading to precipitation, and then the reactor was heated to 100°C and kept at this temperature for 1 h. A complete dissolution was observed after about 30 min. Heating of the reactor was stopped and EtOH abs. (1200 mL, 10V) was added portion-wise with concomitant cooling of the reactor to 0 °C over a period of 3 h. Stirring was continued at this temperature for another 30 min and then the mixture was filtered at 0-25°C. The filter cake was washed with cold (5°C) EtOH abs. (360 mL, 3V) and three times with EtOH abs (3x360 mL, 3x3V) at ambient temperature. The isolated solid was dried in a vacuum oven (32 mbar) at 60°C for 17 h to constant weight (179.4 g, 91%yield, 99.9% assay, 99.86% purity, CPMI<20ppm - less than detection limit in HPLC method 2), 7.66% Cl, KF=0.13%).

Example 56: Process for the preparation of 4-CPDMI

[000173] DMAD (6 g, 37.2 mmol) and sodium bicarbonate (9.38 g, 111.7 mmol) were suspended in n-butanol (90 mL) and heated to reflux. DCP (11.09 g, 74.4 mmol) was added in one portion and the obtained mixture was stirred at reflux for 2 h. The mixture was then cooled to 10°C over a period of 2 h and stirred for one additional hour at 10°C. The resulting precipitate was isolated by filtration and the cake was washed on the filter with ethyl acetate (2x15 mL). The combined filtrates were evaporated to dryness. The resulting residue was triturated with ethyl acetate (150 mL) for 20 min, the suspension was filtered and the filter cake was washed with ethyl acetate (50 mL). The combined filtrates were evaporated to dryness in a rotary evaporator. Purification of the resulting residue by flash column chromatography (SiO₂, F254) (EtOAc: heptane 55:45 → 85:15 v/v) afforded 4-CPDMI (0.69 g, 6.8%) as a yellow powder.

Example 57: Process for the preparation of PZP.HCl

[000174] A 250 mL reactor equipped with a mechanical stirrer was charged with crude PZP.HCl (6.5 g, 95% assay, 0.47% AMBS, 0.7% CPMI) and glacial acetic acid (34.5 mL, 5.3V) was added. The resulting mixture was stirred and heated to 115°C. Stirring was continued for about 25 min leading to complete dissolution. The solution was cooled to 100°C over a period of 60 min and then EtOH abs. (65 mL, 10V) was added drop-wise over 10 min with simultaneous cooling to 87 °C, leading to precipitation. The mixture was then cooled to 0 °C over a period of 4 h and stirring was then continued at the same temperature for 1.5 h. The solids were isolated by filtration and the filter cake was washed with EtOH abs (3x32 mL, 3x5V) at room temperature. The cake was dried in a vacuum oven (35 mbar) at 60 °C for 15 h to give pure PZP.HCl (5.94 g, 91.4% yield, 98.5% assay, 98 ppm CPMI) as a white powder.

Example 58: Process for the preparation of PZP.HCl

[000175] A 250 mL reactor equipped with a mechanical stirrer was charged with crude PZP.HCl (4.5 g, 98.8% assay, 112 ppm CPMI) and glacial acetic acid (23.8 mL, 5.3V) was added. The resulting mixture was stirred and heated to 115°C. Stirring was continued for about 10 min leading to complete dissolution. The solution was cooled to 100°C over a period of 60 min and then EtOH abs. (45 mL, 10V) was added drop-wise over 10 min with simultaneous cooling to 90°C, leading to precipitation. The mixture

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was then cooled to 0°C over a period of 4 h and stirring was then continued at the same temperature for 16 h. The solids were isolated by filtration and the filter cake was washed with EtOH abs (4x13.5 mL, 4x3V) at room temperature. The cake was dried in a vacuum oven (35 mbar) at 60 °C for 48 h to give pure PZP.HCl (4.09 g, 90.9% yield, 99.5% assay, CPMI <20 ppm) as a white powder.

Example 59: Process for the preparation of PZP.HCl

[000176] A 250 mL reactor equipped with a mechanical stirrer was charged with CPMI (5.11 g, 17.76 mmol), AMBS (3.64 g, 19.53 mmol, 1.1 eq) and glacial acetic acid (26 mL, 5.1V) and the reaction mixture was heated to 112 °C with stirring, leading to complete dissolution. After 2.5 h precipitation commenced and after 4 h EtOH abs. (107 mL, 20V) was added drop-wise over a period of 20 min. The resulting mixture was then cooled to 10 °C over 5 h and stirring was continued at the same temperature for an additional 10 h. The solids were filtered and the filter cake was washed with EtOH abs. (15 mL, 3V) at room temperature. The wet cake was then charged to a 100 mL flask along with EtOH (37 mL, 7.2V) and the suspension was heated to reflux for 1 h. The suspension was filtered at room temperature and the cake was washed with EtOH (15 mL, 3V) and dried in a vacuum oven (35 mbar) at 60 °C for 14 h to give pure PZP.HCl (6.85 g, 81.3% yield, 99.7% assay, 99.7% purity 7.31% Cl, Ac-AMBS 0.11%, CPMI < 20 ppm) as an off-white powder.

Example 60: Process for the preparation of PZP.HCl

[000177] A 250 mL reactor equipped with a mechanical stirrer was charged with CPMI (4.84 g, 16.82 mmol), AMBS (3.29 g, 17.66 mmol, 1.05 eq) and 90% acetic acid (29 mL, 6V) and the reaction mixture was heated to 55 °C with stirring, leading to dissolution. After 3.5 h precipitation commenced and the reaction was continue for 22 h in total. The resulting mixture was then heated to 65 °C over 0.5 h and stirring was continued at the same temperature for an additional 5 h. The reaction mixture was then heated to 100 °C over 1 h leading to complete dissolution. Stirring was continued at the same temperature for 0.5 h and then EtOH abs. (48 mL, 10V) was added drop-wise with concomitant cooling to 80 °C over a period of 0.5 h. The mixture was then cooled to 0 °C over a period of 4 h and stirring was continued at the same temperature for 16 h. The solids were filtered and the filter cake was washed with EtOH abs. (4x14.5 mL, 4x3V) at

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room temperature and dried in a vacuum oven (35 mbar) at 60 °C for 22 h to give pure PZP.HCl (7.05 g, 88.5% yield, 99.4% assay, 99.9% purity, 7.32% Cl, CPMI < 20 ppm) as a beige powder.

Example 61: Process for the preparation of PZP.HCl form XII

[000178] PZP.HCl form A (0.181 g) was dissolved at reflux in MeOH (75V) with stirring over a period of 10 min. The resulting clear solution was subsequently cooled to room temperature over 2h, and then stirring was continued for 3 days at this temperature. The resulting precipitate was filtered and the filter cake was dried in a vacuum oven (35 mbar) at 45°C for 70 h to give PZP.HCl form XII as determined by XRD

Example 62: Process for the preparation of PZP.HCl form XII

[000179] PZP.HCl form A (0.620 g) was suspended in MeOH (6.2 mL, 10V). The resulting slurry was stirred at room temperature for 21 h and then the solids were isolated by filtration to give polymorphic form XII.

Example 63: Process for the preparation of PZP.HCl form XII

[000180] PZP.HCl form A (0.500 g) was suspended in MeOH (5.0 mL, 10V). The resulting slurry was stirred at room temperature for 90 h and then the solids were isolated by filtration to give polymorphic form XII.

Example 64: Process for the preparation of PZP.HCl form XII

[000181] CPMI (1.00 g, 3.48 mmol) and AMBS (0.71 g, 3.82 mmol, 1.1 eq) were suspended in MeOH (12.7 mL, 12.7V). The resulting stirred mixture was heated to reflux and stirring was continued at the same temperature (about 65 °C) for 18 h. HCl (4M in dioxane) (5.0 µL, 0.02 mmol, 0.06 eq) was then added (whereby the solids were dissolved and later a precipitate was formed during the reaction) and stirring was continued for another 3 h 45 min before the mixture was allowed to cool to 20 °C and maintained at the same temperature for another 3 days. The reaction mixture was then cooled to 5 °C and stirred at this temperature for 1 h. The solids were filtered and washed on the filter with MeOH (13 mL) to give PZP.HCl polymorphic form XII (99.7% purity, 0.07% AMBS, 0.02% CPMI).

What is claimed is:

1. A process for preparing Pazopanib HCl comprising reacting N-(2-chloropyrimidin-4-yl)-2,3-dimethyl-2H-indazol-6-amine (CPMI) and 5-amino-2-methylbenzenesulfonamide (AMBS) with (i) acetic acid or (ii) a mixture of water and acetic acid.
2. The process according to claim 1 wherein Pazopanib HCl is essentially free from CPMI.
3. The process according to claim 2 wherein Pazopanib HCl contains less than about 0.05% area by HPLC of CPMI.
4. The process according to claim 2 wherein Pazopanib HCl contains less than about 100 ppm of CPMI as measured by a suitable HPLC method.
5. The process according to claim 2 wherein Pazopanib HCl contains less than about 75 ppm of CPMI as measured by a suitable HPLC method.
6. The process according to claim 2 wherein Pazopanib HCl contains an undetectable amount of CPMI as measured by a suitable HPLC method.
7. Pazopanib HCl characterized by data selected from: an X-ray powder diffraction pattern having peaks at 15.1, 16.6, 19.9 and 23.8 ± 0.2 degrees 2-Theta; an X-ray powder diffraction pattern substantially as depicted in figure 20; and combinations thereof.

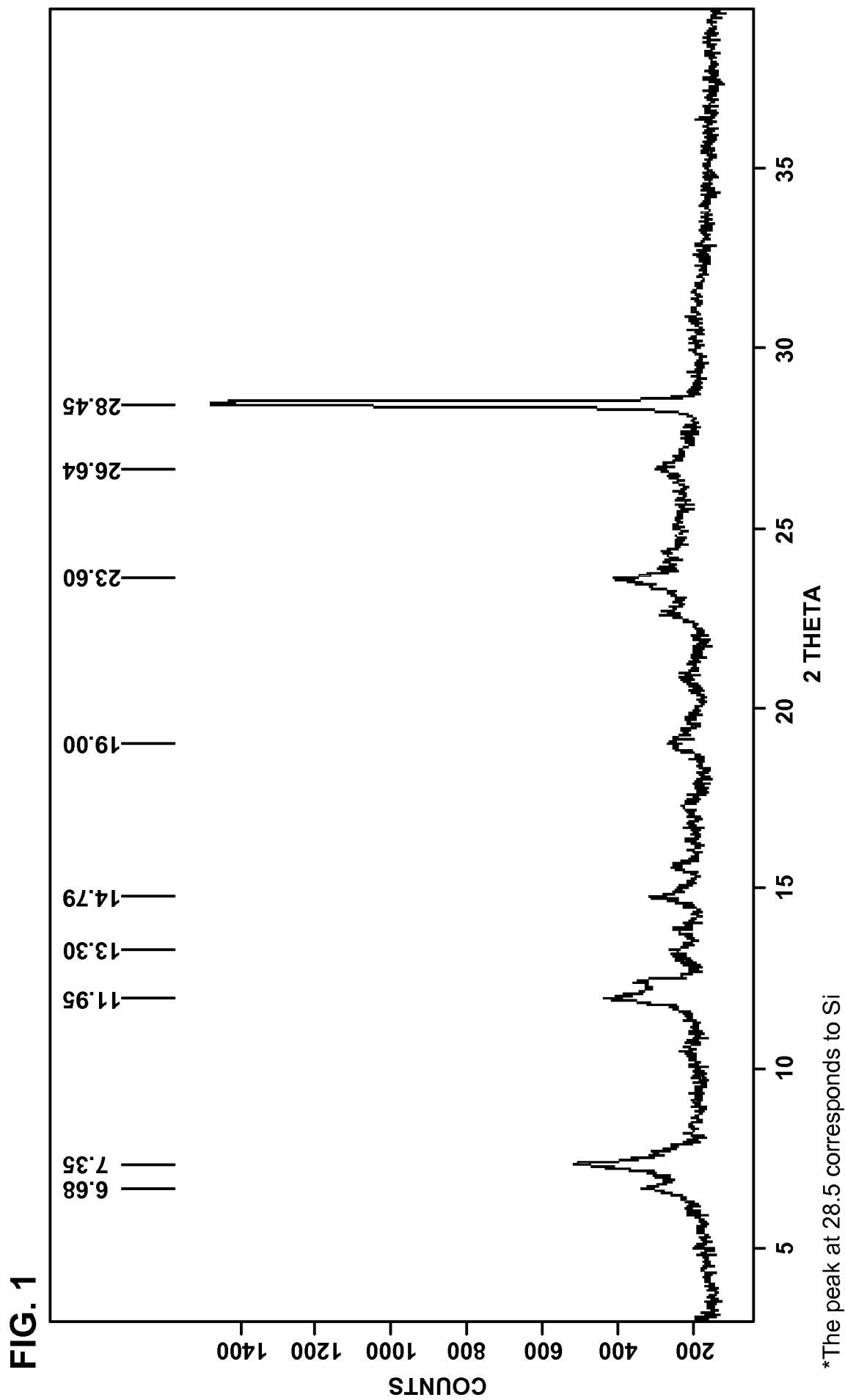


FIG. 2

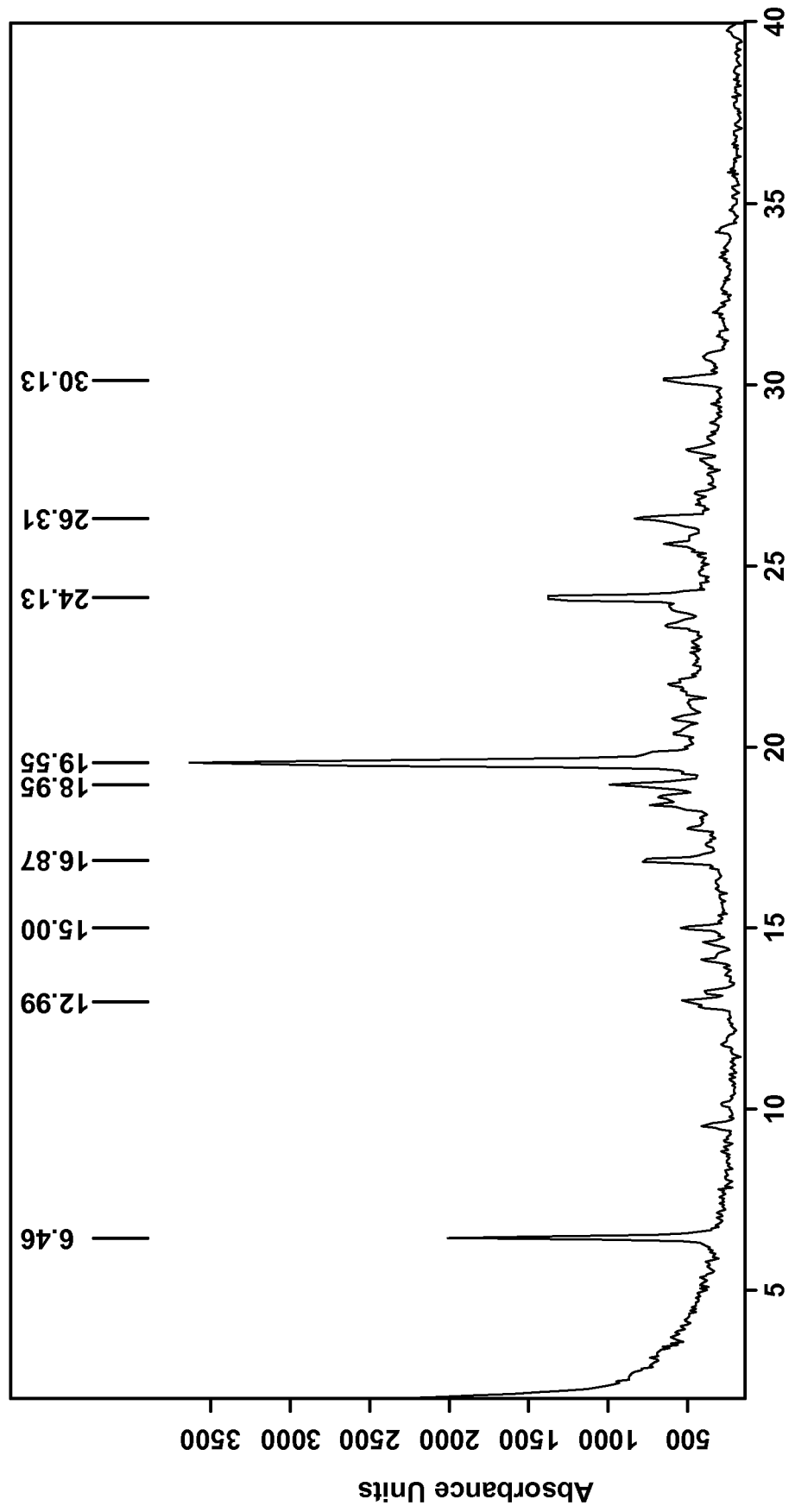


FIG. 3

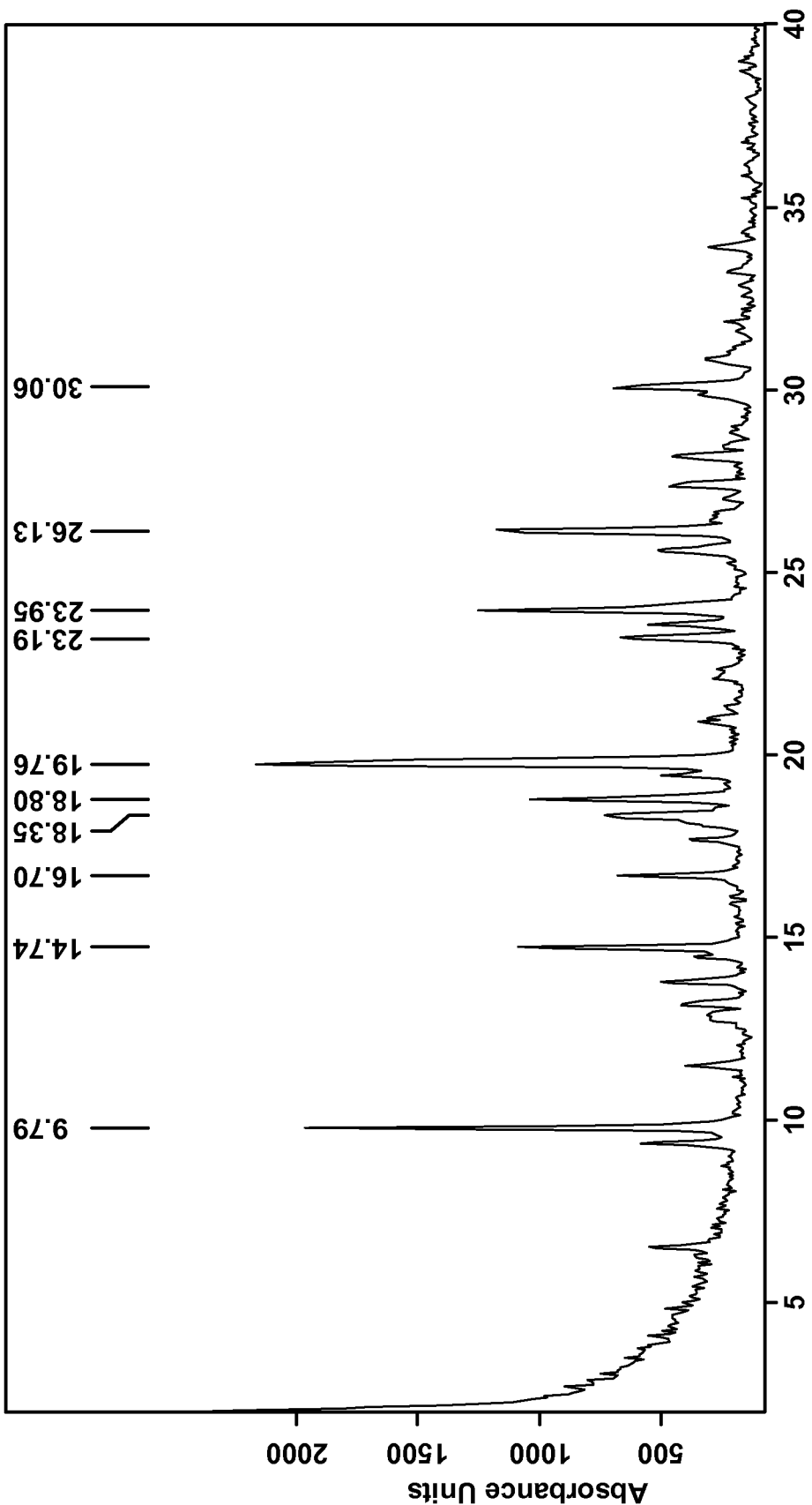
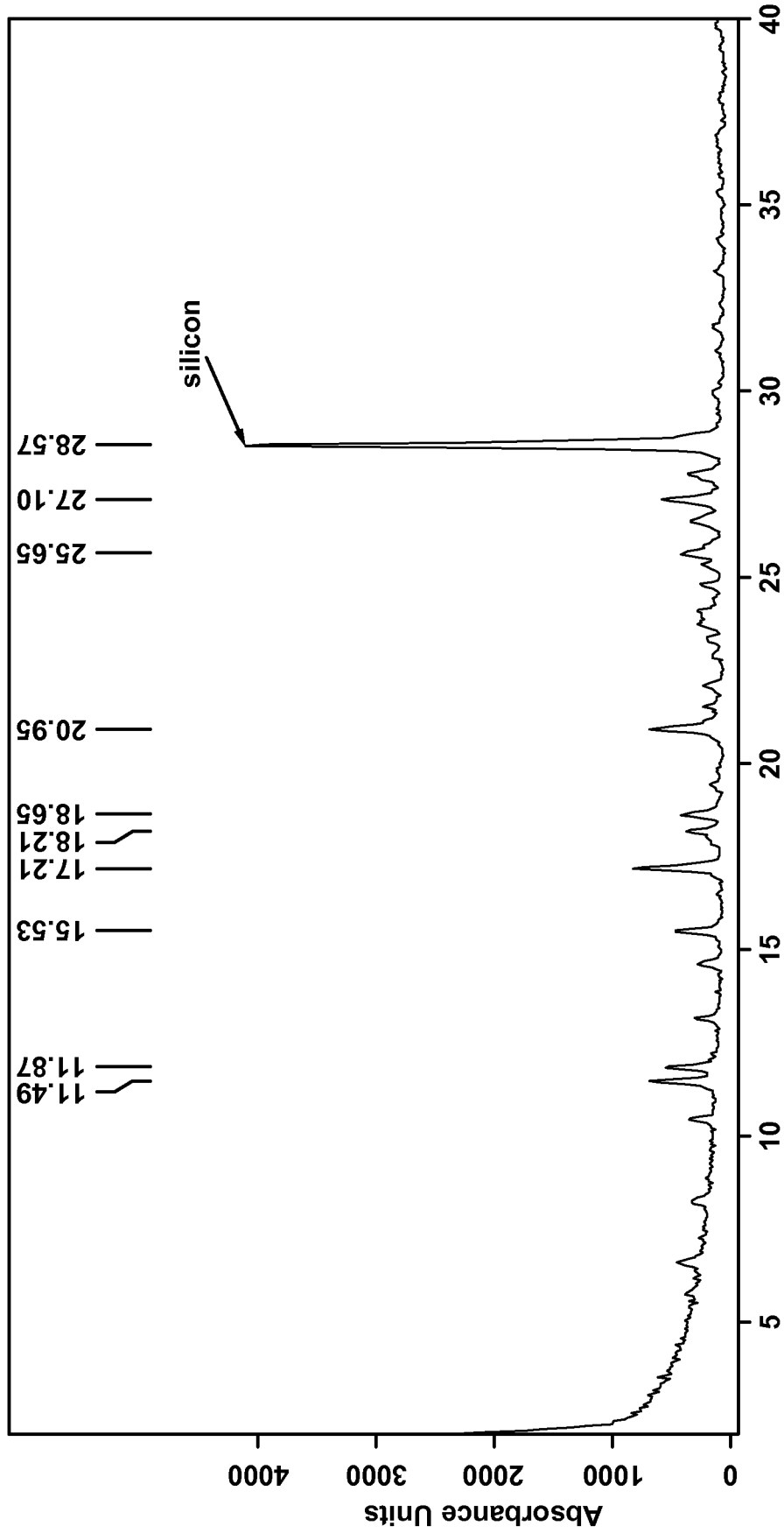


FIG. 4



*The peak at 28.5 corresponds to Si

FIG. 5

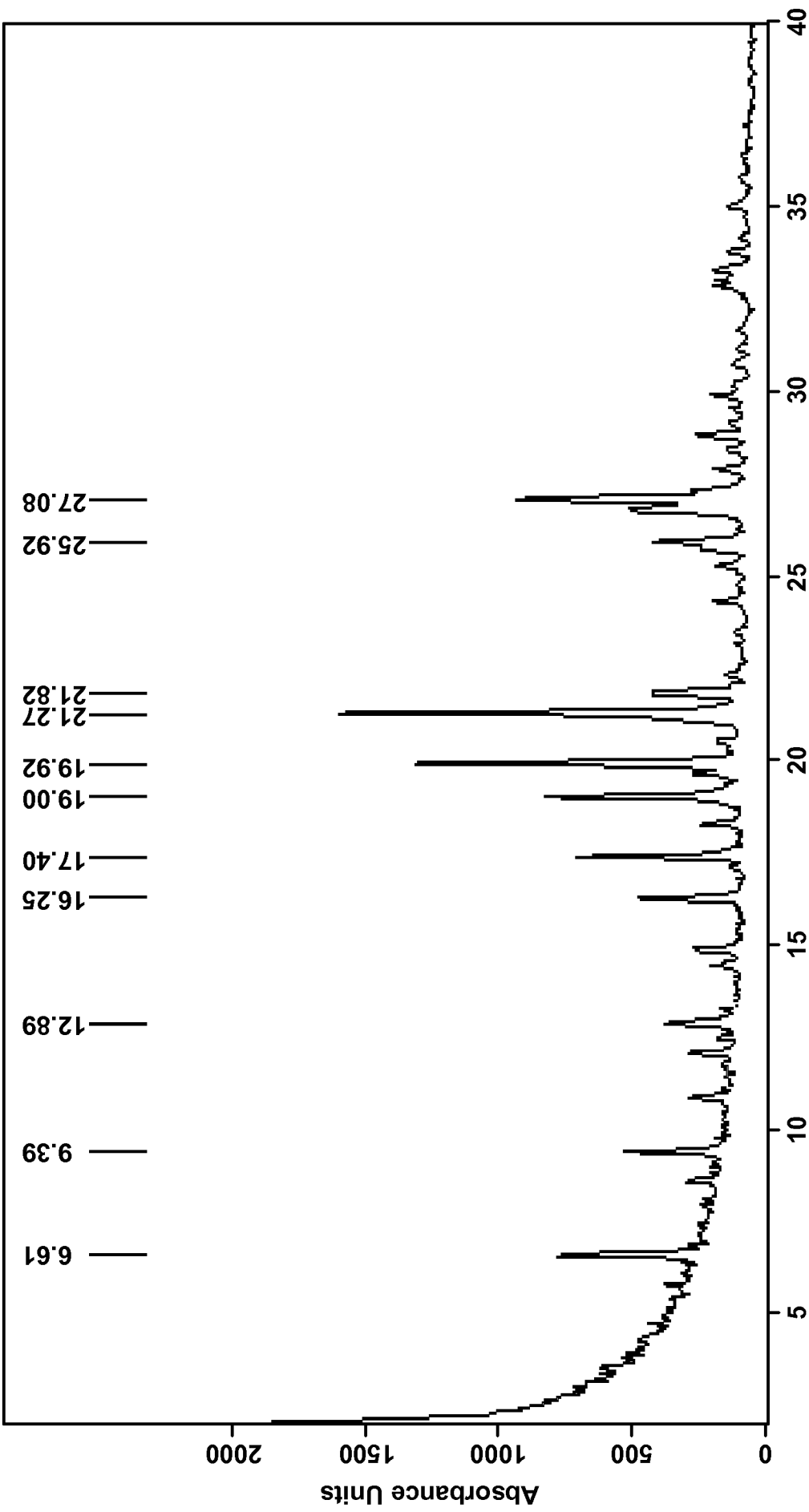
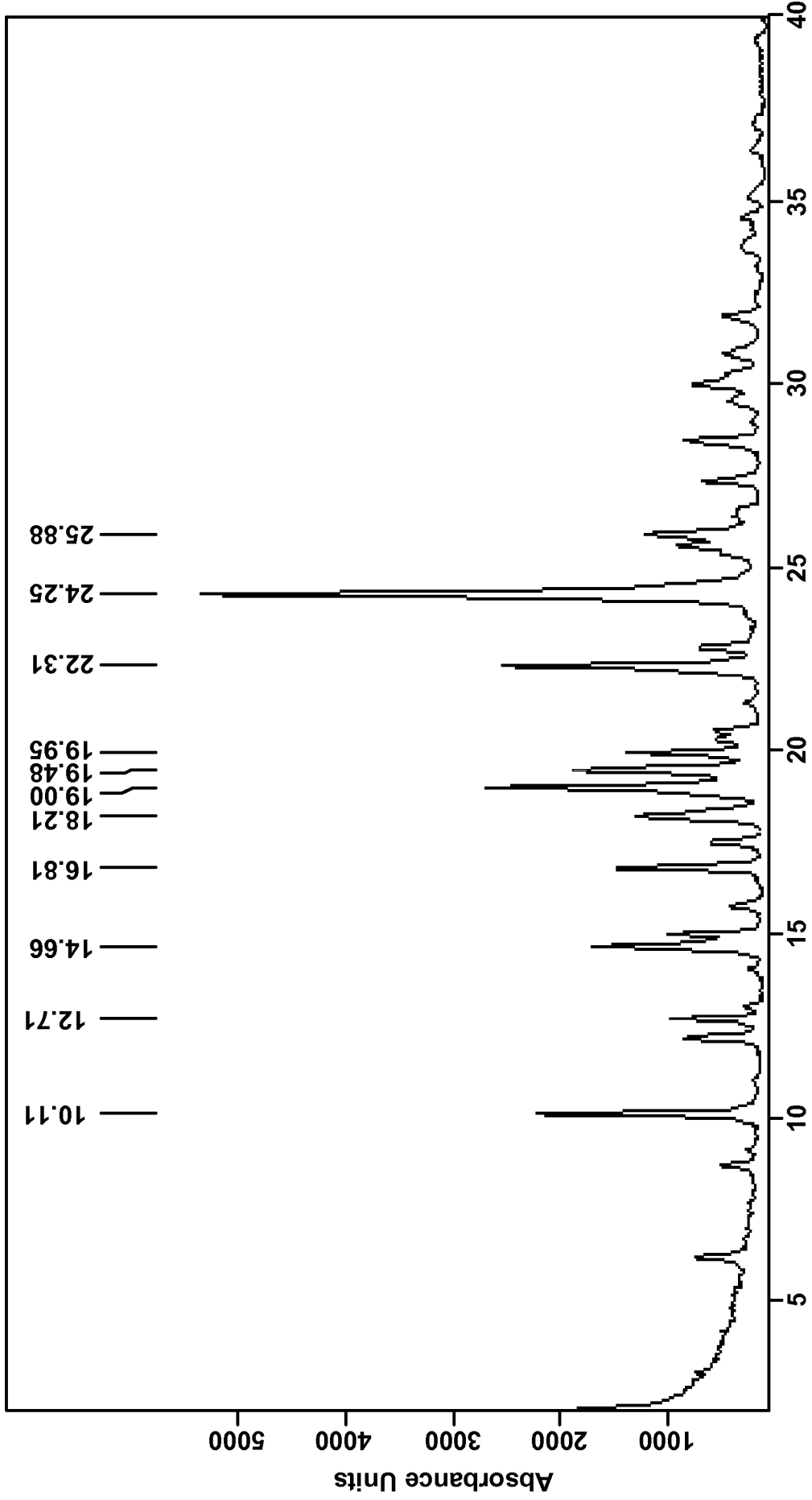


FIG. 6



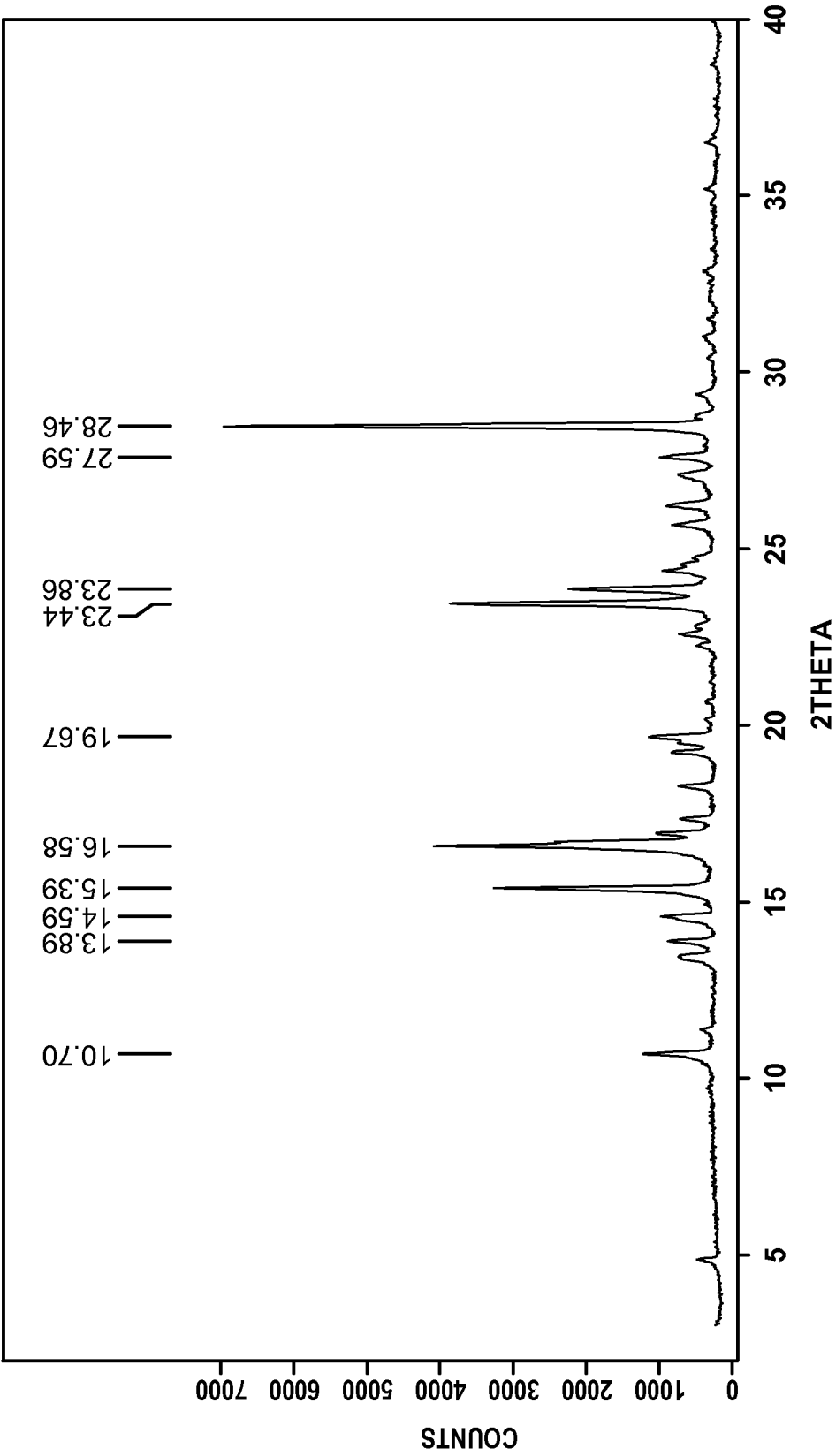
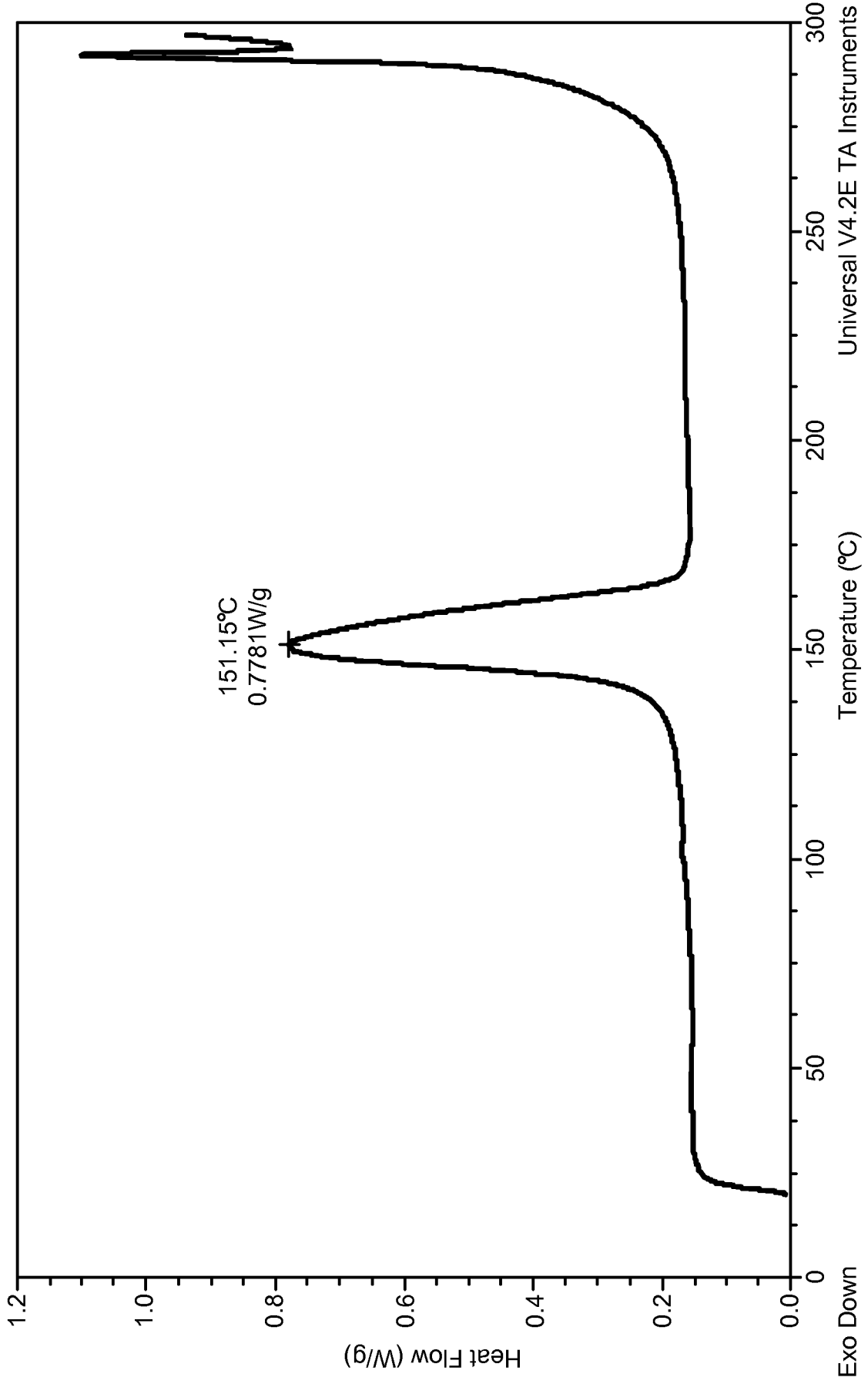


FIG. 7

FIG. 8



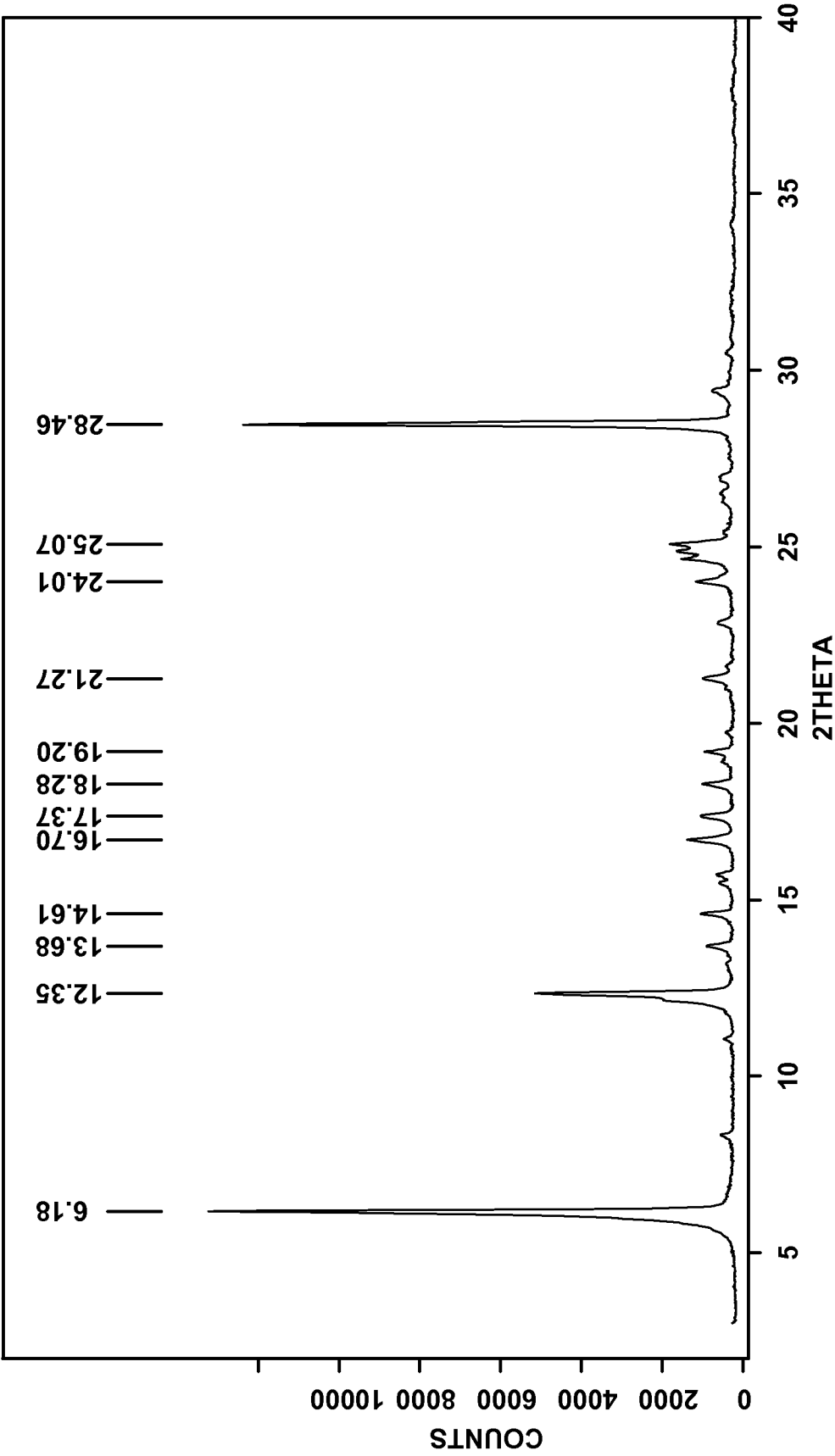
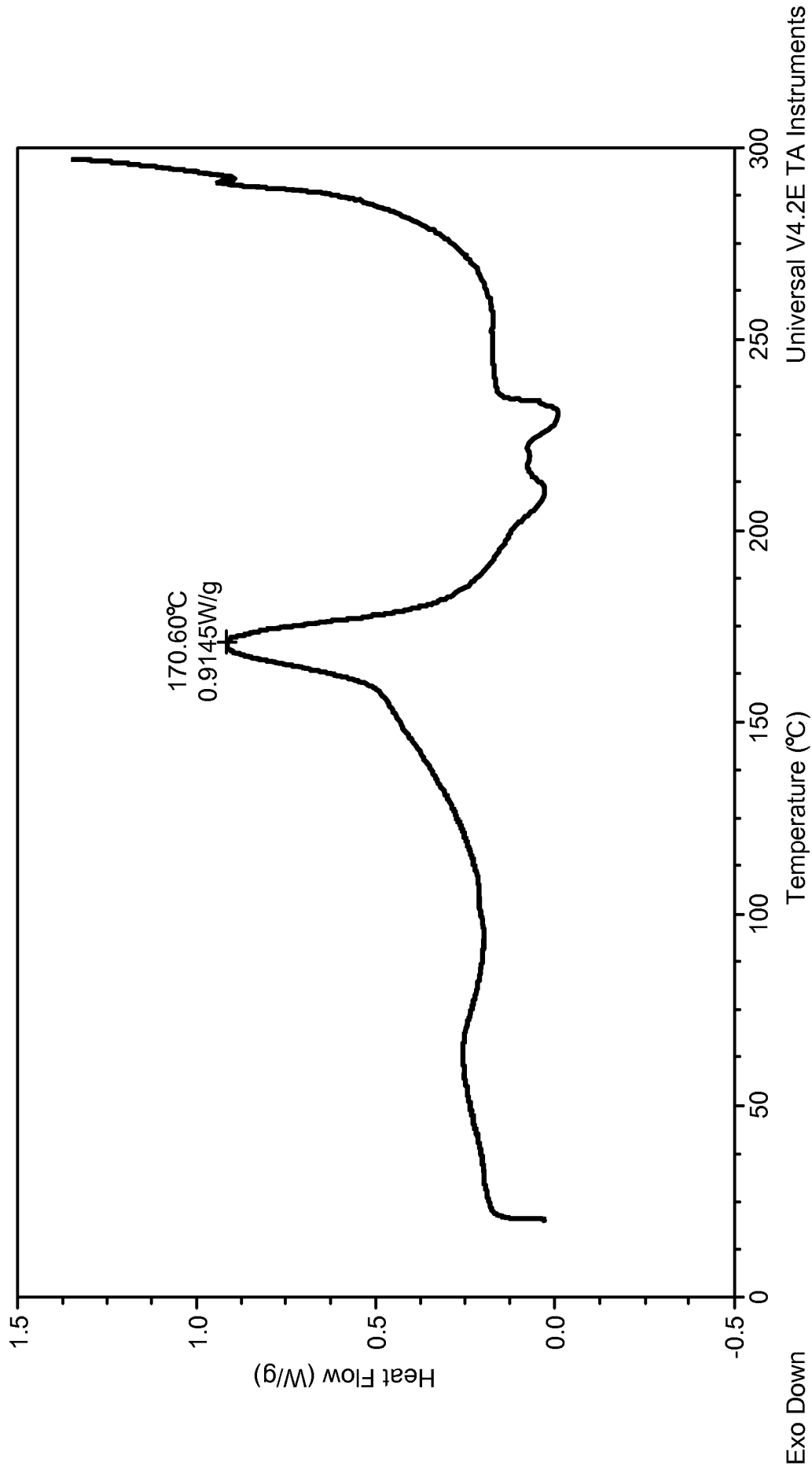


FIG. 9

FIG. 10



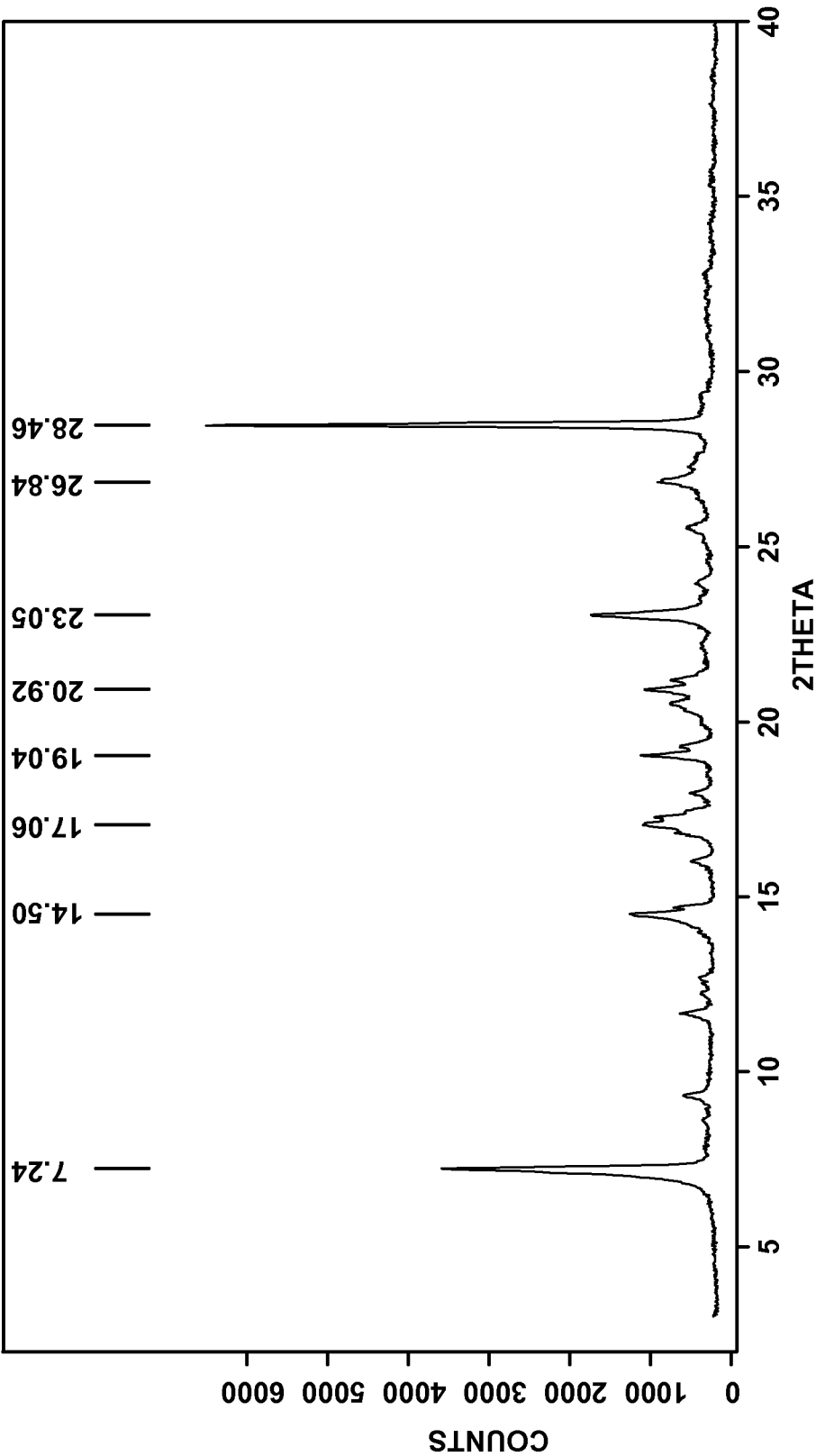


FIG. 11

FIG. 12

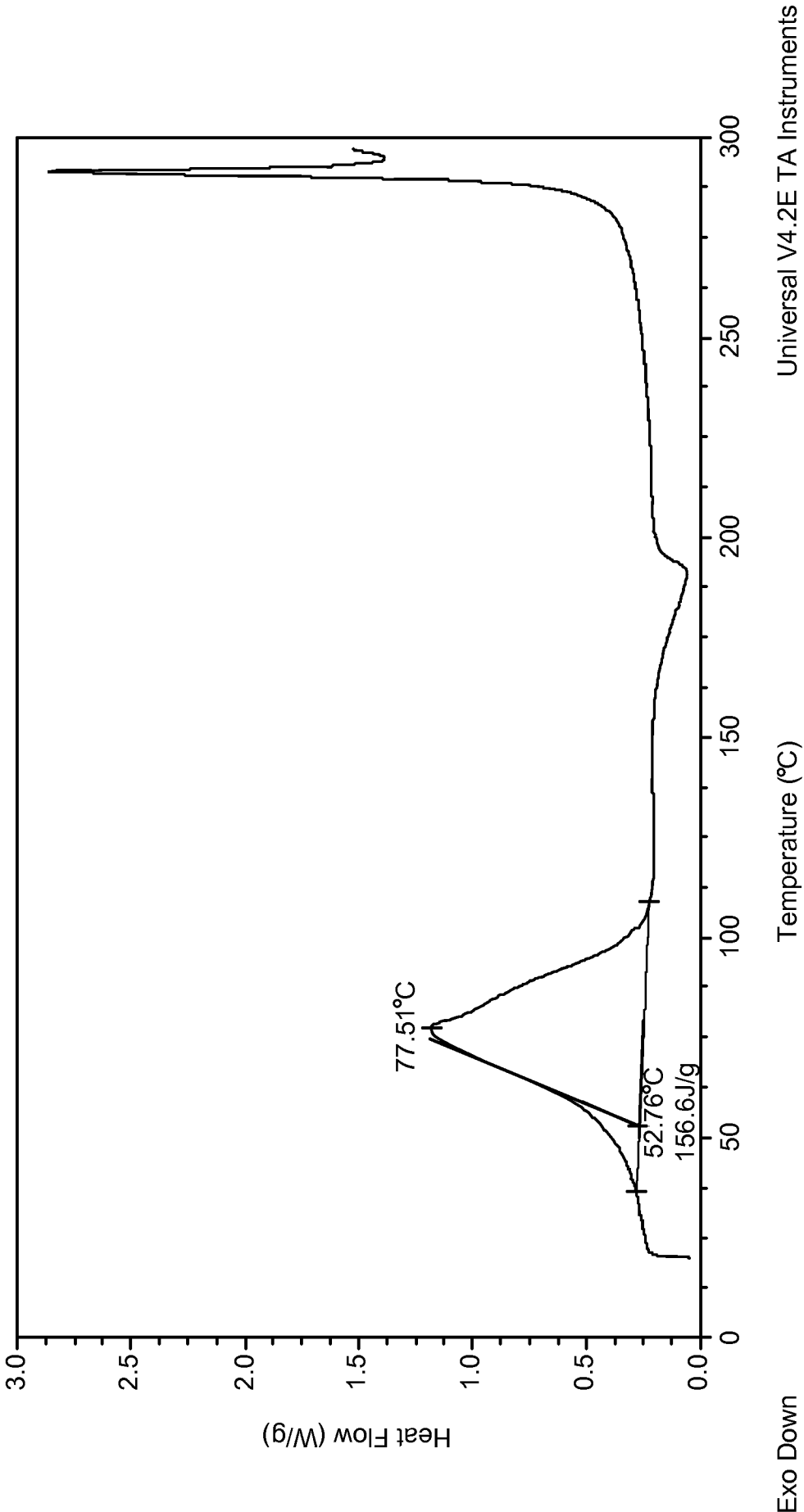


FIG. 13

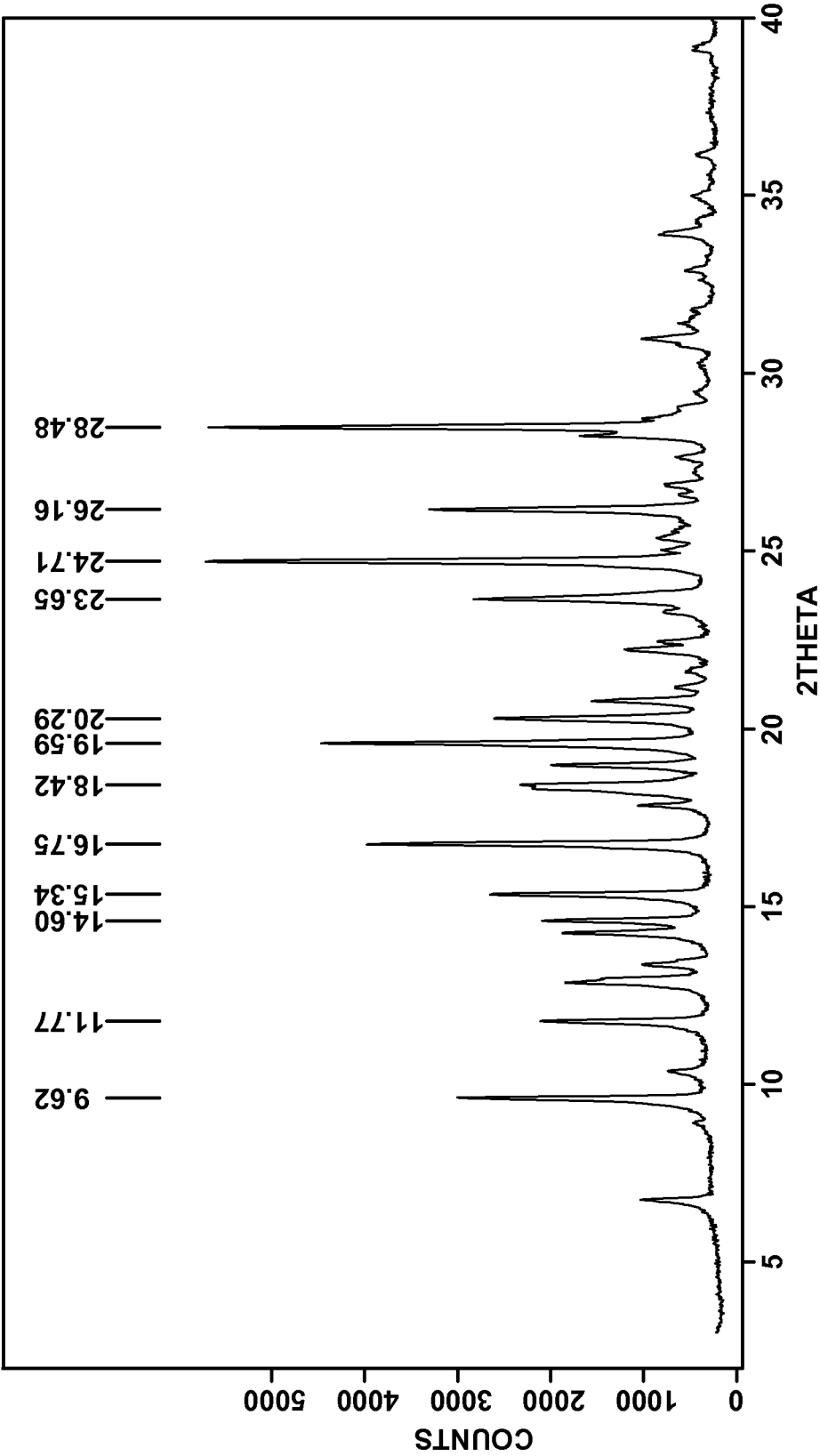
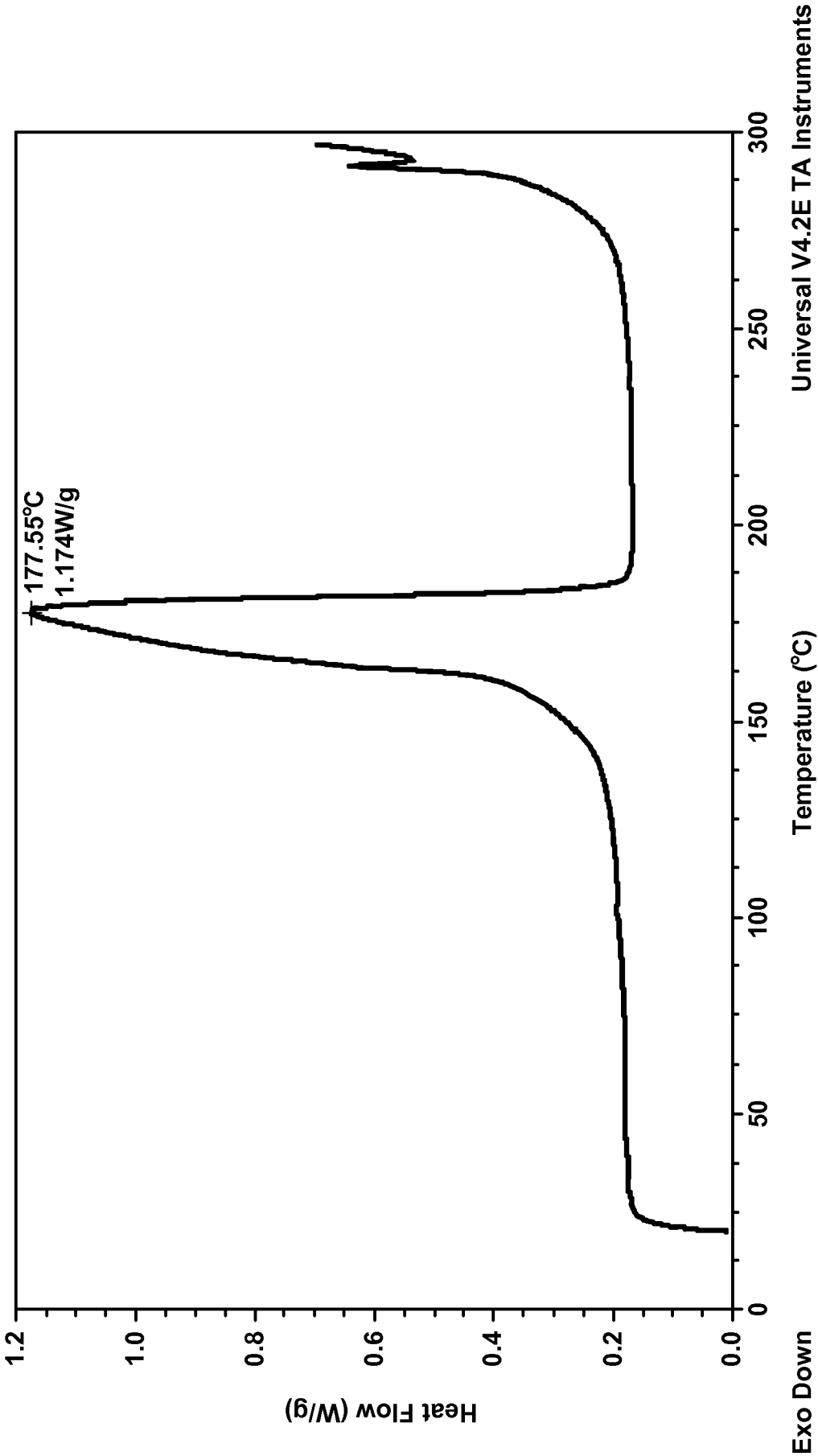


FIG. 14



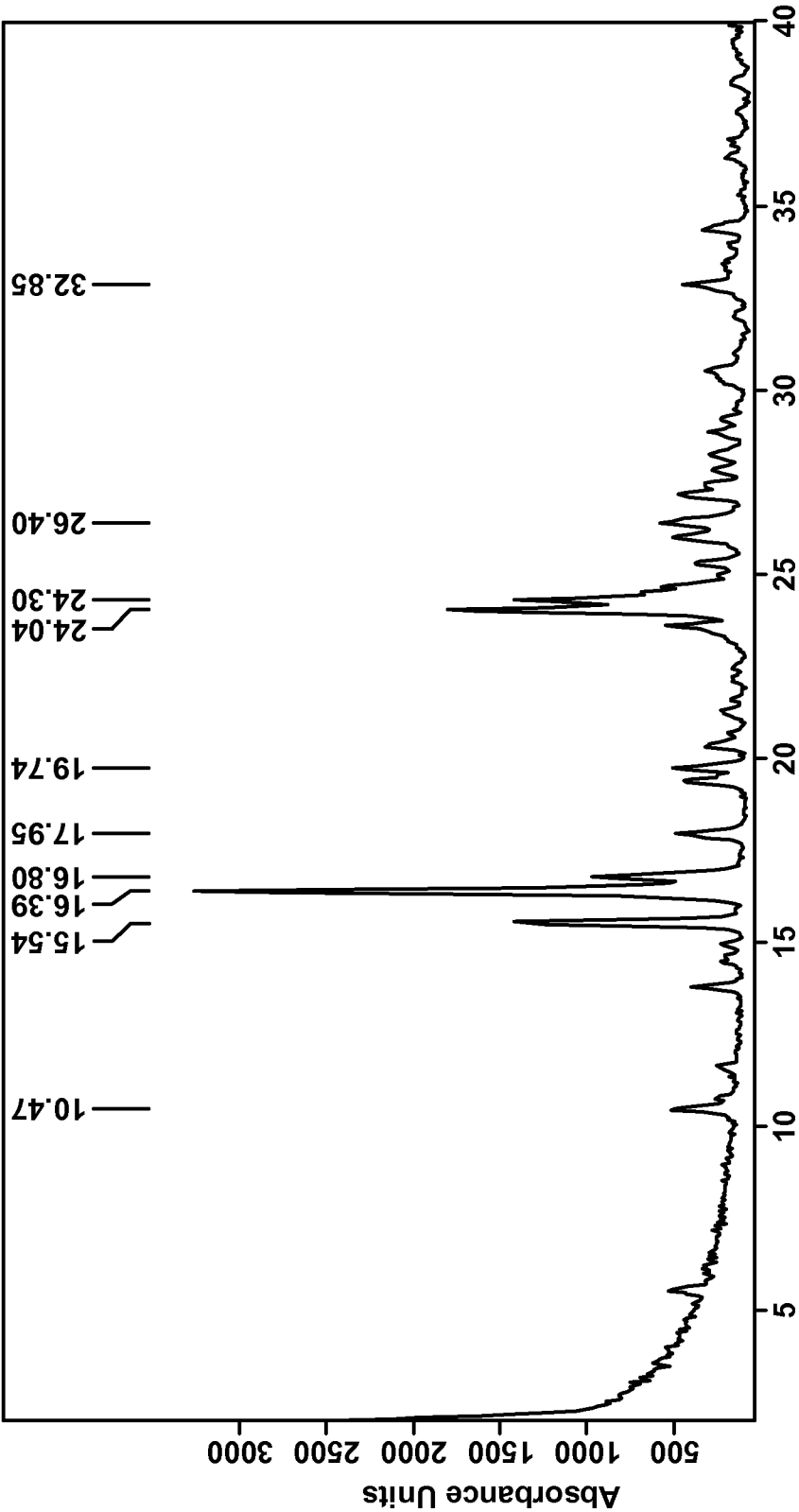


FIG. 15

FIG. 16

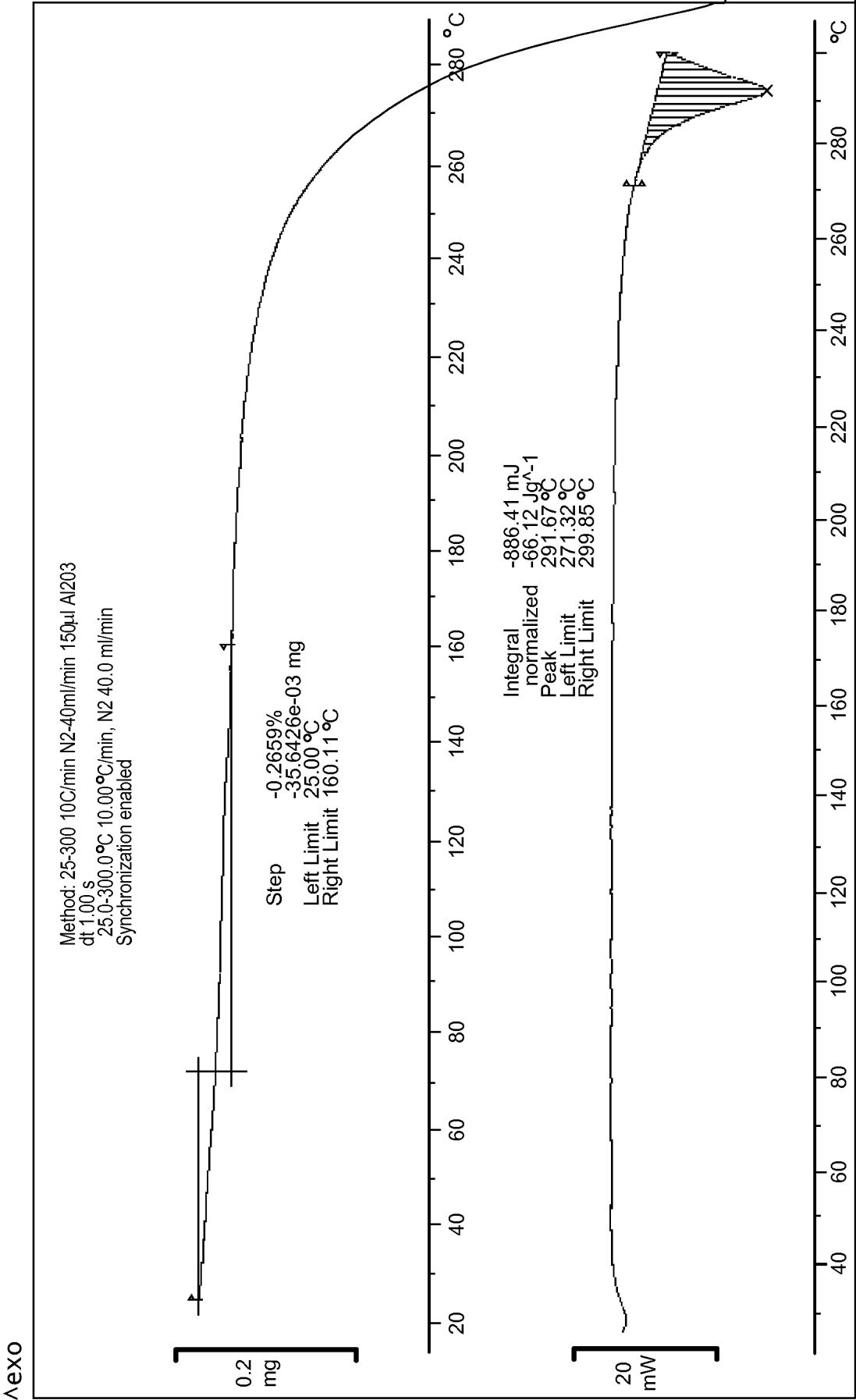


FIG. 17

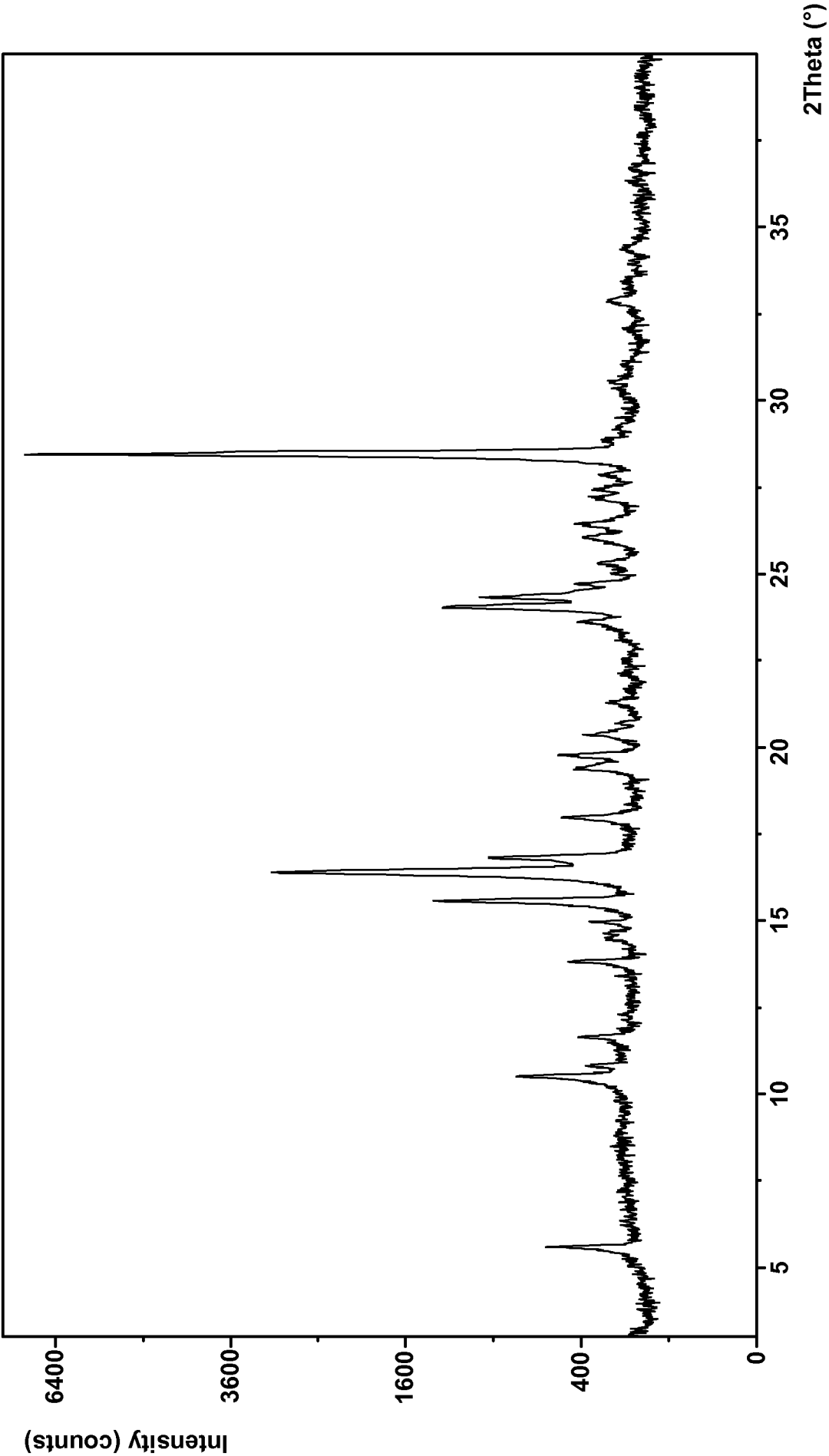


FIG. 18

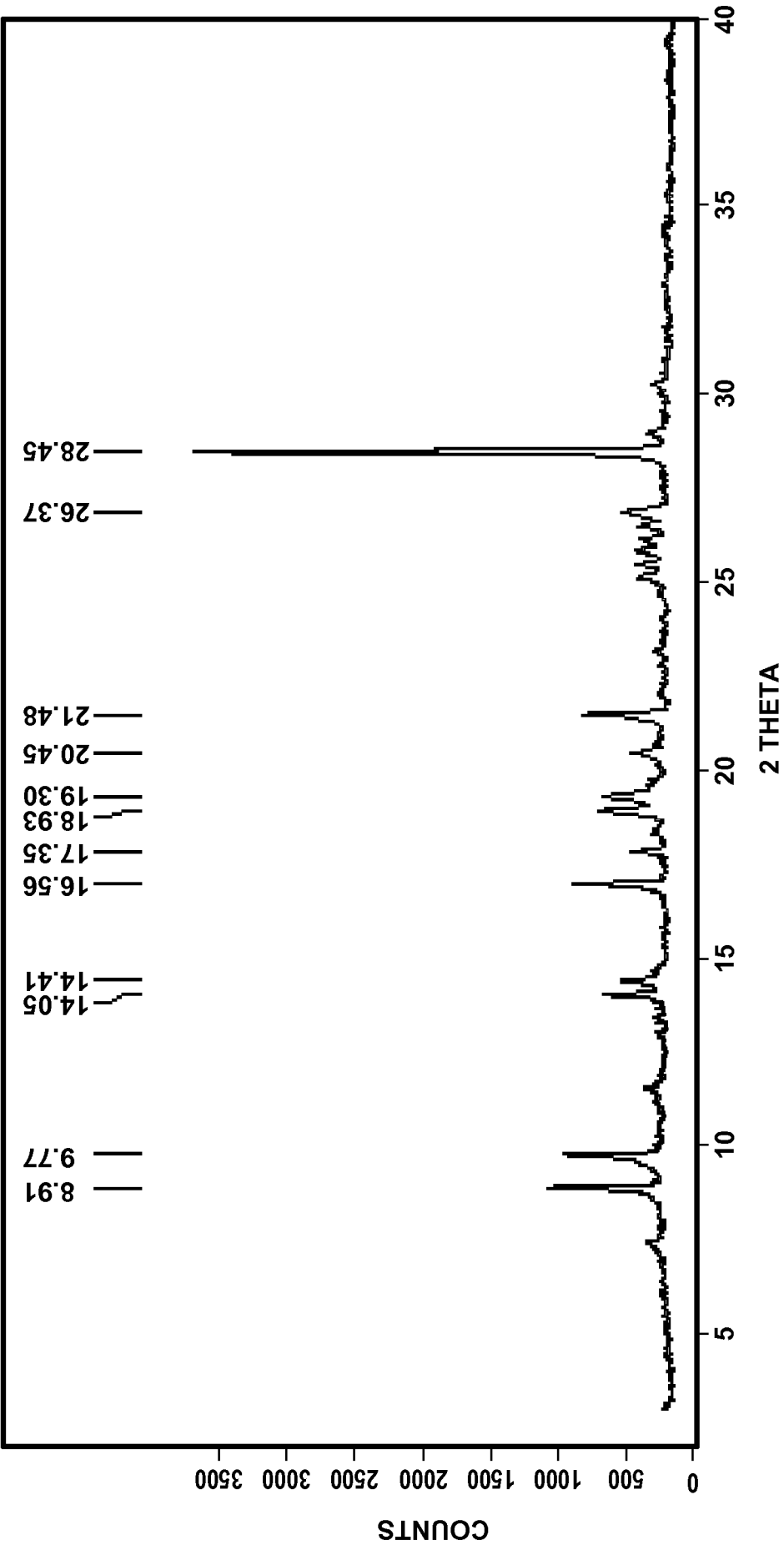


FIG. 19

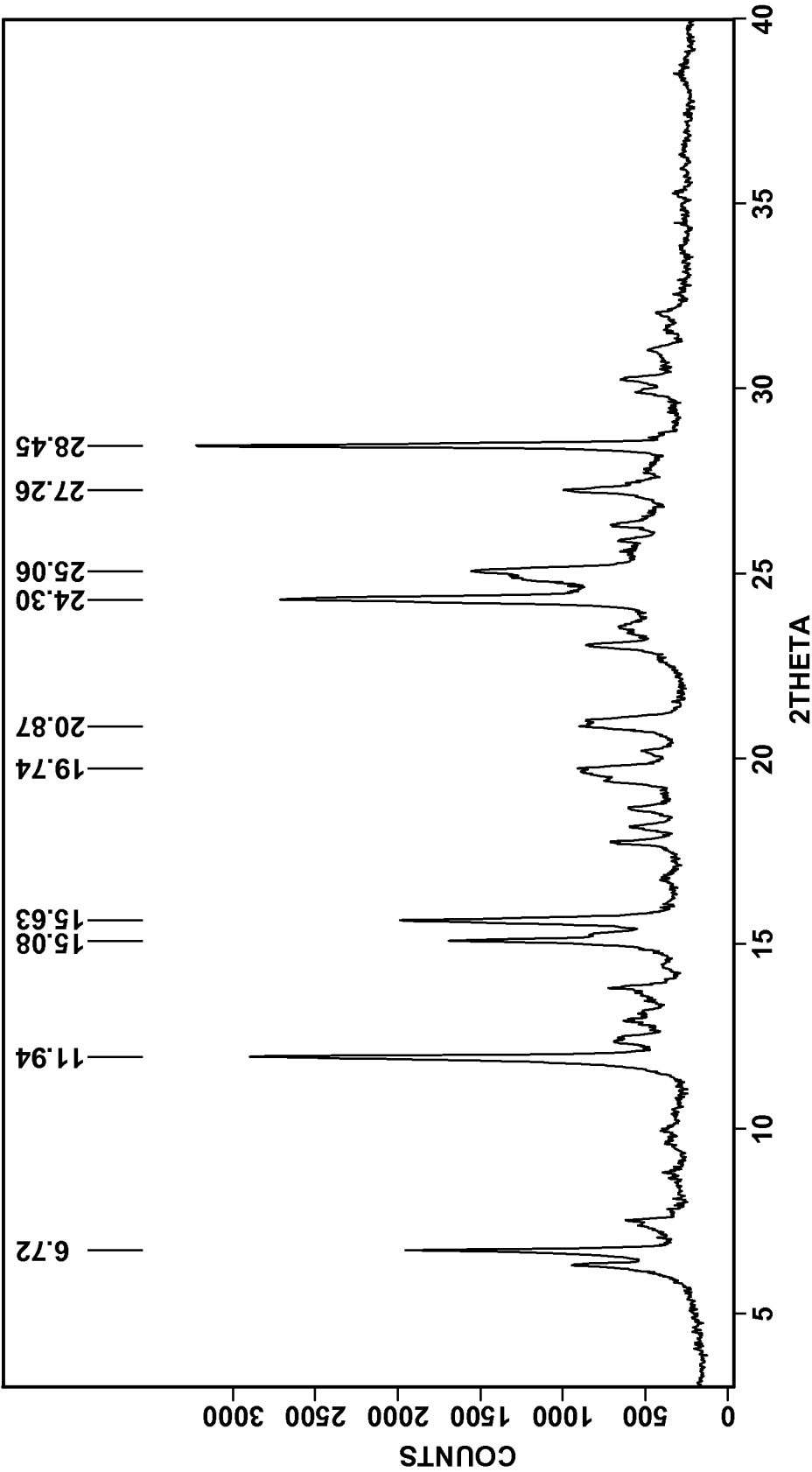


FIG. 20

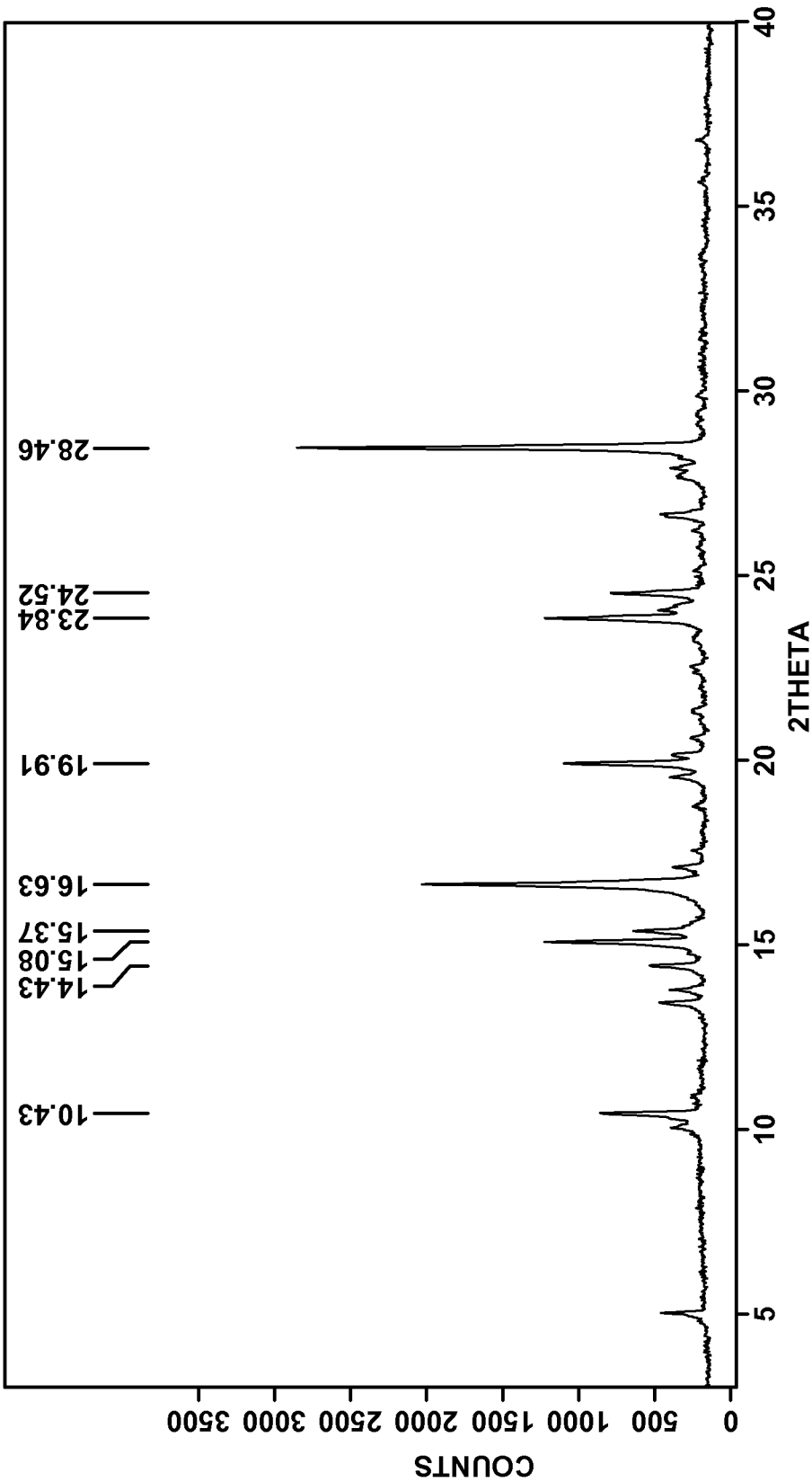


FIG. 21

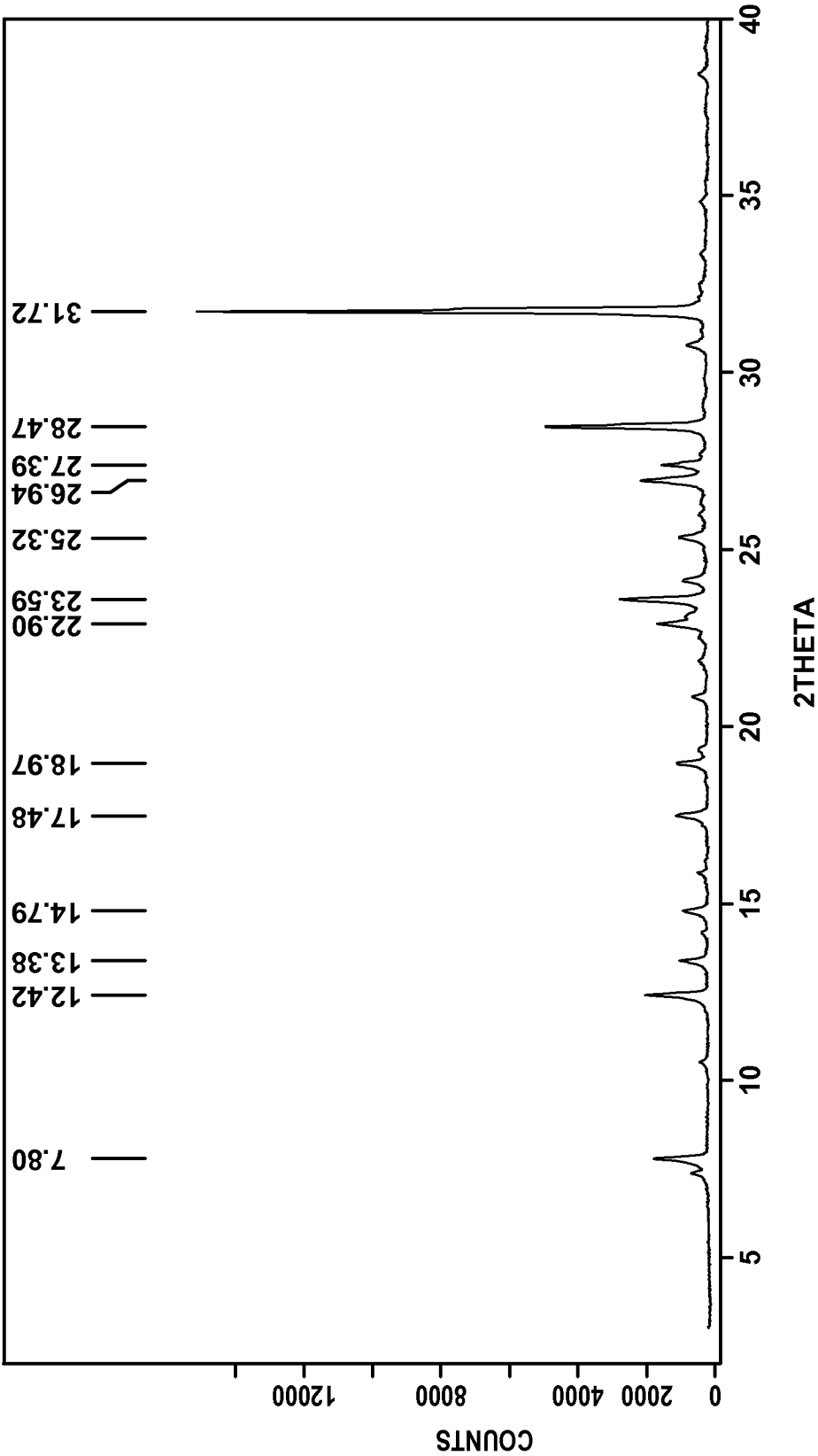


FIG. 22

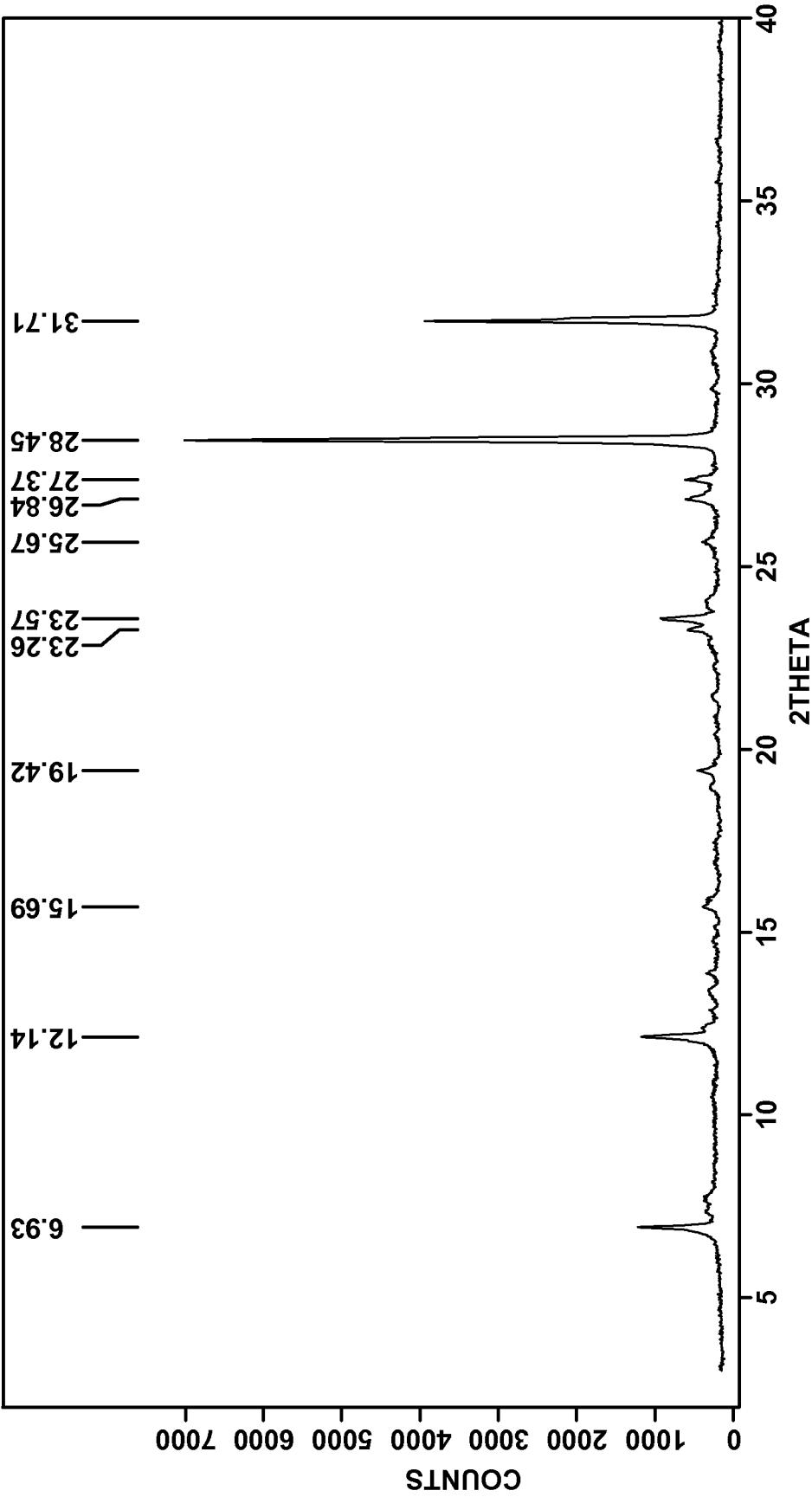
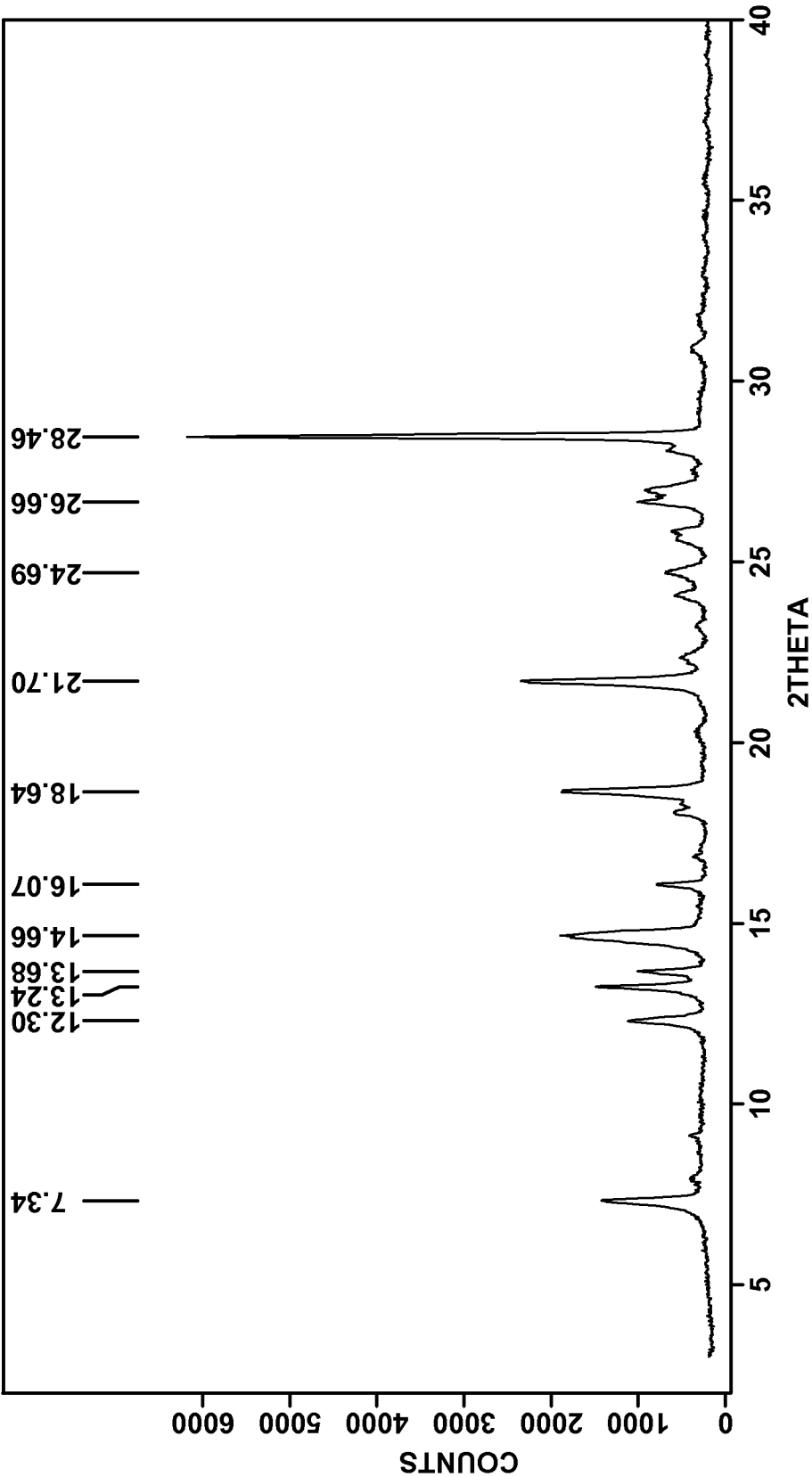


FIG. 23



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/058867

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/506 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/064753 A2 (SMITHKLINE BEECHAM CORP [US]; PANDITE ARUNDATHY NIRMALINI [US]; WHITEH) 7 June 2007 (2007-06-07) cited in the application	7
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X	WO 02/059110 A1 (GLAXO GROUP LTD [GB]; BOLOOR AMOGH [US]; CHEUNG MUI [US]; DAVIS RONDA) 1 August 2002 (2002-08-01) cited in the application	7
A	example 69 -----	1-6



Further documents are listed in the continuation of Box C.



See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but 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

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"&" document member of the same patent family

Date of the actual completion of the international search

9 March 2011

Date of mailing of the international search report

18/03/2011

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Fax: (+31-70) 340-3016

Authorized officer

Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/058867

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