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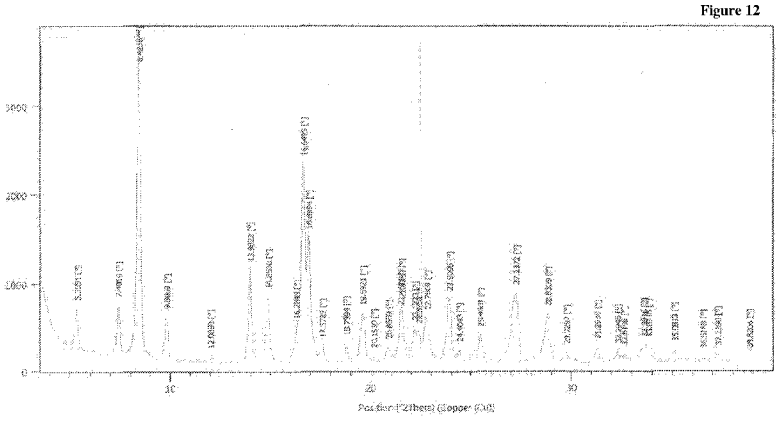
(54) Title: AN IMPROVED PROCESS FOR PREPARATION OF APREMILAST AND NOVEL POLYMORPHS THEREOF

Figure 12



(57) Abstract: The present invention provides an improved process for preparation of an intermediate of apremilast. The present invention also provides an improved process for preparation of apremilast. This invention also provides novel polymorphs of apremilast. The present invention also provides pharmaceutical compositions of novel polymorphs of apremilast. This invention also provides a process for preparation of novel polymorphs of apremilast, which are cost-effective, robust, and viable at plant scale.

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AN IMPROVED PROCESS FOR PREPARATION OF APREMILAST AND NOVEL POLYMORPHS THEREOF

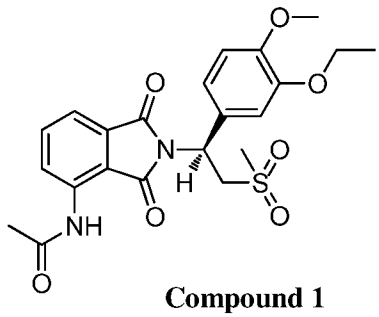
Field of invention

The present invention provides an improved process for preparation of an apremilast. The present invention also provides novel polymorphs of apremilast and processes for their preparation and pharmaceutical compositions for the treatment of psoriatic arthritis.

Background of invention

Tumor necrosis factor alpha (TNFα) is a cytokine produced by monocytes and macrophages. It is found in synovial cells and macrophages in the tissues. It can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons.

Apremilast is a TNFα inhibitor and marketed in United States under the brand name OTEZLA®. Apremilast is indicated for the treatment psoriatic arthritis. It is also used to treat moderate to severe plaque psoriasis in certain patients. The chemical structure of apremilast described in compound 1 as below.



Compound 1

Apremilast is a white to pale yellow powder in appearance. The drug substance is the S- enantiomer of N-[2-[1-(3-ethoxy-4-methoxy-phenyl)-2-(methylsulfonyl) ethyl]-2, 3-dihydro--1, 3-dioxo-1H-isoindol-4-yl] acetamide.

The US Patent 8,242,310 describes a process for preparation of amine compound of formula (I) by reacting benzonitrile compound of formula (IV) with

Lithiumdimethylsulfone compound. The present invention also provides the process for preparation of intermediate of formula A and its conversion to apremilast in subsequent steps.

The US Patent 7,427,638 describes S - enantiomer of apremilast as a product and process for preparation thereof.

The US Patent 7,893,101 and US Patent 8,093,283 discloses a Form A, Form B, Form C, Form D, Form E, Form F and Form G of apremilast and process for preparation thereof.

Summary of invention

The invention provides an improved process for preparation of Apremilast.

The present invention also provides novel polymorphs of apremilast and processes for preparation thereof. Particularly, these polymorphs of apremilast are viable and stable at plant scale. Further, present invention provides pharmaceutical compositions comprising apremilast and one or more pharmaceutically acceptable excipients and their use for the treatment of psoriatic arthritis.

In one aspect of the present invention provides crystalline Form M of apremilast, characterized by at least one of the following properties

i) Powder X-Ray diffraction pattern (PXRD) substantially in accordance with Figure 12;

ii) Powder X-Ray diffraction (PXRD) pattern having peaks at 5.3, 8.4, 13.98, , 16.64, 21.46, $\pm$ 0.2° 2theta values;

iii) thermogravimetric analysis (TGA) substantially in accordance with Fig 13.

iv) differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 14.

In one of the embodiment, the crystalline Form M of apremilast is stable

In another aspect of the present invention provides a process of preparing Form M of apremilast comprising

a) contacting apremilast with at least one solvent;

b) heating the mixture of step a);

c) adding the mixture of step b) to water;

d) cooling the mixture; and

e) isolating the crystalline Form M of apremilast.

Another aspect of the present invention provides a crystal of Form M of apremilast and process for preparation thereof.

Another aspect of the present invention provides crystalline Form L of apremilast, characterized by PXRD pattern having peaks at 11.17, 14.0, 16.17, 17.90, and 26.86, ± 0.2° 2theta values; or characterized by X-ray diffraction pattern as depicted in Fig 5.

Another aspect of the present invention provides crystalline Form N of apremilast, characterized by PXRD pattern having peaks at 7.90, 14.64, 17.20, 19.06, and 24.95, ± 0.2° 2theta values; or characterized by X-ray diffraction pattern as depicted in Fig 10.

Another aspect of the present invention provides crystalline Form O of apremilast, characterized by PXRD pattern having peaks at 7.30, 11.16, 17.60, and 26.18, ± 0.2° 2theta values; or characterized by X-ray diffraction pattern as depicted in Fig 11.

Another aspect of the present invention provides pharmaceutical compositions comprising crystalline apremilast Form M or Form O or Form N or Form L and one or more pharmaceutically acceptable excipients.

In another aspect of the present invention provides the use of these polymorphs for the treatment of psoriatic arthritis.

Objective of the invention

The object of this invention is to provide an improved process for preparation of racemic amine of compound of formula (A), which is an intermediate of apremilast.

In another object of the present invention is to provide an improved process for preparation of apremilast from racemic amine compound of formula (A).

In another object of the present invention is to provide a novel process for preparation apremilast through green, eco-friendly, feasible and cost-effective method.

In another object of the present invention is to provide novel polymorphs of apremilast which are more stable, cost-effective, and viable at plant scale.

Brief Description of Drawings

Fig. 1 depicts Differential Scanning Calorimetry (DSC) of apremilast.

Fig. 2 depicts Thermal Gravimetric Analysis (TGA) of apremilast.

Fig. 3 depicts Infra- red Spectroscopy (IR) of apremilast.

Fig. 4 depicts X- ray Powder Diffraction (XRPD) of apremilast.

Fig 5 depicts Powder X-Ray diffraction pattern of Form L of apremilast.

Fig 6 depicts TG thermogram of Form L of apremilast.

Fig 7 depicts DSC thermogram of Form L of apremilast.

Fig 8 depicts Powder X-Ray diffraction of Form M of apremilast.

Fig 9 depicts TG thermogram of Form M of apremilast.

Fig 10 depicts Powder X-Ray diffraction pattern of Form N of apremilast.

Fig 11 depicts Powder X-Ray diffraction pattern of Form O of apremilast.

Fig 12 depicts Powder X-Ray diffraction pattern of Form M of apremilast prepared by acetone and water.

Fig 13 depicts TG thermogram of Form M of apremilast prepared by acetone and water.

Fig 14 depicts DSC thermogram of Form M of apremilast prepared by acetone and water.

Fig 15 depicts Powder X-Ray diffraction pattern of Form M of apremilast (25°C/60%RH/2M)

Fig 16 depicts Powder X-Ray diffraction pattern of Form M of apremilast (40°C/75%RH/2M)

Fig 17 depicts Crystal data of Form M of apremilast.

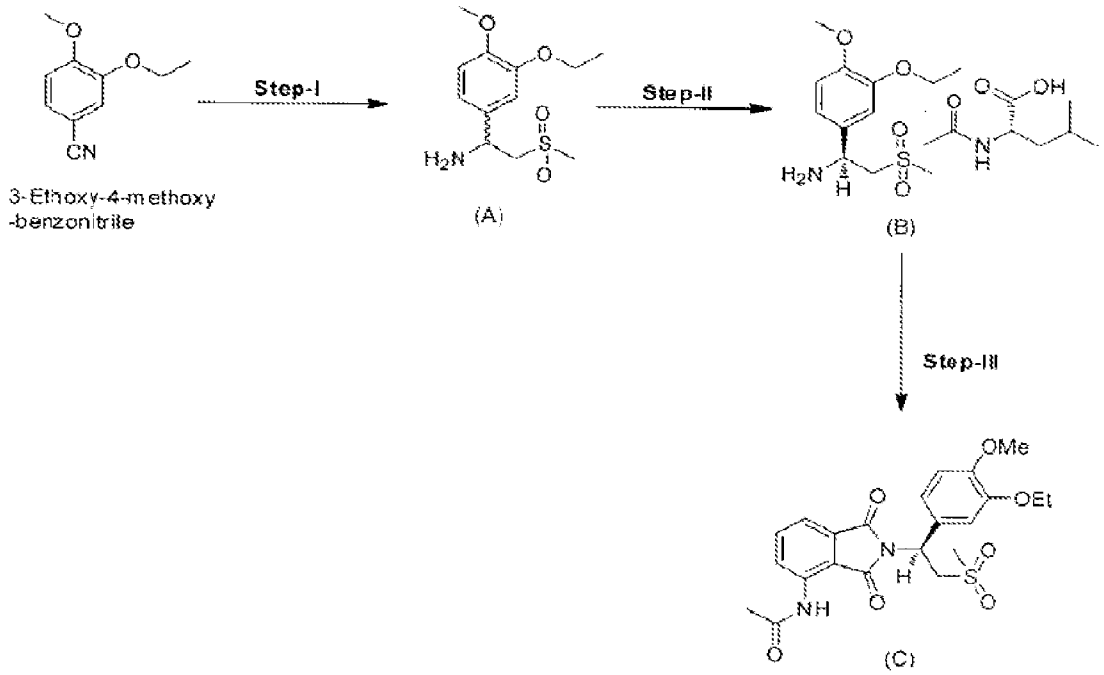
Fig 17A depicts **Oak Ridge Thermal Ellipsoid Plot** (ORTEP) diagram of Form M of apremilast with 50% thermal ellipsoid.

Fig 17B depicts Rietveld plots of Form M of apremilast.

Fig 17C depicts crystal structure of Form M of apremilast.

Detailed description

The present invention provides an improved process for preparation of apremilast via intermediate of formula A and its process. This intermediate is prepared by using cheap, cost effective and non-hazardous reagents. The present invention provides an improved process for preparation of apremilast (compound C) as below in reaction scheme 1.



Reaction Scheme 1

One of the aspects of this invention is to provide a process for preparing compound of formula (A) i.e. racemic amine in step-1 in which 3-ethoxy-4-methoxybenzonitrile is reacted with dimethyl sulfone and a base in an organic solvent. The reaction mass is treated with a reducing agent to give racemic amine compound of formula (A). The base used is in organic or organic base known in the art. The base includes, but not limited to sodium hydride, sodium hydroxide, potassium hydroxide, potassium-HMDS, sodium- HMDS, triethylamine, and diisopropyl amine etc. The organic solvent used in this reaction can be selected from methanol, ethanol, n-butanol, diethyl ether, diisopropyl ether, ethyl acetate, and tetrahydrofuran solvent. The reducing agent can be used as lithium aluminium hydride, sodium borohydride, DIBAL, etc. or any reducing agent known in the art. In step-1, the reaction can be carried out about 0 to 65 °C. The compound of formula (A) may be in isolated or non-isolated form. The compound of formula (A) can be recrystallized with the use of solvent or mixture of solvents known in the art.

The racemic amine can be converted to their chiral acid salts i.e. the compound of formula (B). The compound *I* salts include, but not limited to salts formed with alanine, aspartic acid, glutamine, N-acetyl-leucine, phenylethylamine, mandelic acid, tartaric acid and citric acid. The preferred acid for preparation of amine salt is N-acetyl-L- leucine. This reaction can be carried out in any water miscible or immiscible solvent/s known in the art.

Another aspect of this invention is to provide an improved process for preparation of apremilast i.e. compound of formula (C) from amine salt. The chiral amine salt is reacted with 3-acetamidophthalic anhydride in presence of a solvent or mixture of solvents or an acid or base condition. The solvents include, but not limited to water miscible or immiscible solvents. Organic acid or inorganic acid, such as acetic acid, trifluoroacetic acid, hydrochloric acid, sulfuric acid etc.

After completion of reaction, the resultant solid can be treated with an organic solvent or mixture of solvents. The solvent include, but not limited to ketone, alcohol, hydrocarbon, ether, water, ester, nitrile, halohydrocarbon and amide solvents or water miscible or immiscible solvents known in the art.

The precipitated final compound can be treated with solvents include, not limited to, ketone, alcohol, hydrocarbon, ether, water, ester, nitrile, halohydrocarbon and amide solvents or water miscible or immiscible solvents known in the art.

In another aspect, the apremilast obtained by the process of invention can be converted into novel polymorphs.

This present invention also provides novel polymorphs of apremilast.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray

diffraction peaks. Solvent medium and mode of crystallization play very important role in obtaining a new salt or a crystalline form over the other.

The present invention provides a novel polymorphs of apremilast, which are stable throughout its shelf life and is clinically bioequivalent under FDA standards for this product.

The present invention also provides a crystal of Form M of apremilast. The crystal of Form M of apremilast is stable.

The present invention provides processes for preparation of novel polymorphs of apremilast, wherein, the apremilast can be treated with a water miscible or water immiscible solvents selected from ketone, ester, hydrocarbons, amide, halocarbons, alcohol and ether solvents at a particular temperature. The resulting solid is filtered, washed and dried at higher temperature. The solvent/s have treated can be selected from water, acetone, diethylketone, methylisobutylketone, N-methylpyrrolidone, ethylacetate, n-hexane, n-heptane, toluene, xylene, cyclohexane, N,N'-Dimethylformamide, N,N'-Dimethylacetamide, chloroform, dichloromethane, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, diethyl ether, isopropyl ether, dioxane, tetrahydrofuran and acetonitrile in a single solvent or mixture of solvents said herein. The temperature used in the process of present invention may be -5 to 100°C.

The resultant solid analyzed by different techniques such as, thermogravimetric analysis, differential scanning calorimetry, moisture content, powder x-ray diffraction and other available analytical techniques well-known in the literature with the available procedures.

The present invention provides new and stable polymorphs of apremilast. These polymorphs are stable and viable at any scale. More specifically, a novel polymorph apremilast, designated as Form M, is stable at longer durations as per ICH and USP guidelines.

The Form M of apremilast has good solubility in various medium such as water, hydrochloric acid, acetate Buffer, and phosphate Buffer at different pH.

The term "stable" with respect polymorph or to a drug dosage form, refers to the chemical and physical integrity of the polymorph or dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination..

The Form M of apremilast is stable at different set of conditions such as 25 °C to 40 °C temperature, 5% to 75% humidity (RH) for durations as depicted in Fig 15 and Fig 16.

The process of the novel polymorphs of apremilast is feasible at all scale and avoids use of harmful chemicals and solvents. This process for preparation of Form M of apremilast is eco-friendly cost effective, green and industrial applicable.

Molar equivalents of solvent/s employed for this invention vary with respect to apremilast equivalents.

In the present invention the content of water in apremilast ranges from about 0.1% to about 6.0%. The isolation of this crystalline solid polymorph is carried out by the conventional techniques known in the prior art such as filtration, concentration, and evaporation etc.

In the present invention, apremilast used as a starting material is obtained by the processes known in the art. Thus, apremilast prepared by US Patent 6,962,940 or US Patent 7,427,638 can be used as starting materials for the preparation of the novel polymorph/s of apremilast of the present invention.

According to another aspect of the present invention, a stable crystalline Form M of apremilast characterized by atleast one of the following properties is provided:

i) Powder X-Ray diffraction pattern as described in Figure 8 and or Figure 12 having peaks at 5.3, 8.4, 9.8, 13.98, 14.85, 16.64, 19.59, 21.46, 27.23 $\pm$ 0.2° 2theta values;

ii) Thermogravimetric analysis curve (TGA) shows in Figure 13;

iii) Differential scanning calorimetric (DSC) thermogram as depicted in Figure 14.

Analytical Methods

1) Powder X-Ray Diffraction (PXRD)

Using a PANalytical X'Pert powder diffraction meter, the x-ray powder diffraction pattern was measured at room temperature using a Cu Kα filled tube (45 kV 40 mA) as the x-ray source. Data collection was done in 2theta continuous scan mode in the range of 3.5° to 40°.

For crystal study, PXRD data of Form M of apremilast were collected at 293(2) K on a Bruker D8 Advance diffractometer operating in the Bragg–Brentano geometry with CuKα radiation (λ = 1.5418 Å). The PXRD patterns were indexed using the NTREOR code in the program EXPO 2014 yielding monoclinic unit cells. Given the volume of unit cell and consideration of density, the number of formula units in the unit cell turned out as Z = 2. The unit cell parameters (Figures 17, 17A & 17B) and space group ($P2_1$) assignments were validated by a Le-Bail fit of PXRD data using a pseudo-Voigt peak profile function with FOX. Structure solution was carried out by global optimization of structural models in direct space based on a Monte Carlo search using the simulated annealing technique (in parallel tempering mode), as implemented in the program FOX. The best solution (i.e., the structure with lowest Rwp) was used as the structural model of Form M for Rietveld refinement, which was carried out using the GSAS program. The final Rietveld plots of Form M showed good agreement between the observed P-XRD profile and powder pattern calculated.

2) Thermogravimetric analysis

Thermogravimetric analysis was performed using a Pyris 1 TGA PERKIN ELMER measurement unit. 2-5 mg samples were placed in open Platinum pans and heated from 25 °C to 300 °C in a dry nitrogen atmosphere at a heating rate of 10 °C/min.

3) Differential Scanning Calorimetry

Differential Scanning Calorimetry was performed using a Diamond DSC PERKIN ELMER differential instrument. 2-3 mg samples were placed in crimped aluminum pans and heated from 30 °C to 250 °C in a dry nitrogen atmosphere at a heating rate of 10 °C/minute.

4) Water content

Karl-Fischer auto titrator Metrohm Titrando was used for detection of water content as per methods known in the art.

5) Nuclear Magnetic Resonance

H^1NMR and ^{13}CMR was performed using Bruker NMR instrument at 400 MHz in CDCl3 as solvent.

6) Infra- red Spectoscopy

IR spectroscopy was performed using a Spectrum 400 using a neat liquid sample or dispersion of solid sample material in KBr.

7) Mass Spectrometry

Measurements of mass of sample which is subject to a temperature program were obtained on Waters.

The described novel polymorphs of apremilast may be used as a pharmaceutical composition with the particular dosage forms for treating the psoriasis or psoriasis related disorders.

Pharmaceutical formulations novel polymorphs of apremilast according to the present invention comprises of one or more pharmaceutically acceptable carriers or excipients such as binders, fillers, disintegrants, surfactants, lubricants or combinations thereof and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared.

Binders for use in the formulations of the present invention include binders commonly used in the formulation of pharmaceuticals. Examples of binders for use in accordance with the present invention include but are not limited to cellulose derivatives (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, and

sodium carboxymethyl cellulose), glycol, sucrose, dextrose, corn syrup, polysaccharides (including acacia, targacanth, guar, alginates and starch), corn starch, pregelatinized starch, modified corn starch, gelatin, polyvinylpyrrolidone, polyethylene, polyethylene glycol, combinations thereof and the like.

Fillers or diluents for use in the formulations of the present invention include fillers or diluents typically used in the formulation of pharmaceuticals. Examples of fillers or diluents for use in accordance with the present invention include but are not limited to sugars such as lactose, dextrose, glucose, sucrose, cellulose, starches and carbohydrate derivatives, polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cycludextrins, calcium carbonates, magnesium carbonates, microcrystalline cellulose, combinations thereof, and the like. In certain preferred embodiments the filler or diluent is lactose, microcrystalline cellulose, or combination thereof. Several types of microcrystalline cellulose are suitable for use in the formulations described herein, for example, microcrystalline cellulose selected from the group consisting of Avicel™ types: PH101, PH102, PH103, PH105, PH 112, PH113, PH200, PH301, and other types of microcrystalline cellulose, such as silicified microcrystalline cellulose. Several types of lactose are suitable for use in the formulations described herein, for example, lactose selected from the group consisting of anhydrous lactose, lactose monohydrate, lactose fast flo, directly compressible anhydrous lactose, and modified lactose monohydrate.

Disintegrants for use in the formulations of the present invention include disintegrants commonly used in the formulation of pharmaceuticals. Examples of disintegrants for use in accordance with the present invention include but are not limited to starches, clays, alginates and gums and crosslinked starches, celluloses and polymers, microcrystalline cellulose, croscarmellose sodium, alginic acid, sodium alginate, crosprovidone, agar and related gums, sodium starch glycolate, corn starch, potato starch, sodium starch glycolate, Veegum HV, methylcellulose, agar, bentonite, carboxymethylcellulose, alginic acid, guar gum combinations thereof, and the like.

Surfactants for use in the formulations of the present invention include surfactants commonly used in the formulation of pharmaceuticals. Examples of surfactants for use in

accordance with the present invention include but are not limited to ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, such as ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, lecithins, phospholipids, combinations thereof, and the like.

Lubricants for use in the formulations of the present invention include lubricants commonly used in the formulation of pharmaceuticals. Examples of lubricants for use in accordance with the present invention include but are not limited to magnesium carbonate, magnesium laurylsulphate, calcium silicate, talc, fumed silicon dioxide, magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, polyethylene glycol, sodium lauryl sulphate, magnesium lauryl sulphate, sodium benzoate, colloidal silicon dioxide, magnesium oxide, microcrystalline cellulose, starches, mineral oil, waxes, glyceryl behenate, polyethylene glycol, sodium acetate, sodium chloride, combinations thereof, and the like.

Other polymers commonly used as excipients include but are not limited to methylcellulose (MC), ethylcellulose (EC), hydroxyethylcellulose (HEC), methyl hydroxyethylcellulose (MHEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC), and the like. These polymers, either alone or in various combinations, may serve multiple purposes including but not limited to controlling release of the formulations of the present invention.

The present invention will now be further illustrated by reference to the following examples, which do not limit the scope of the invention any way.

Example 1-Step-I: Process for preparation of 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine:

In a 2 litre round bottom flask, 300 ml of tetrahydrofuran was charged followed by 32 gms of dimethylsulfone. This reaction mass was cooled for 15 to 20 minutes at 0°C. After cooling, potassium-hexamethyldisilazane was added followed by 20 ml of

tetrahydrofuran. The reaction mass was stirred for an hour at 0 to 5 °C. After stirring, 30 gms of 3-ethoxy-4-methoxybenzonitrile was dissolved in 90 ml tetrahydrofuran and was added to the above reaction mass. The reaction mass was stirred for 30 minutes. After stirring, 23 gms of sodium borohydride was added followed by tetrahydrofuran and acetic acid and the total reaction mass was stirred for 2 hours at 0 to 5 °C. After completion of reaction, sodium hydroxide solution was added to it and stirred for 30 minutes. The reaction mass was warmed and further heated for 3 to 4 hours at 60 to 62°C. After completion of reaction, the reaction solution was allowed to cool to room temperature for half an hour. The layers were separated. The aqueous layer was treated with ethyl acetate and the organic layer was treated with hydrochloric acid. The solution was stirred. The layers were separated. The organic layer was treated with 20% sodium hydroxide solution and the solid was precipitated. The solid was filtered, washed and dried at 50°C and further 30.2 gms of material was unloaded.

Step-II: Process for preparation of 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine N-acetyl-L-leucine salt:

In a 500 ml round bottom flask, 200 ml of methanol was added followed by 20 gms of 2-(3-ethoxy-4-methoxyphenyl)-l-(methanesulfonyl)-eth-2-ylamine. The reaction mass was stirred and 76 gms of N-Acetyl-L-Leucine added and reaction mass was stirred. The reaction mass was heated for 2 hours at 60 to 65°C, After heating, the reaction mass was cooled at room temperature and it was stirred at room temperature for 3 to 4 hours. The slurry was filtered. Washed with 30 ml methanol, material was unloaded and dried under vacuum for 2 hours at 45°C. Yield: 14.36 gm. Further, this material is purified with methanol.

Step-Ill: Process for preparation of Apremilast:

In a 250 ml round bottom flask, 50 ml acetic acid was charged followed by 10 gms of 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine N-acetyl-L-leucine salt and it was stirred at room temperature for a few minutes. Then 4.82 gms of 3-acetamidophthalic anhydride was added and reaction mass was heated for 11 to 12 hours at 80 to 90 °C. The solvent was removed under vacuum and ethyl acetate was added followed by sodium bicarbonate solution. The layers were separated. The organic layer

was washed and solvent was evaporated under vacuum. In the distilled residue, 90 ml ethanol and 30 ml acetone added and was stirred it for 2 hours at room temperature. The solid was precipitated. The solid was filtered and washed with ethanol. The material was unloaded and dried under vacuum for longer hours at 60 ^{o} C. Yield: 6.41 gm. This material will be crystalized using a solvent or mixture of solvents known in the art.

Example 2-Step-I: Process for preparation of 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine:

In a flask, 5 litres of tetrahydrofuran was charged followed by 1.06 kg of dimethylsulfone. This reaction mass was cooled for 25 to 30 minutes at 0°C. After cooling, 1M potassium-hexamethyldisilazane was added followed by 10 litres of tetrahydrofuran. The reaction mass was stirred for an hour at 0 to 10 °C. After stirring, 1 kg of 3-ethoxy-4-methoxybenzonitrile was dissolved in 2 litres tetrahydrofuran and was added to the above reaction mass. The reaction mass was stirred for 30 minutes and cooled. After cooling, 0.433 kg of sodium borohydride was added followed by tetrahydrofuran and 5 litres of acetic acid and the total reaction mass was stirred for 3- 4 hours at 0 to 10 °C. After completion of reaction, sodium hydroxide solution was added to it and stirred for 45 minutes. The reaction mass was warmed and further heated for 3 to 4 hours at 60 to 65°C. After completion of reaction, the reaction solution was allowed to cool to room temperature for half an hour. The layers were separated. The combined organic layer was treated with aq. HCl and water was added to the concentrated mass. The aqueous layer was treated with ethyl acetate. Finally sodium hydroxide solution was added to the aqueous layer and solid was precipitated. The solid was filtered, washed with water and dried at 50°C and further 1.0 kg (65%) of material was unloaded.

Step-II: Process for preparation of 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine N-acetyl-L-leucine salt:

In a flask, 10 litres of methanol was added followed by 1 kg of 2-(3-ethoxy-4-methoxyphenyl)-l-(methanesulfonyl)-eth-2-ylamine. The reaction mass was stirred and 0.38 kg of N-Acetyl-L-Leucine added and reaction mass was stirred. The reaction mass was heated for 2- 3 hours at 60 to 70°C. After heating, the reaction mass was cooled at room temperature and it was stirred at room temperature for 3 to 4 hours. The slurry was

filtered and washed with 1.5 litres of methanol. The wet cake was washed with adequate quantities of methanol and water. Material was unloaded and dried under vacuum for 2 hours at 45°C. Yield: 0.60 kg (73.5%).

Step-Ill: Process for preparation of Apremilast:

In a flask, 5 litres of acetic acid was charged followed by 1 kg of 2-(3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine N-acetyl-L- leucine salt and it was stirred at room temperature for a few minutes. Then 0.482 kg of 3- acetamidophthalic anhydride was added and reaction mass was heated for 11 to 12 hours at 75 to 90 °C. Cool the reaction mass. The solvent was removed under vacuum and ethyl acetate was added followed by sodium bicarbonate solution. The layers were separated. The slurry of carbon in ethyl acetate is added to the above reaction mass. Stir and filter the mass. The organic layer was washed with ethyl acetate and solvent was evaporated under vacuum. In the residue, is added 5 litres of acetone and heated to 40-50 ^{0}C. The clear solution is filtered through micron paper. The solution is partially distilled and 6 litres of methanol is added to it. The solution is seeded with Apremilast. The solid was precipitated. The slurry is stirred for 3-4 hours at room temperature and was filtered and washed with methanol. The material was unloaded and dried under vacuum for longer hours at 50- 60^{0}C. Yield: 0.75 gm (72.8%).

The H^{1}NMR data is ($CDCl_3$) δ: 1.471, t, 3H; 2.264, s, 3H; 2.884, s, 3H; 3.851, s, 3H; 3.73- 3.77, dd, 1H; 4.08- 4.13, q, 2H; 4.52- 4.58, dd, 1H; 5.85- 5.89, dd, 1H; 6.83- 8 .75, m, 6H; 9.461, s, 1H. The C^{13}MR data is ($CDCl_3$) δ: 14.58, 24.84, 41.51, 48.38, 54.27, 55.81, 64.38, 111.30, 112.26, 114.99, 118.08, 120.17, 124.80, 135.99, 137.47, 148.48, 149.58, 167.36, 169.07, and 169.36. DSC at 159.14°C.

Example 3-Process for preparation of Form L of apremilast:

In a 2L round bottom flask, 10.3 gm of apremilast was added followed by 14 ml of N,N-dimethylformamide. The reaction temperature was raised to 90 °C and was stirred for 30 minutes. After stirring, the reaction mass was stirred for 30 minutes at 30 to 40 °C. The 500 ml distilled water was slowly added and stirred for 9 to 10 hours at room temperature. After stirring, the resultant solid was filtered and washed with 100 ml water. The solid was dried for 8 hours at 45°C. Yield: 9.6 gm., Moisture content: 0.651%. The

Powder X-Ray diffraction pattern, TG thermogram and DSC thermogram had obtained identical with Fig. 5, 6 and 7 respectively.

Example 4-Process for preparation of Form M of apremilast:

In a 2L round bottom flask, 10 gm of apremilast was added followed by 10 ml of N, N-dimethylformamide. The reaction temperature was raised to 80 °C and was stirred for 10 minutes. After stirring, the reaction mass was cooled down to 25 to 30 °C and 500 ml water was added in dropwise fashion. The slurry was stirred overnight at 25 °C. The solid was filtered under vacuum and was dried under vacuum for 15 to 20 hours at 45 °C. Yield: 8.5 gm. Moisture content: 3 to 3.28%. The P-X Ray diffraction TGA data had obtained identical with Fig 8 and 9 respectively.

Example 5-Process for preparation of Form N of apremilast:

In a 500 ml round bottom flask, 4 gm of apremilast was added followed by 10 ml of chloroform and 155 ml of cyclohexane. The reaction mass stirred for 26 to 27 hours at 25 to 30 °C and solid was generated. The 0.2 gm of apremilast was seeded and solid material was filtered. The solid was dried under vacuum for 10 minutes at room temperature and then in vacuum for 14 to 15 hours at 45 °C. Yield: 3.1 gm. DSC data: 155.98 to 157.72 °C. The Powder X-Ray diffraction pattern had obtained identical with Fig. 10 respectively.

Example 6-Process for preparation of Form O of apremilast:

In a 100 ml round bottom flask, 3 gm of apremilast was added followed by 5 ml of N-methylpyrrolidone and was heated to 60 °C for 5 minutes. The solid material was filtered at room temperature. The filtrate was left for slow evaporation in a freeze for near about 24 hours at -5 to -10 °C. The precipitate was filtered and dried in a vacuum oven for 4 hours at 45 °C. The dried product was further dried for 7 hours at 45 °C. Yield: 1.49 gm. The Powder X-Ray diffraction pattern had obtained identical with Fig. 11 respectively.

Example 7-Process for preparation of Form M of apremilast:

In a 500 ml round bottom flask, 100 ml acetone was charged followed by addition of 25 gm of apremilast and was heated at 45 °C to 55 °C to form clear solution. This clear solution was filtered through filter paper and washed with acetone. In another flask, DM water was taken and was chilled to lower temperature. The above acetone solution was added to the chilled water slowly. After addition, reaction mass was maintained for 14 to 21 hours at lower temperature. The solid was precipitated and was filtered, washed with DM water and dried under vacuum at below 45 °C. Yield of the solid was 21.5 gm. The Powder X-Ray diffraction pattern, TG, and DSC thermogram had obtained identical with Figure 12, 13 and 14 respectively.

Example 8-Process for preparation of Form M of apremilast:

In a 500 ml round bottom flask, 100 ml aqueous acetone solution was charged followed by addition of 25 gm of apremilast and was heated at 45 °C to 55°C to form clear solution. This clear solution was filtered through filter paper and washed with acetone. In another flask, DM water was taken and was chilled to lower temperature. The above acetone solution was added to chilled water slowly. After addition, reaction mass was maintained for 14 to 18 hours at lower temperature. The solid was precipitated and was filtered and washed with 500 ml DM water and dried under vacuum at below 45 °C. Yield: 21 gm.

Example 9-Process for preparation of Form M of apremilast:

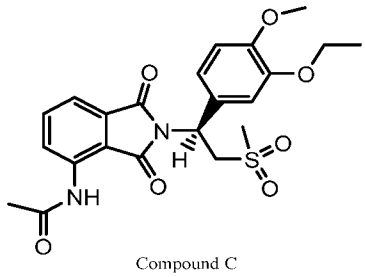
In a 500 ml round bottom flask, 100 ml acetone was charged followed by addition of 20 gm of apremilast and was heated at 45 °C to 50 °C to form clear solution. This clear solution was cooled. In another flask, water was cooled and above reaction solution was added. The slurry was formed. The resultant slurry was stirred for 7 to 10 hours at 10 °C to 15 °C. The solid was filtered, washed with water and was dried for 10-15 hours. The product was yielded in 15 gm.

Example 10-Crystal structure of Form M of apremilast:

The crystal structure of Form M of apremilast was obtained from high resolution X-Ray diffraction patterns. The asymmetric unit was consisted of one unit of apremilast and one mole of water (Figure 17A). The water molecules present in a discrete manner and hydrogen bonded to –OMe group of apremilast via auxiliary interactions (Figure 17C).

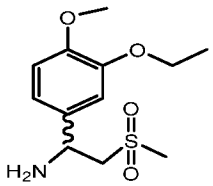
CLAIMS

1. An improved process for preparation of Apremilast of formula C, comprising steps:



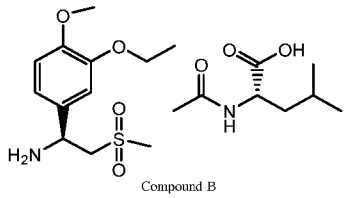
Compound C

a) treating 3- ethoxy- 4-methoxy-benzonitrile with dimethyl sulfone and a base in an organic solvent to get compound A, in presence of reducing agent,



Compound A

b) treating compound A with chiral acid in organic solvent to give compound B, 2-(-3-ethoxy-4-methoxyphenyl)-1-(methanesulfonyl)-eth-2-ylamine N-acetyl-L-leucine salt,



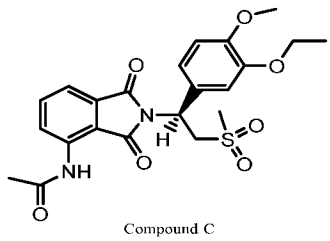
Compound B

c) treating step b) with 3-acetamidophthalic anhydride in presence of solvent,

d) isolating Apremilast from reaction mixture thereof.

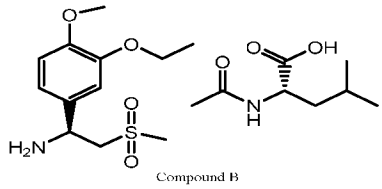
2. The process according to claim 1, wherein the reducing agent is sodium borohydride.

3. A process for preparation of Apremilast of formula C, comprising:



Compound C

a) reacting Compound A with N- acetyl L- leucine in organic solvent to give Compound B; 2-(-3-ethoxy-4-methoxyphenyl)-1- (methanesulfonyl)-eth-2-ylamine N-acetyl-L-leucine salt,



Compound B

b) treating step (a) with 3-acetamidophthalic anhydride in presence of solvent and isolating Apremilast.

4. A process for the preparation of compound A comprising of steps:

a) reacting 3- ethoxy- 4- methoxy- benzonitrile with dimethyl sulfone in presence of base in an organic solvent,

b) treating step a) with reducing agent in an organic solvent,

c) isolating the compound of formula A.

5. The process of claim 4, wherein the bases are sodium hydride, sodium hydroxide, potassium hydroxide, potassium-HMDS, sodium HMDS, triethyl amine, and diisopropyl amine etc.

6. The process according to claim 5, wherein base is potassium-HMDS.

7. The process according to claim 4, wherein the organic solvents are methanol, ethanol, n-butanol, diethyl ether, diisopropyl ether, tetrahydrofuran, ethyl acetate.

8. The process according to claim 7, wherein the solvent is methanol.

9. A stable crystalline Form M of apremilast.

10. The Apremilast form M of claim 9, has moisture content below 1% to 5%.

11. The stable crystalline Form M of apremilast of claim 9, characterized by atleast one of the following properties

i) a Powder X-Ray diffraction (PXRD) pattern substantially in accordance with Figure 12;

ii) a Powder X-Ray diffraction (PXRD) pattern having peaks at 5.3, 8.4, 9.8, 13.98, 14.85, 16.64, 19.59, 21.46, 27.23 $\pm$ 0.2° 2theta value;

iii) a Thermogravimetric analysis (TGA) substantially in accordance with Figure 13.

iv) a differential scanning calorimetric (DSC) thermogram substantially in accordance with Figure 14 .

12. A process of preparing Form M of apremilast comprising:

a) contacting apremilast with at least one solvent;

b) heating the mixture of step a);

c) adding water to the mixture of step b) ;

d) thereafter cooling the mixture; and

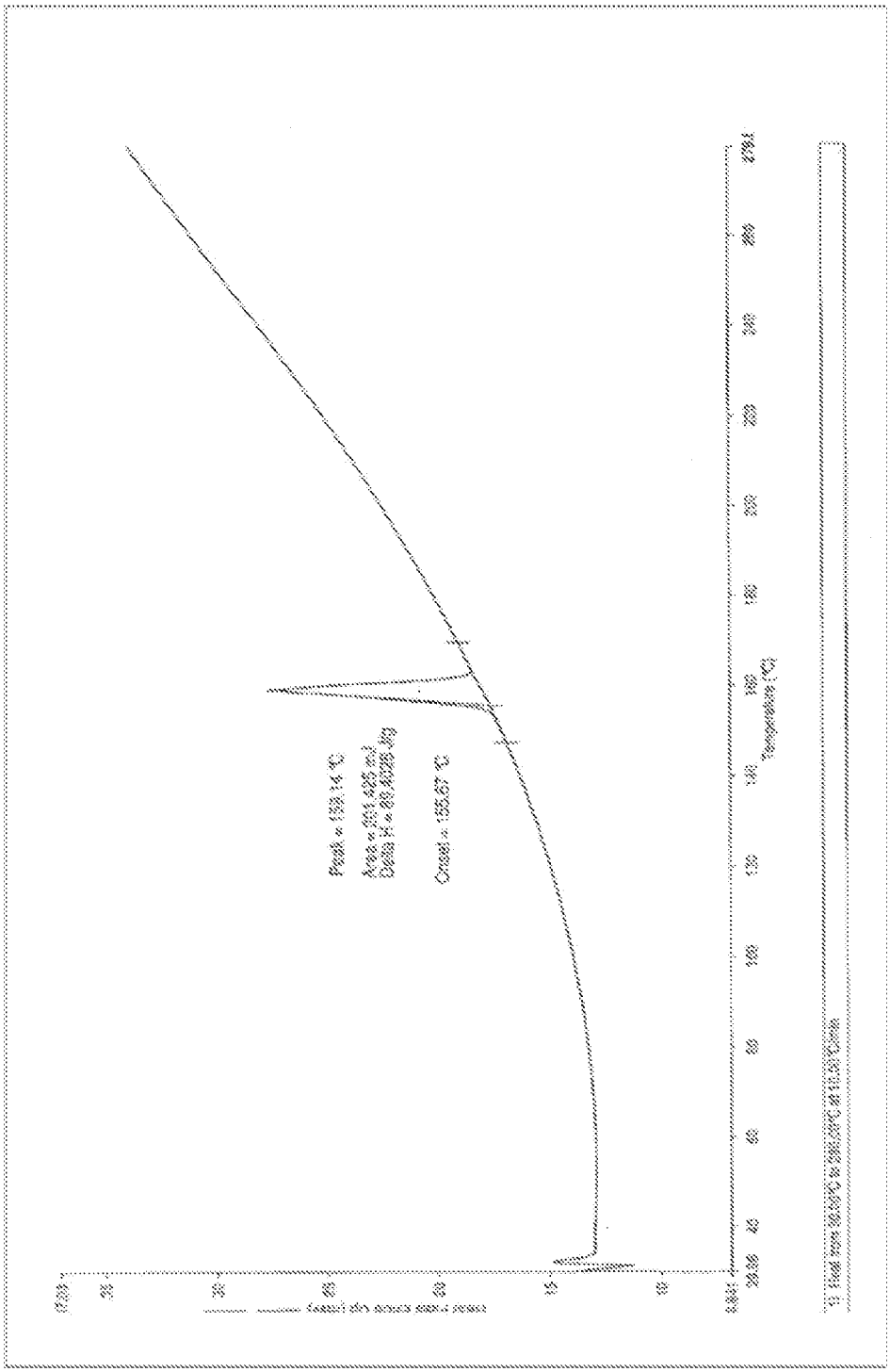
e) isolating the Form M of apremilast.

13. The process of claim 12, wherein in step b), the mixture is heated to a temperature from about 30 °C to about 60 °C.

14. The process of claim 12, wherein in step c), the mixture is cooled to a temperature of about 0 °C to about 20 °C.

15. The process of claim 12, wherein the solvent is selected from the group consisting of acetone, tetrahydrofuran, and N, N-dimethylformamide; or mixture of at least two thereof.

16. A pharmaceutical composition comprising Form M of apremilast and one or more pharmaceutically acceptable excipients.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Area = 651.425 mJ
Delta H = 80.8268 J/g
Onset = 155.67 °C
Temperature (°C)

Figure 1

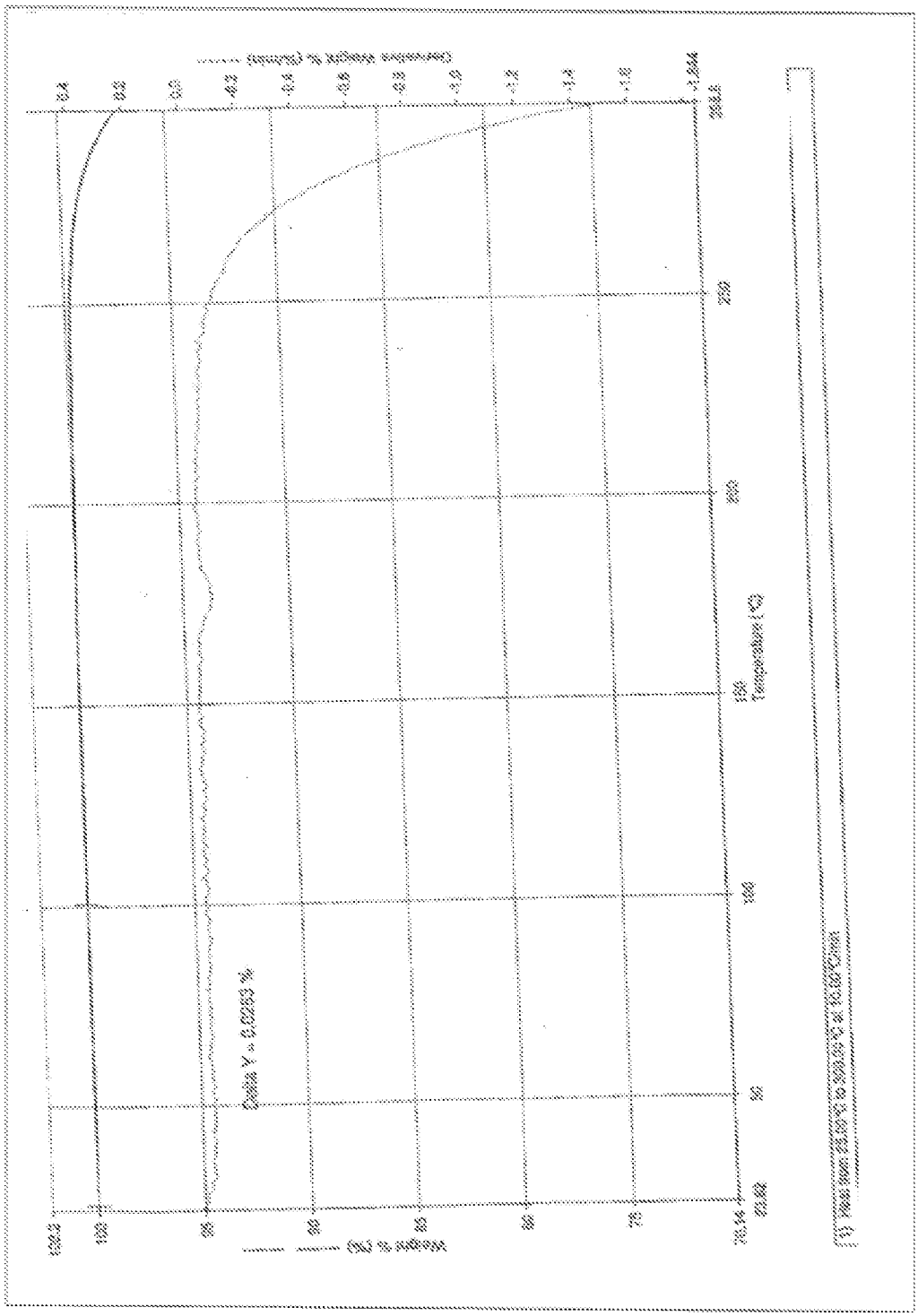


Figure 2

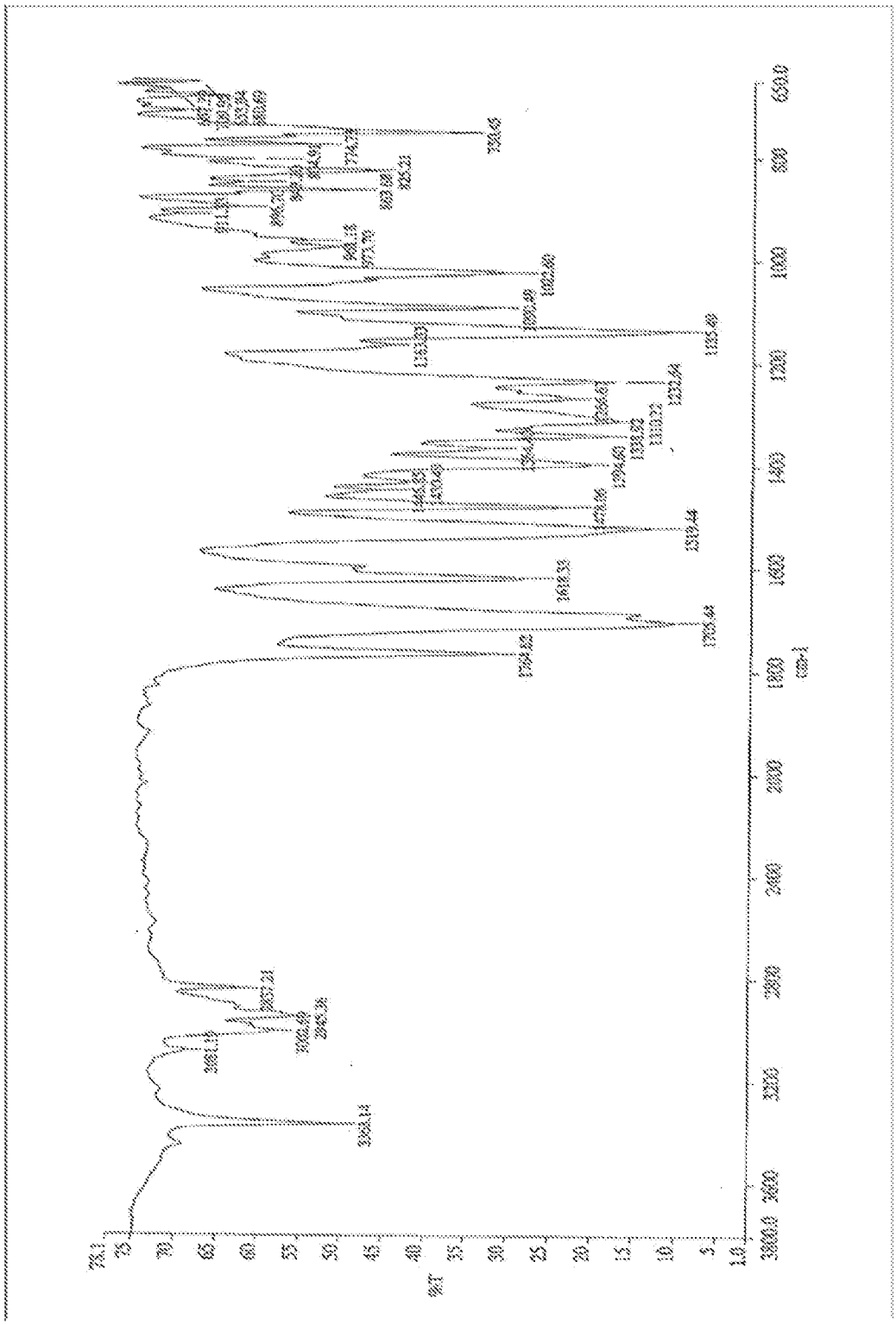


Figure 3

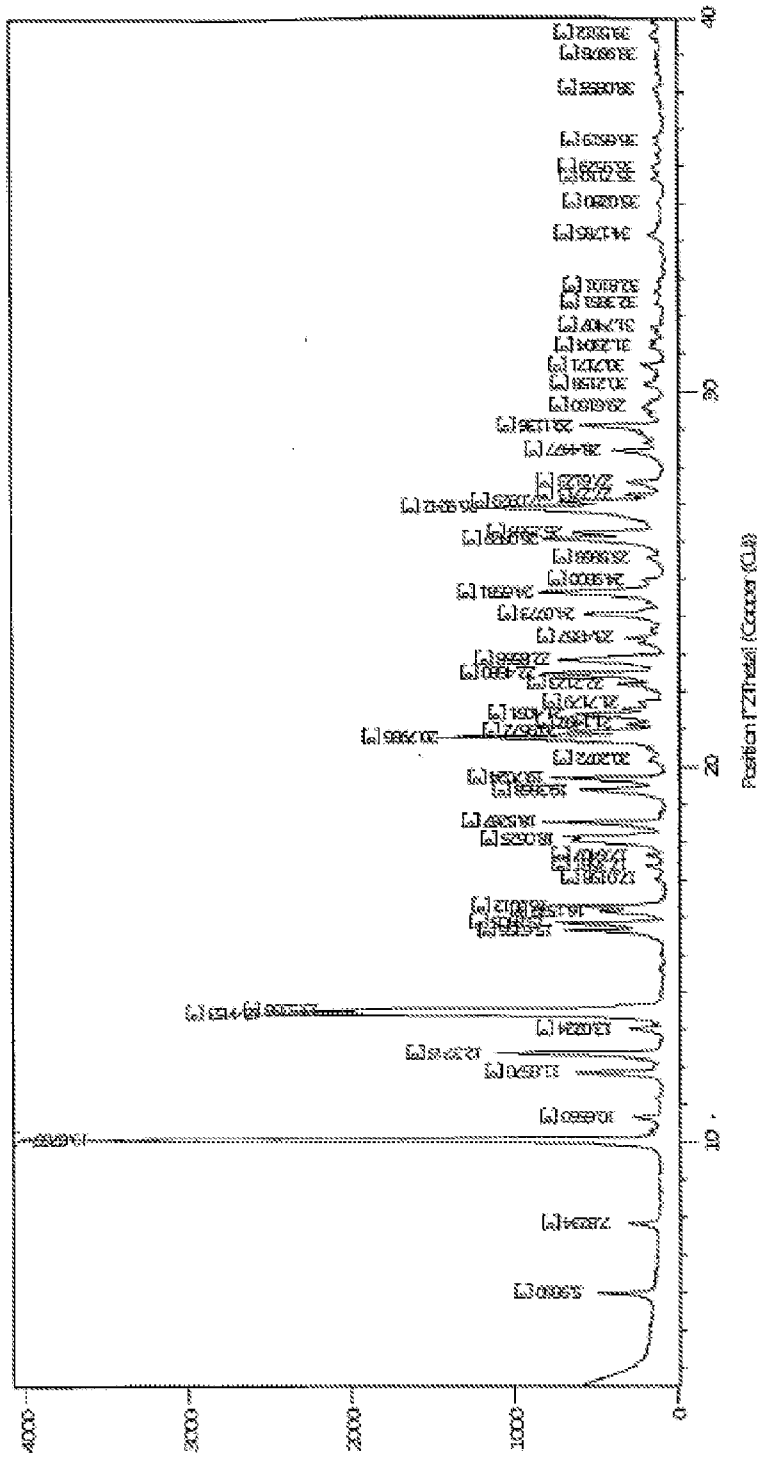


Figure 4

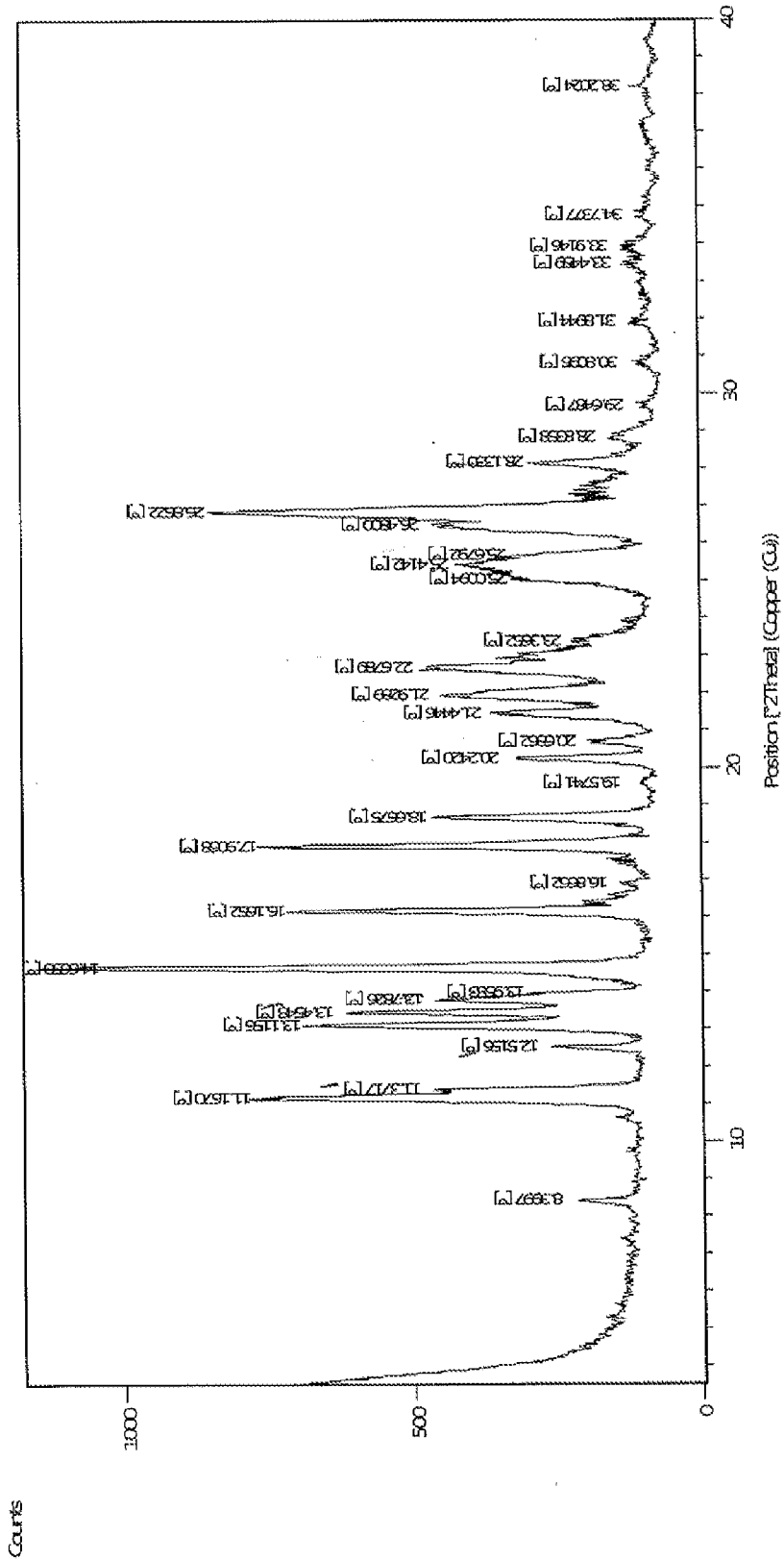
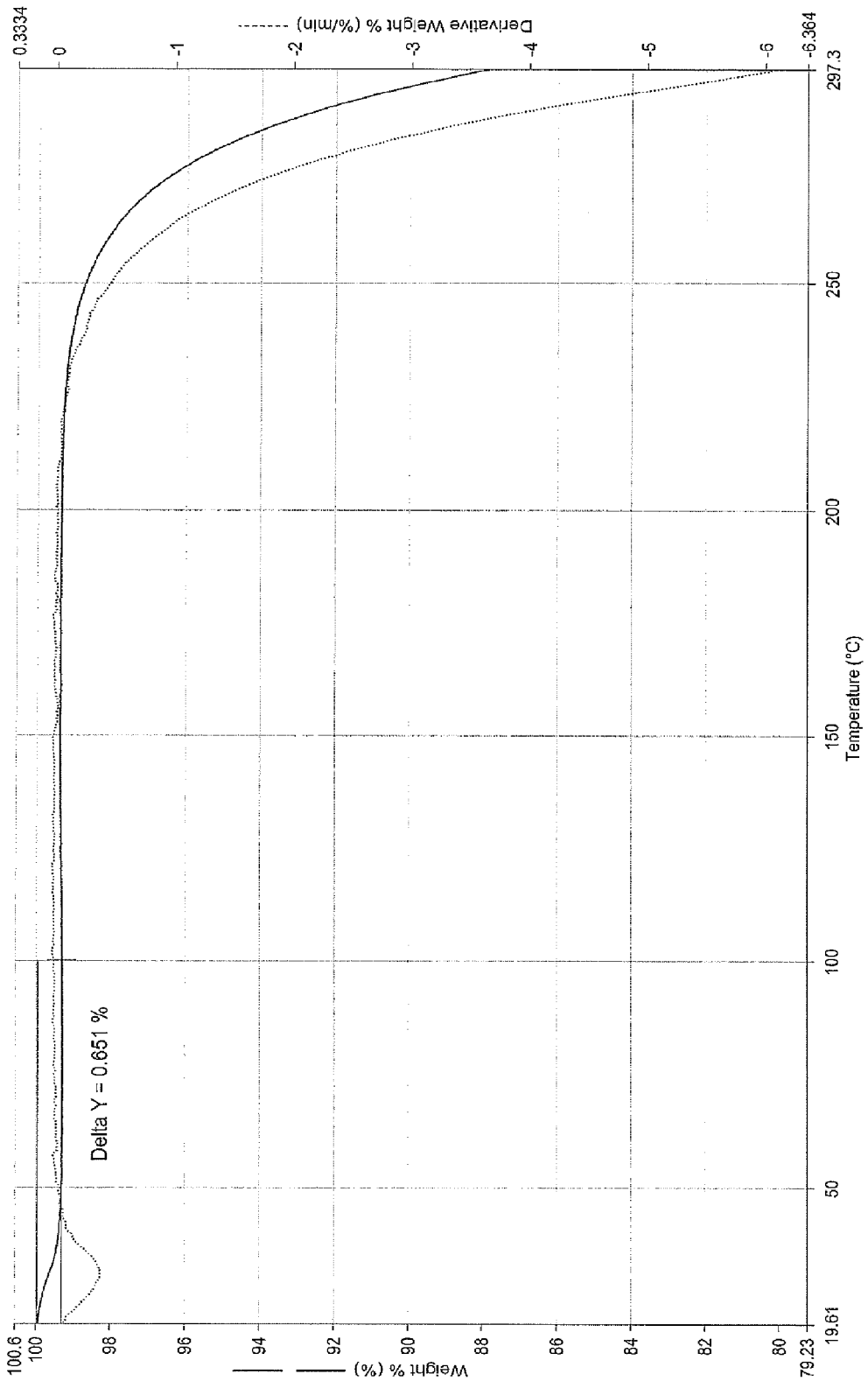


Figure 5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-4
-5
-6
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200
150
100
50
19.61
Temperature (°C)
Delta Y = 0.651 %
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100
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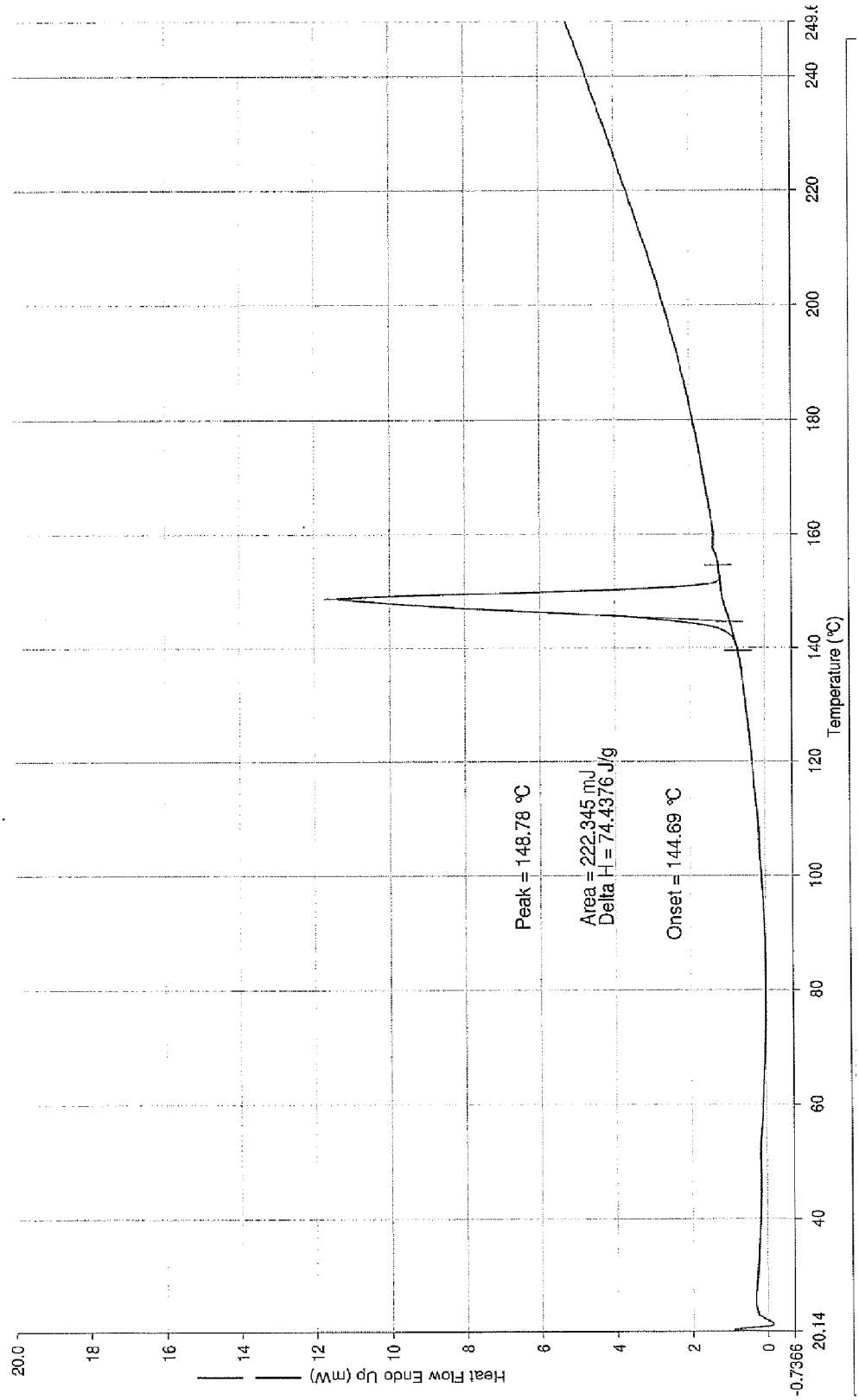
96
94
92
90
88
86
84
82
80
79.23
Weight % (%)

Figure 6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Onset = 144.69 °C
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16
14
12
10
8
6
4
2
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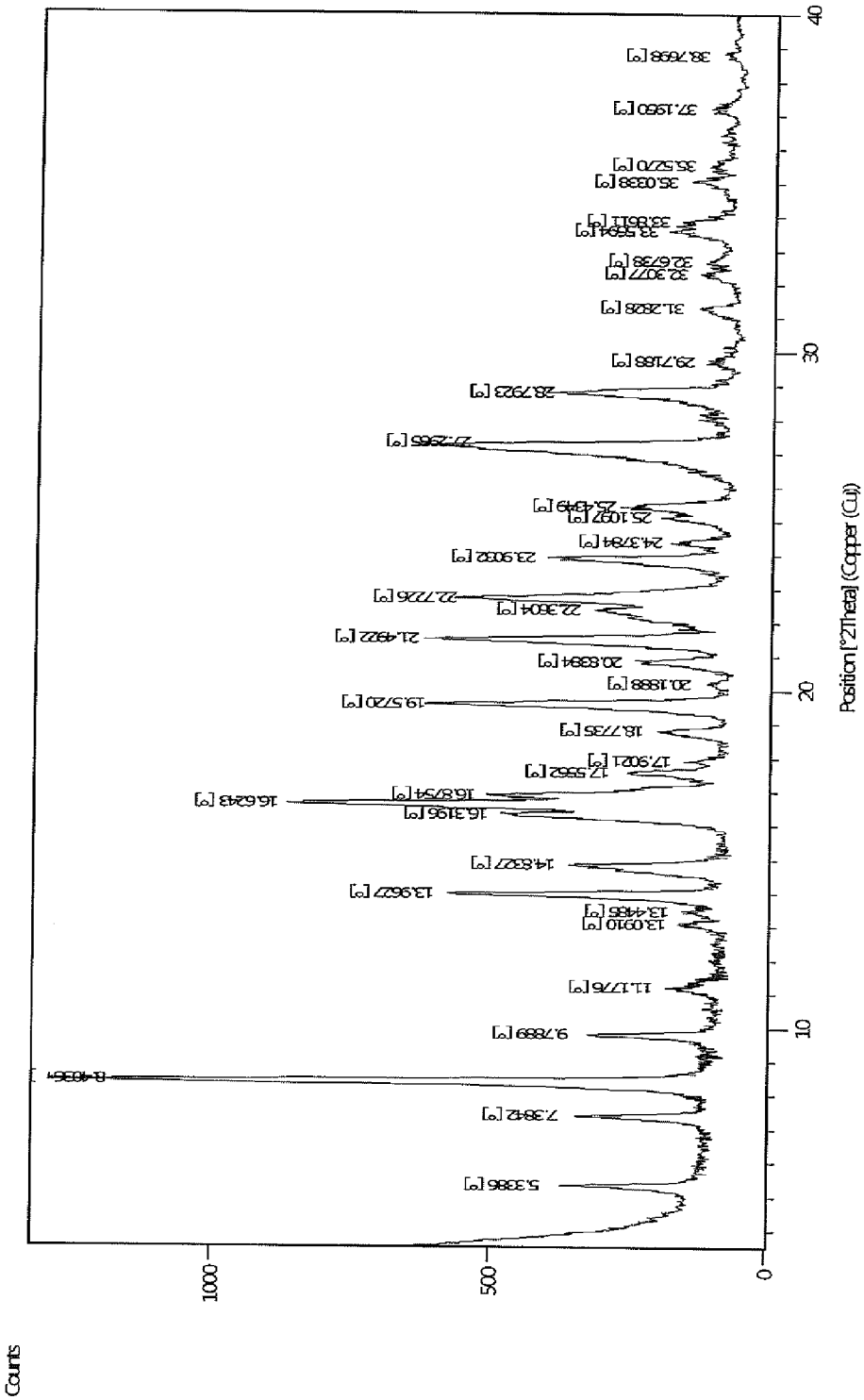
40
60
80
100
120
140
160
180
200
220
240
249.6

Figure 7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14.8327[°]
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17.9021[°]
18.7735[°]
19.5720[°]
20.1888[°]
20.8384[°]
21.4922[°]
22.3604[°]
22.7726[°]
23.9082[°]
24.3784[°]
25.1092[°]
25.4949[°]
27.2665[°]
28.7923[°]
29.7188[°]
31.2828[°]
32.3077[°]
32.6738[°]
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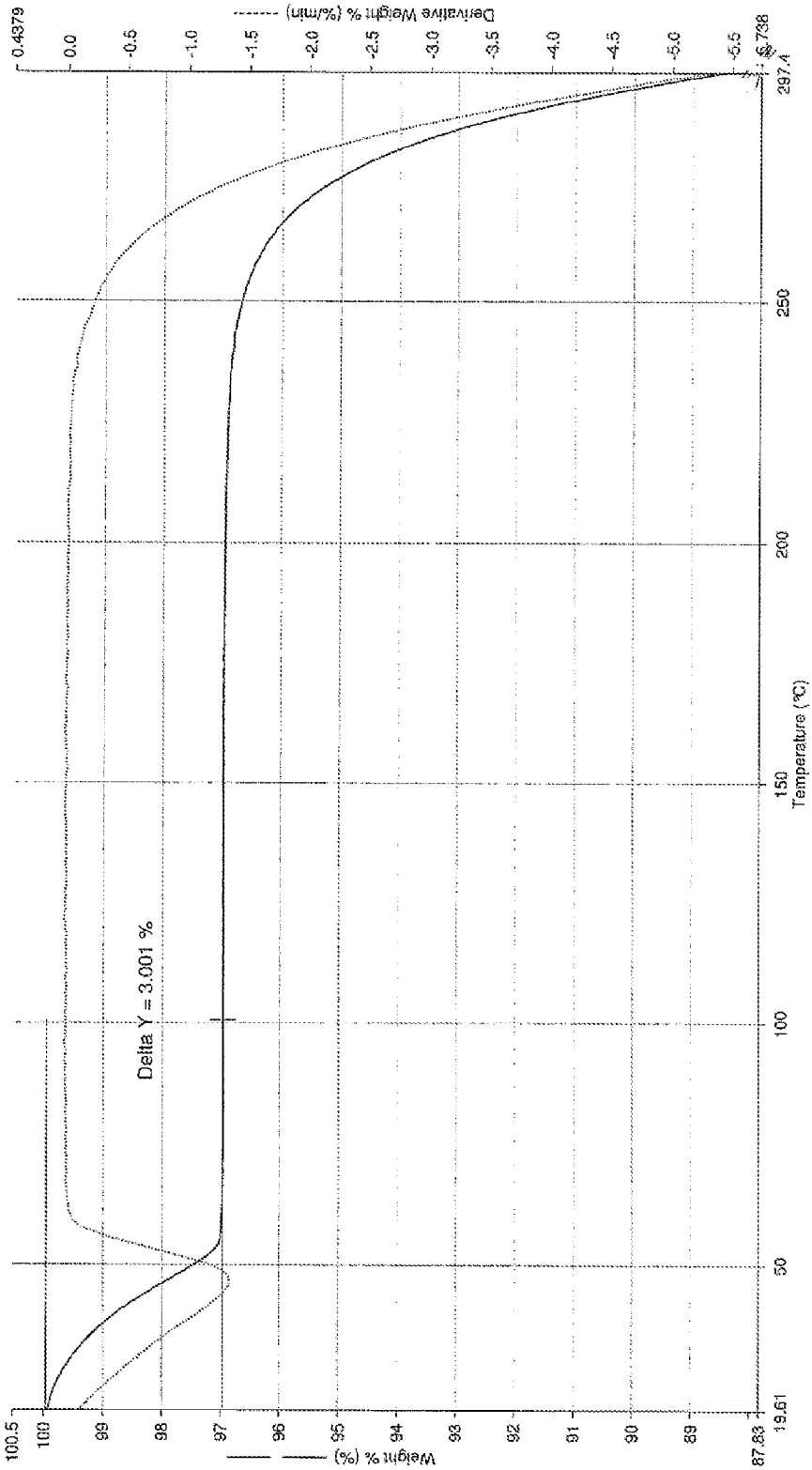
35.5270[°]
37.1960[°]
38.7698[°]

Figure 8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-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.738
297.4
250
200
150
Temperature (°C)
100
50
19.61
Delta Y = 3.001 %
Weight % (%)
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100
99
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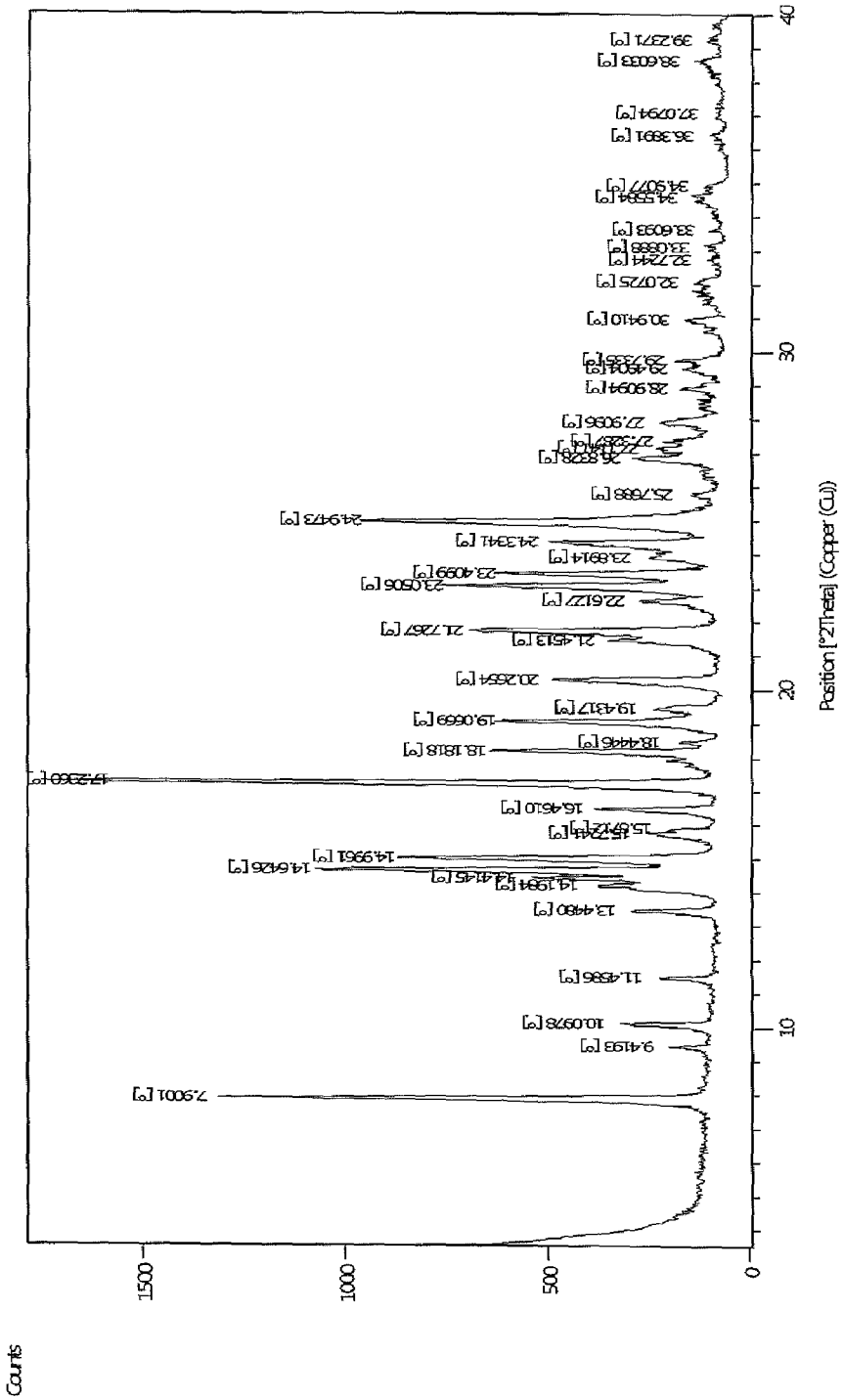
97
96
95
94
93
92
91
90
89
87.83

Figure 9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14.6426 [°]
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15.2244 [°]
15.6742 [°]
16.4610 [°]
17.2360 [°]
18.1818 [°]
18.4446 [°]
19.0669 [°]
19.4317 [°]
20.2554 [°]
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21.7267 [°]
22.6127 [°]
23.0506 [°]
23.4099 [°]
23.8914 [°]
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24.9173 [°]
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32.0725 [°]
32.7244 [°]
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33.6038 [°]
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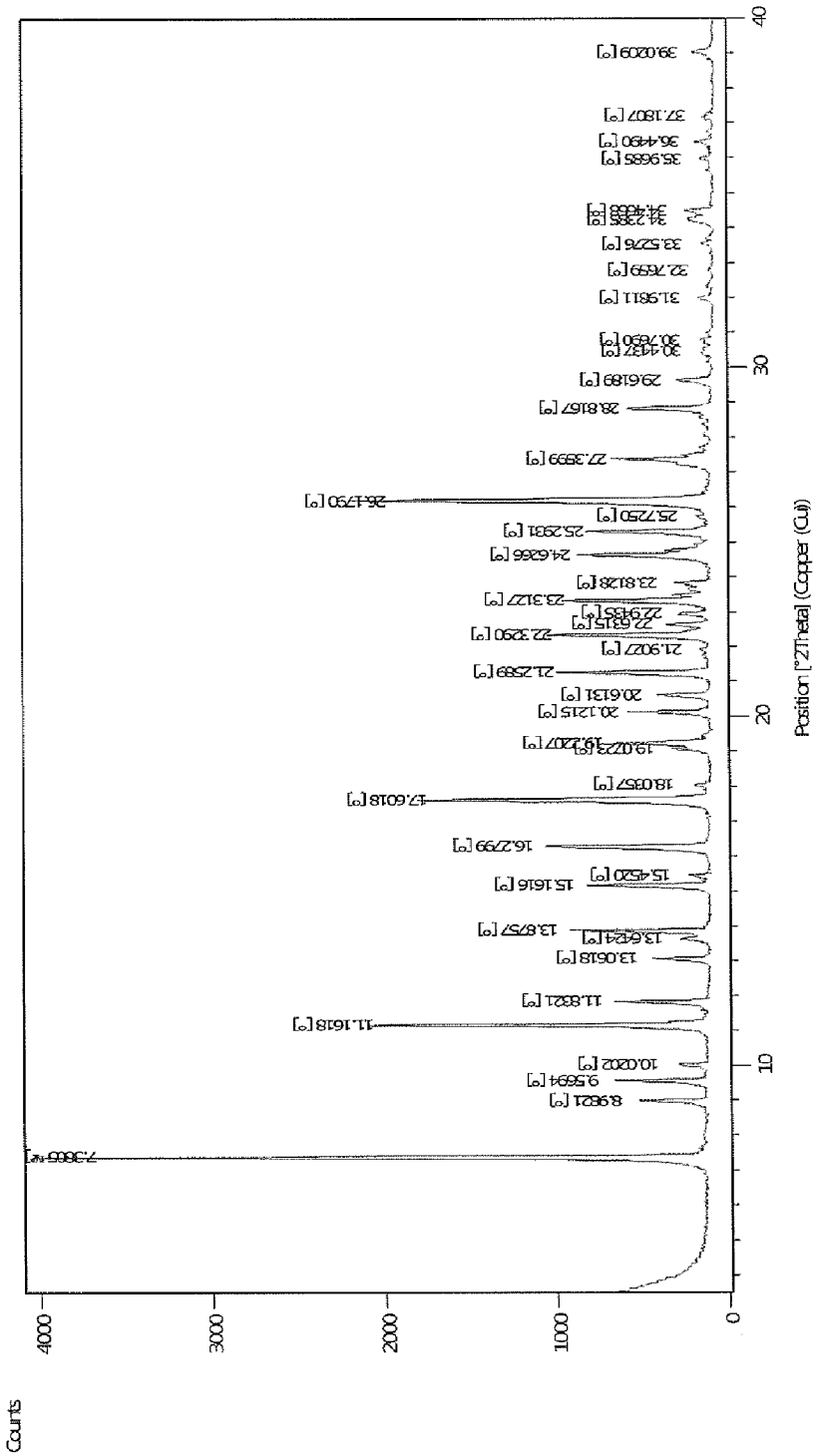
37.0794 [°]
38.6033 [°]
39.2371 [°]

Figure 10


Counts
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2000
1000
0
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30
20
10
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37.1807 [°]
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35.9685 [°]
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34.2385 [°]
33.5276 [°]
32.7659 [°]
31.9611 [°]
30.7650 [°]
30.4437 [°]
29.6189 [°]
28.8167 [°]
27.3999 [°]
26.4750 [°]
25.7250 [°]
25.2931 [°]
24.6266 [°]
23.8128 [°]
23.3127 [°]
22.9485 [°]
22.6815 [°]
22.3290 [°]
21.9027 [°]
21.2589 [°]
20.6131 [°]
20.1215 [°]
19.7207 [°]
19.0223 [°]
18.0357 [°]
17.6018 [°]
16.2799 [°]
15.4520 [°]
15.1616 [°]
13.8757 [°]
13.6424 [°]
13.0618 [°]
11.8321 [°]
11.1618 [°]
10.0202 [°]
9.5694 [°]
8.9821 [°]
7.3669 [°]

Figure 11

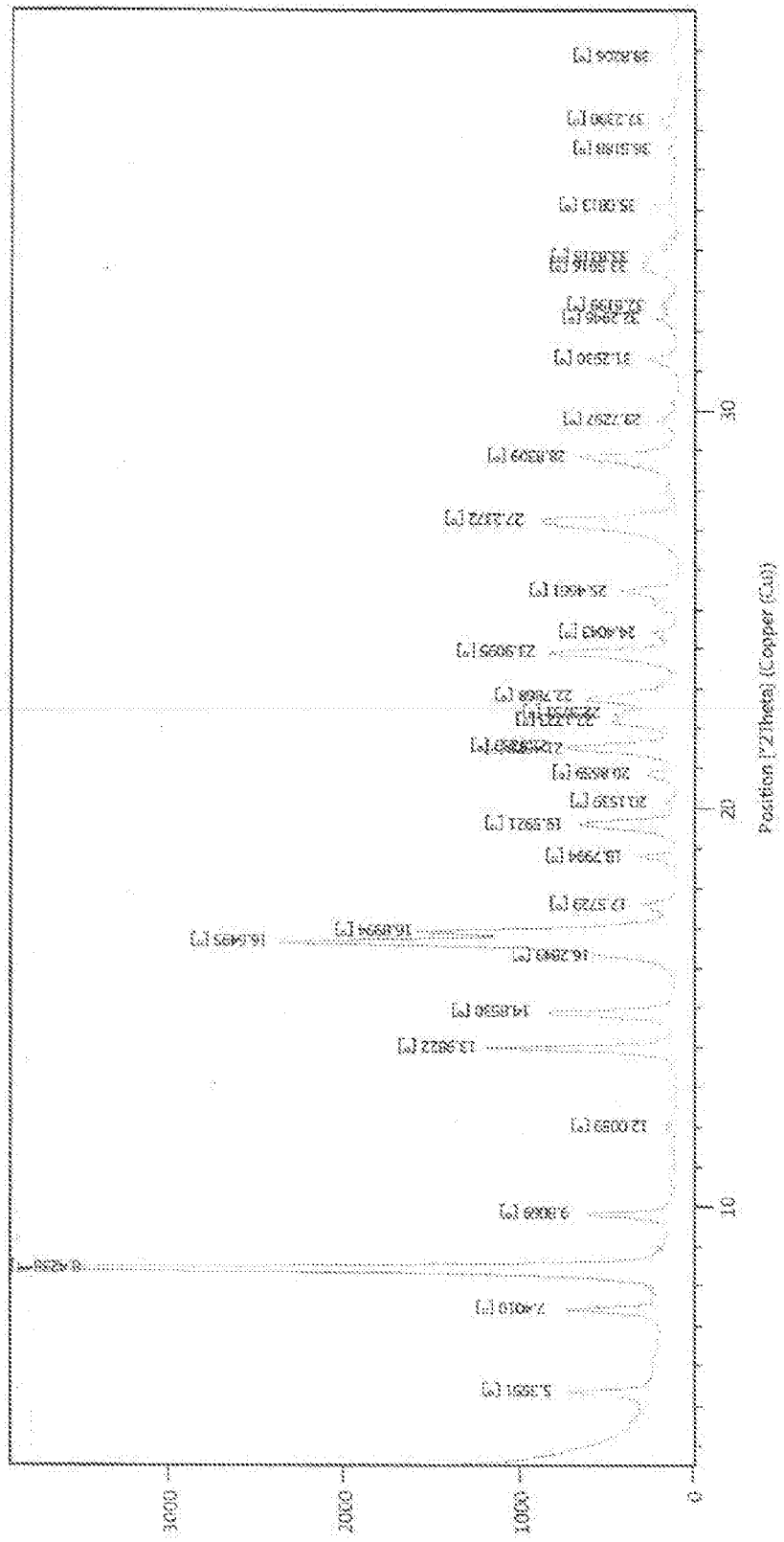
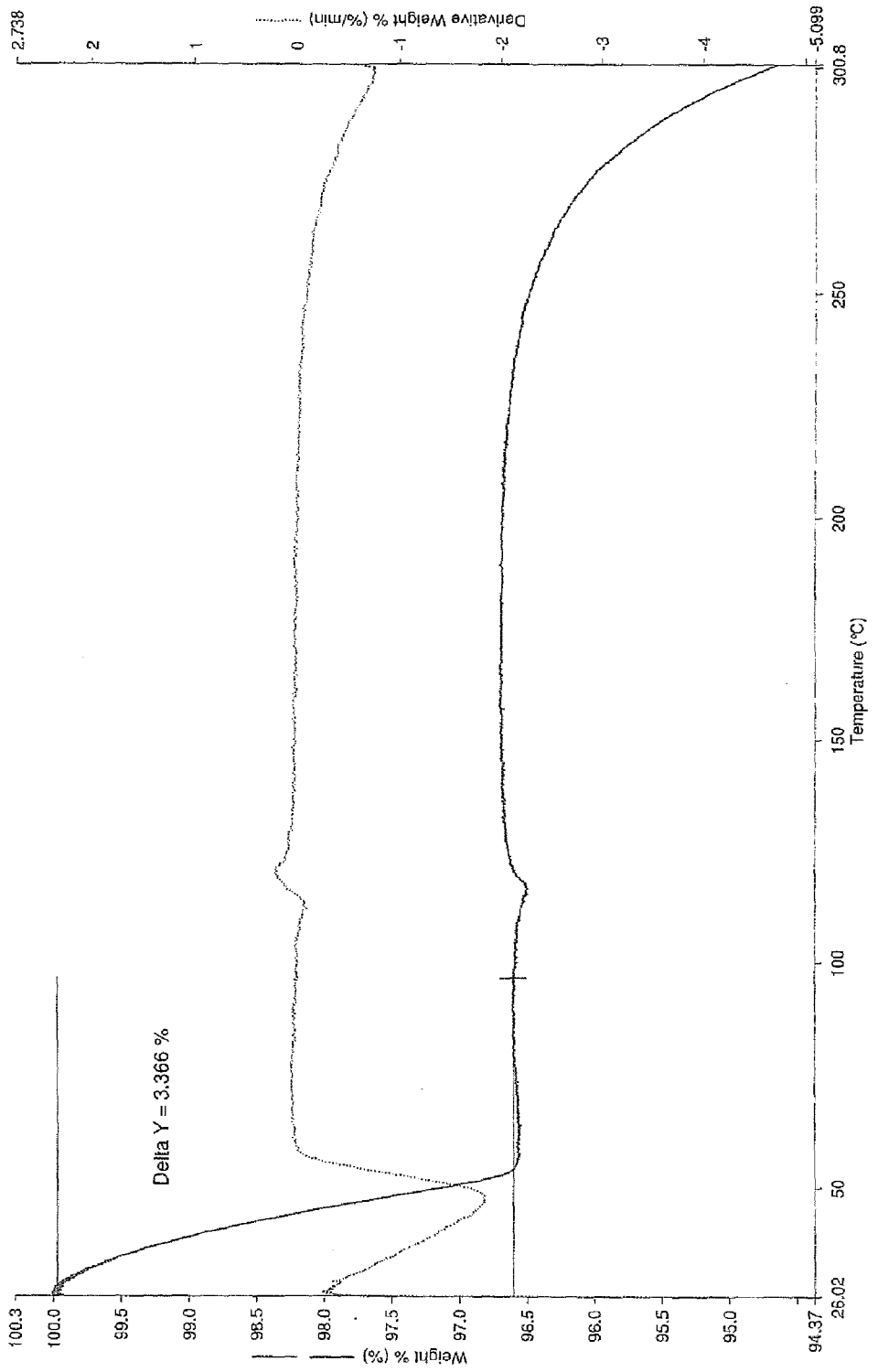


Figure 12


Derivative Weight % (%/min)
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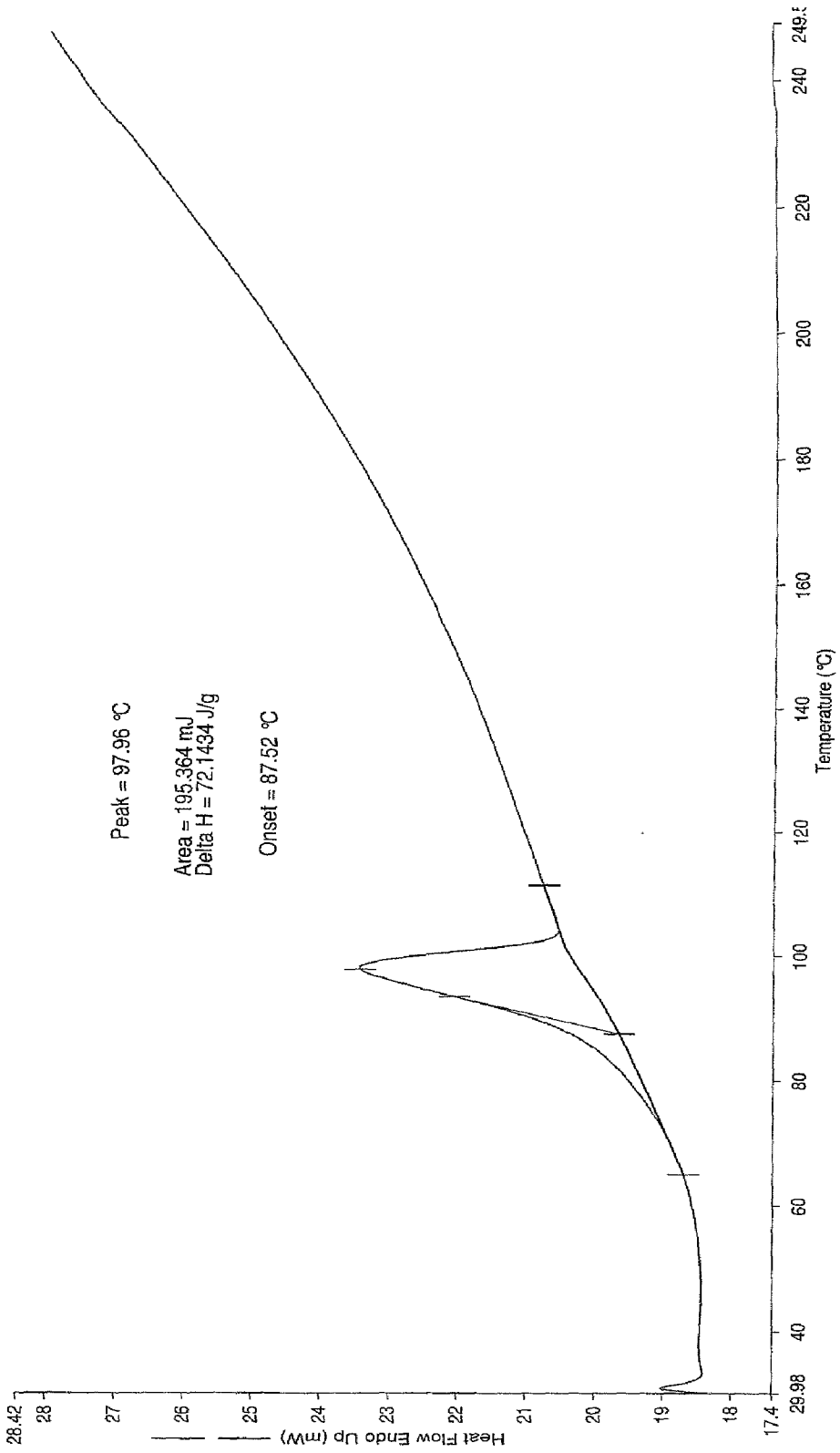
1
0
-1
-2
-3
-4
-5.099
300.8
250
200
150
100
50
26.02
Temperature (°C)
Delta Y = 3.366 %
100.3
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
95.5
95.0
94.37
Weight % (%)

Figure 13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Heat Flow Endo Up (mW)
Temperature (°C)
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17.4
29.98
249.5

Figure 14

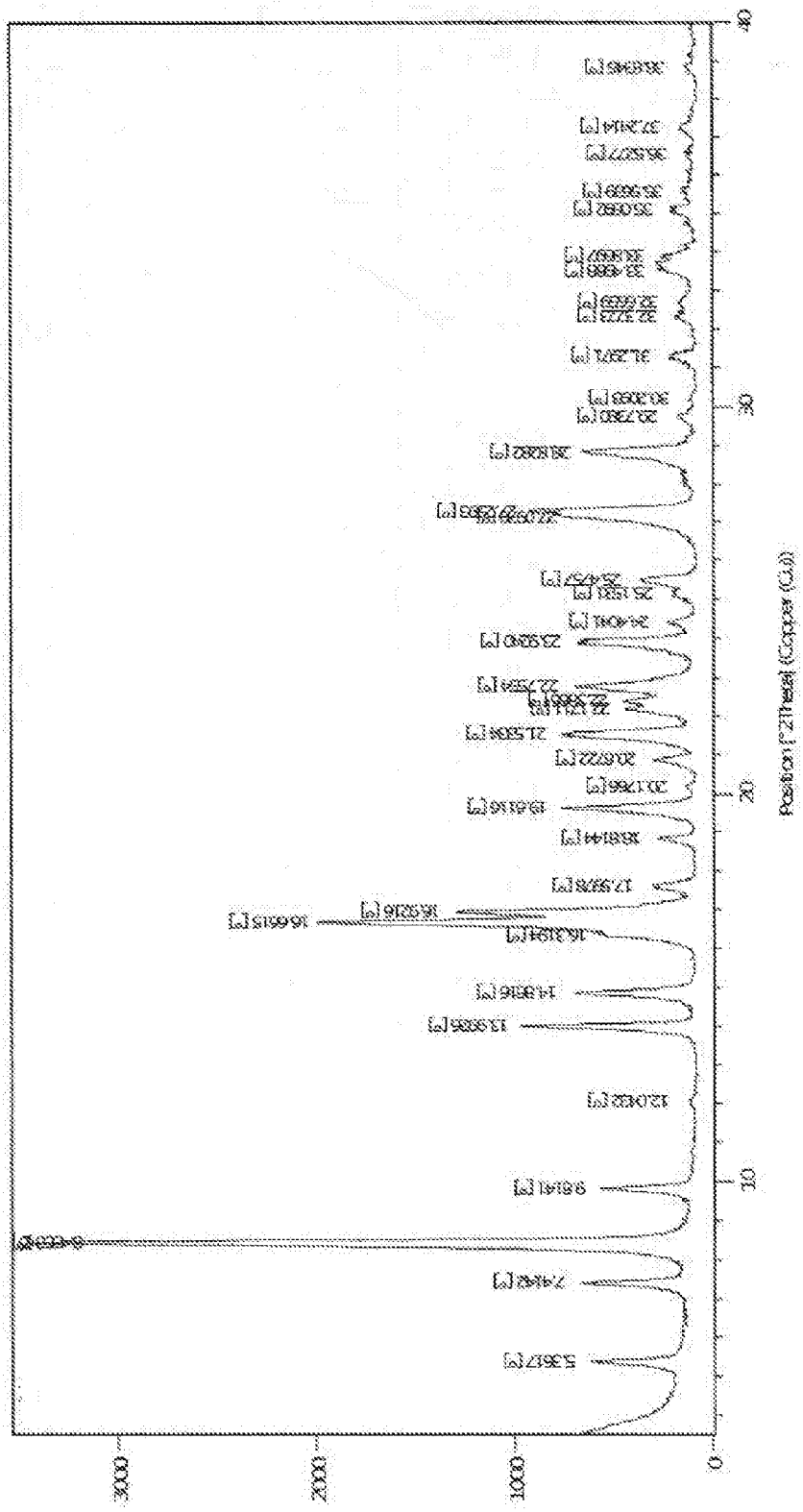

Figure 15

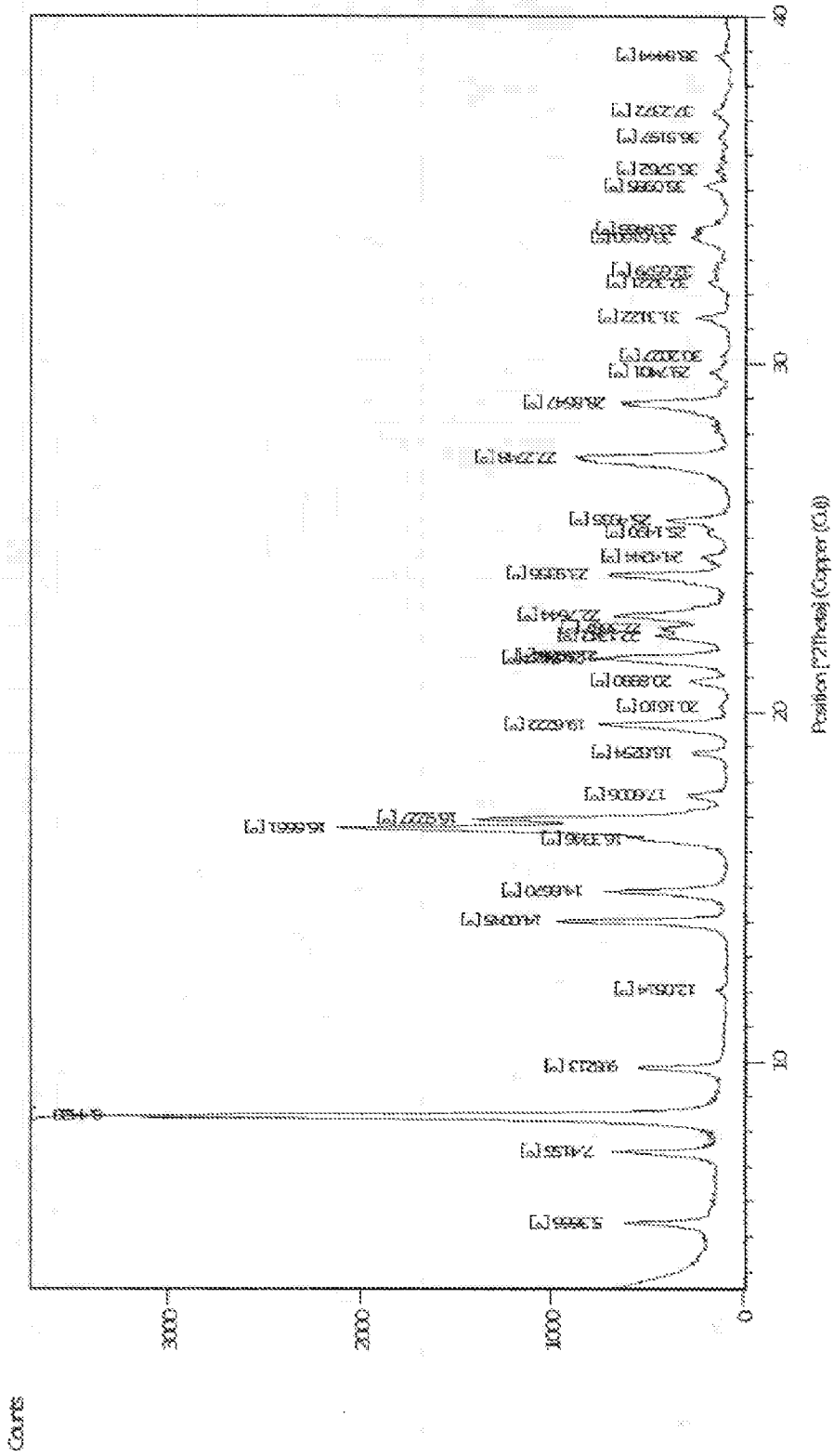

Figure 16

Crystal data of Form M of apremilast

Chemical formula	$C_{22}H_{24}N_2O_7S$, H_2O
Formula Weight	478.52
Temperature (K)	293(2)
Wavelength (Å)	1.5418
Crystal lattice	monoclinic
Space group	$P2_1$
a, b, c [Å]	16.6797(15) 5.7377(5) 12.0688(11)
α, β, γ [°]	90, 99.186(7), 90
V [Å^3]	1140.21(18)
Z	2
D(calc) [g/cm^3]	1.394
Refined parameters	180
No. of background points	25
R_p	0.0233
wR_p	0.0316
$R(F^2)$	0.0753
χ^2	3.663

Figure 17

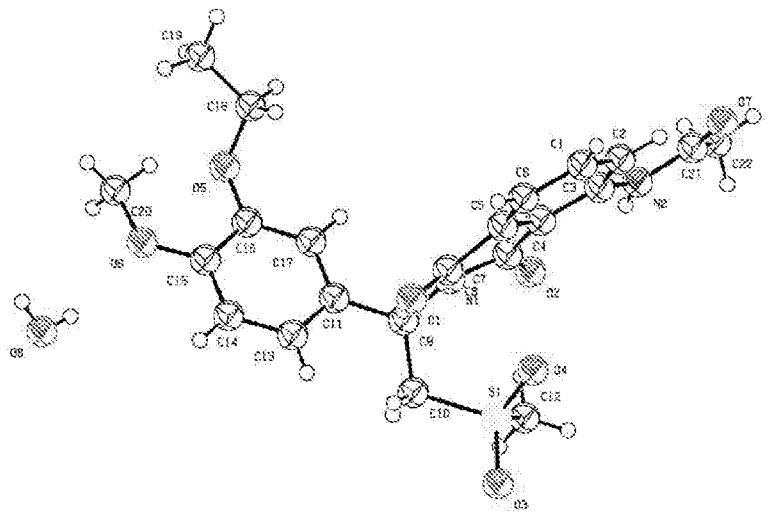

Figure 17A

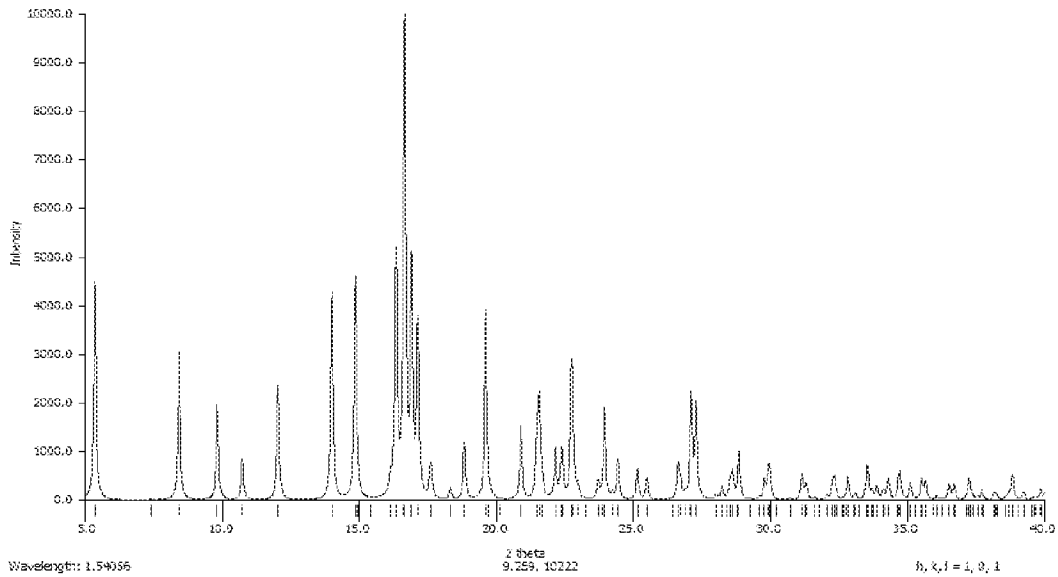

Figure 17B

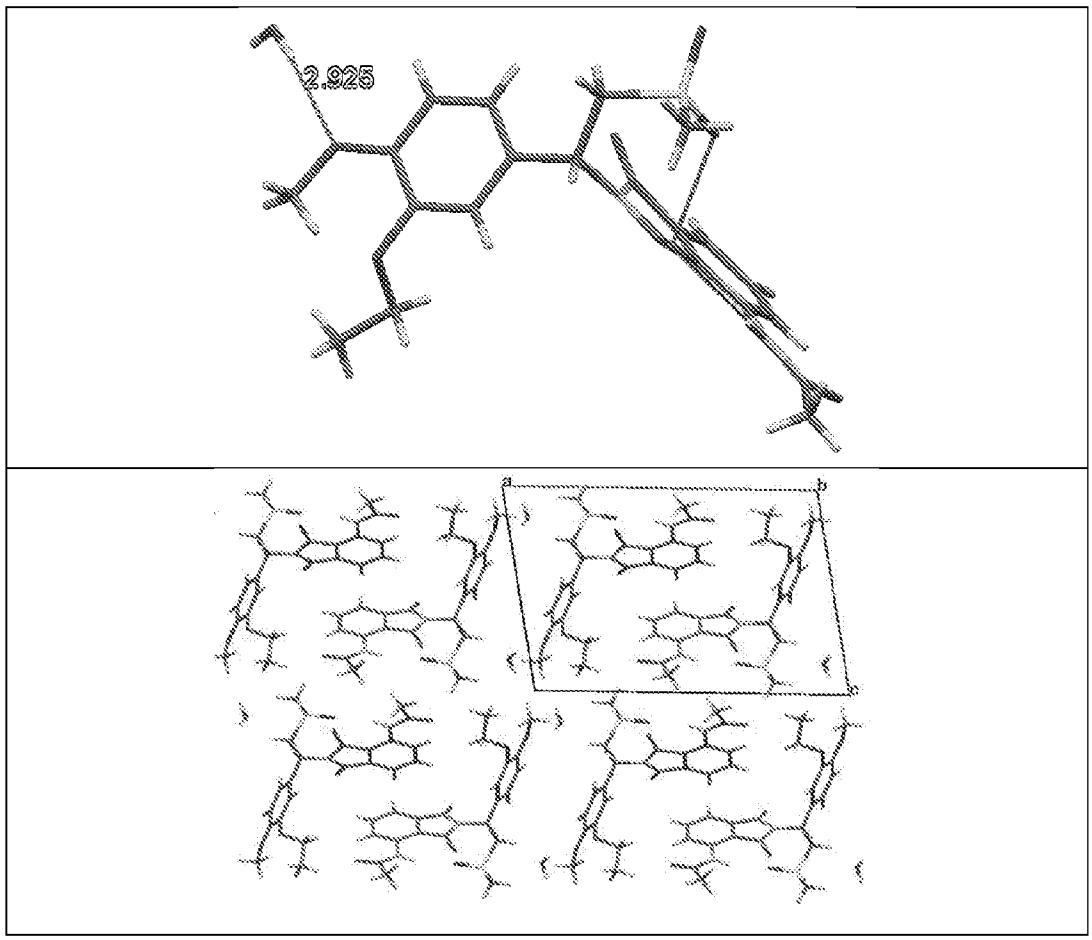

Figure 17C

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053083

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/48 C07C315/04 C07C317/28
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 C07C

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, 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	US 8 242 310 B2 (SAINDANE MANOHAR T [US] ET AL) 14 August 2012 (2012-08-14) cited in the application columns 1,2 column 6, line 59 - column 7, line 34 column 9, line 25 - column 10, line 57 -----	1-4,7
X	US 2013/217919 A1 (CONNOLLY TERRENCE J [US] ET AL) 22 August 2013 (2013-08-22) page 1, paragraph 4 - page 2, paragraph 5; examples 1,3 page 6, paragraph 54 paragraph [0103] -----	1-4,7,8
X	US 7 427 638 B2 (MULLER GEORGE W [US] ET AL) 23 September 2008 (2008-09-23) cited in the application figure 1; example 2 -----	3

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2016	13/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Guspanovā, Jana

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053083

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053083

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-8

   A process for the preparation of compound A and a process for the preparation of apremilast.

   ---

2. claims: 9-16

   A stable crystalline Form M of apremilast, its preparation and a pharmaceutical composition thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053083

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