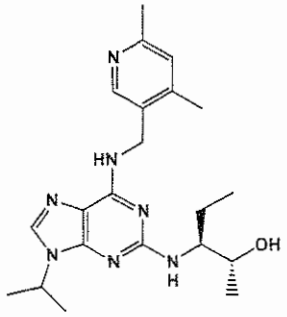
STATEMENT OF INVENTION

In one aspect, there is provided a crystalline form of compound (I),



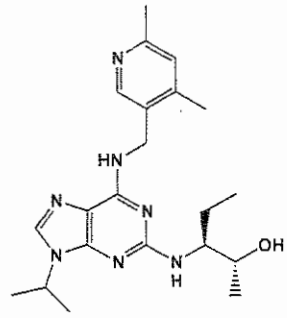
(I)

wherein said compound is in the form of an L-tartrate salt or a pharmaceutically acceptable solvate thereof, and is characterized by:

(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 6.67 ± 0.2, 8.237± 0.2, 9.777 ± 0.2, 11.96 ± 0.2, 12.38 ± 0.2, 13.06 ± 0.2, 13.38 ± 0.2, 13.94 ± 0.2, 14.90 ± 0.2, 15.40 ± 0.2, 15.95 ± 0.2, 16.27 ± 0.2, 16.54 ± 0.2, 17.36 ± 0.2, 17.57 ± 0.2, 17.86 ± 0.2, 19.64 ± 0.2, 19.86 ± 0.2, 20.12 ± 0.2, 20.73 ± 0.2, 21.14 ± 0.2, 21.58 ± 0.2, 22.57 ± 0.2, 22.95 ± 0.2, 23.29 ± 0.2, 23.57 ± 0.2, 24.07 ± 0.2, 24.63 ± 0.2, 25.30 ± 0.2, 26.38 ± 0.2, 27.09 ± 0.2, 27.67 ± 0.2, 27.97 ± 0.2, 28.91 ± 0.2, 29.28 ± 0.2, 30.08 ± 0.2, 30.41 ± 0.2, 31.90 ± 0.2 and 34.49 ± 0.2 (Form E) when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 6.67 ± 0.2, 13.06 ± 0.2, 13.38 ± 0.2, 14.90 ± 0.2, 17.36 ± 0.2, 17.57 ± 0.2, 19.64 ± 0.2, 20.73 ± 0.2, 23.57 ± 0.2 and 25.30 ± 0.2 (Form E); or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 20°C per minute which shows a maximum endothermic peak at a temperature between 176°C and 185°C.

In another aspect, there is provided a crystalline form of compound (I),



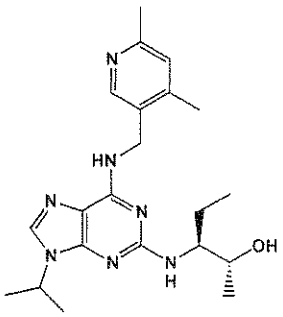
(I)

wherein said compound is in the form of an L-tartrate salt or a pharmaceutically acceptable solvate thereof, and is characterized by:

(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 3.82 ± 0.2, 7.57 ± 0.2, 8.12 ± 0.2, 10.53 ± 0.2, 11.39 ± 0.2, 12.00 ± 0.2, 13.54 ± 0.2, 15.15 ± 0.2, 16.35 ± 0.2, 16.88 ± 0.2, 17.37 ± 0.2, 18.51 ± 0.2, 18.98 ± 0.2, 19.77± 0.2, 21.06 ± 0.2, 22.70 ± 0.2, 23.47 ± 0.2, 24.66 ± 0.2 and 28.73 ± 0.2 [Form D] when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 3.82 ± 0.2, 7.57 ± 0.2, 15.15 ± 0.2, 16.88 ± 0.2, 19.77± 0.2, 22.70 ± 0.2, 23.47 ± 0.2, 24.66 ± 0.2 and 28.73 ± 0.2 [Form D]; or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows a maximum endothermic peak at a temperature between 145°C and 154°C.

In yet another aspect, there is provided a crystalline form of compound (I),



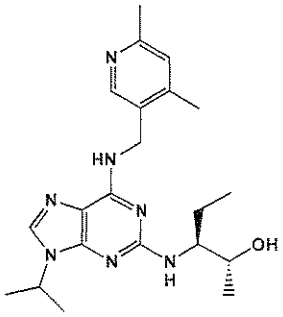
(I)

wherein said compound is in the form of a citrate salt or a pharmaceutically acceptable solvate thereof, and is characterized by:

(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 5.14 ± 0.2, 7.73 ± 0.2, 10.24 ± 0.2, 12.70 ± 0.2, 13.06 ± 0.2, 14.42 ± 0.2, 15.30 ± 0.2, 15.98 ± 0.2, 16.74 ± 0.2, 17.24 ± 0.2, 18.05 ± 0.2, 19.04 ± 0.2, 20.23 ± 0.2, 21.04 ± 0.2, 22.45 ± 0.2, 22.75 ± 0.2, 24.01 ± 0.2, 25.43 ± 0.2, 26.51 ± 0.2, 27.48 ± 0.2, 28.77 ± 0.2 and 29.71 ± 0.2 [Form F] when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 17.24 ± 0.2, 18.05 ± 0.2, 19.04 ± 0.2, 22.45 ± 0.2, 22.75 ± 0.2, 24.01 ± 0.2 and 25.43 ± 0.2 [Form F]; or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows maximum endothermic peaks at a temperature between 145°C and 155°C and between 165 °C and 200°C.

In yet another aspect, there is provided a crystalline form of compound (I),



(I)

wherein said compound is in the form of a phosphate salt or a pharmaceutically acceptable solvate thereof, and is characterized by:

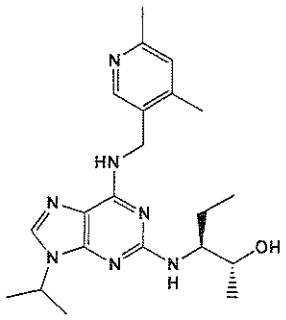
(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 6.46 ± 0.2, 8.88 ± 0.2, 9.67 ± 0.2, 10.47 ± 0.2, 12.78 ± 0.2, 15.33 ± 0.2, 16.12 ± 0.2, 16.82 ± 0.2, 18.13 ± 0.2, 19.38 ± 0.2, 19.95 ± 0.2, 20.97 ± 0.2, 24.11 ± 0.2, 24.83 ± 0.2, 26.54 ± 0.2 and 28.11 ± 0.2 [Form B] when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 6.46 ± 0.2, 16.12 ± 0.2, 18.13 ± 0.2, 19.38 ± 0.2, 19.95 ± 0.2, 20.97 ± 0.2, 24.11 ± 0.2 and 24.83 ± 0.2 [Form B]; or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows maximum endothermic peaks at a temperature between 65°C and 90°C and between 114°C and 130°C; or

(iii) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 6.49 ± 0.2, 8.91 ± 0.2, 9.75 ± 0.2, 10.52 ± 0.2, 13.03 ± 0.2, 15.44 ± 0.2, 16.27 ± 0.2, 17.85 ± 0.2, 18.29 ± 0.2, 19.52 ± 0.2, 20.02 ± 0.2, 21.11 ± 0.2, 22.80 ± 0.2, 24.92 ± 0.2, 28.33 ± 0.2 and 29.41 ± 0.2 [Form C] when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 6.49 ± 0.2, 16.27 ± 0.2, 18.29 ± 0.2, 19.52 ± 0.2, 20.02 ± 0.2, 21.11 ± 0.2, 22.80 ± 0.2, 24.92 ± 0.2 and 29.41 ± 0.2 [Form C]; or

(iv) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows maximum endothermic peaks at a temperature between 66°C and 90°C and between 120°C and 135°C.

In yet another aspect, there is provided a crystalline form of compound (I),



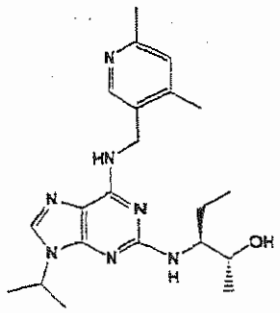
(I)

wherein said compound is in the form of a fumarate salt or a pharmaceutically acceptable solvate thereof, and is characterized by:

(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 3.8 ± 0.2, 7.7 ± 0.2, 8.1 ± 0.2, 8.8 ± 0.2, 10.2 ± 0.2, 11.3 ± 0.2, 13.1 ± 0.2, 15.2 ± 0.2, 15.5 ± 0.2, 16.5 ± 0.2, 17.7 ± 0.2, 19.1 ± 0.2, 19.6 ± 0.2, 20.0 ± 0.2, 20.9 ± 0.2, 21.5 ± 0.2, 21.9 ± 0.2, 22.7 ± 0.2, 23.2 ± 0.2, 23.8 ± 0.2, 24.1 ± 0.2, 25.0 ± 0.2, 25.3 ± 0.2, 26.7 ± 0.2, 27.9 ± 0.2 and 28.9 ± 0.2 [Form P] when using Cu Kα radiation and a scan speed of 0.146°/s; or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows a maximum endothermic peak at a temperature of about 140°C, or a differential scanning calorimetry trace substantially in accordance with Figure 33.

Disclosed isA first aspect of the invention relates to a crystalline form of compound (I),



(I)

wherein said compound is in the form of the free base or a pharmaceutically acceptable salt thereof, or a solvated form of the free base or salt form thereof.

The crystalline forms of the invention typically demonstrate one or more improved properties over the amorphous form. Suitable properties include, for example, better storage stability, improved ease of handling (flowability, compressibility, stability), easier purification, and easier synthetic scale up

In yet anotherA second aspect, there is provided of the invention relates to a pharmaceutical composition comprising a crystalline form as described above as an active ingredient and a pharmaceutically acceptable diluent, excipient or carrier.

In yet anotherA third aspect of the invention relates to, there is provided a crystalline form as described above for use in medicine.

In yet anotherA fourth aspect of the invention relates to, there is provided a crystalline form as described above for use in the prevention or treatment of proliferative disorders, immune-mediated and inflammatory disorders, autoimmune and autoimmune-mediated disorders, kidney disorders, cardiovascular disorders, ophthalmic disorders, neurodegenerative disorders, psychiatric disorders, viral disorders, metabolic disorders and/or respiratory disorders.

Also disclosed is theA fifth aspect of the invention relates to use of a crystalline form as described above in the preparation of a medicament for the prevention or treatment of proliferative disorders, immune-mediated and inflammatory disorders, autoimmune and autoimmune-mediated disorders, kidney disorders, cardiovascular disorders, ophthalmic disorders,

neurodegenerative disorders, psychiatric disorders, viral disorders, metabolic disorders and/or respiratory disorders.

Also disclosed is ~~A sixth aspect of the invention relates to~~ a method for the prevention or treatment of proliferative disorders, immune-mediated and inflammatory disorders, autoimmune and autoimmune-mediated disorders, kidney disorders, cardiovascular disorders, ophthalmic disorders, neurodegenerative disorders, psychiatric disorders, viral disorders, metabolic disorders and/or respiratory disorders, said method comprising administering a pharmacologically effective amount of a crystalline form as described above to a subject in need thereof.

Also disclosed are ~~A seventh aspect of the invention relates to~~ processes for preparing crystalline forms as described above.

In yet another aspect, there is provided a process for preparing a crystalline L-tartrate salt (Form D) of compound (I) as defined above which comprises the steps of:

(i) preparing a reaction mixture comprising compound (I) in free base form, L-tartaric acid and ethyl acetate; and

(ii) isolating the crystalline L-tartrate salt (Form D) from the reaction mixture.

In yet another aspect, there is provided a process for preparing a crystalline L-tartrate salt (Form E) of compound (I) as defined above which comprises the steps of:

(A) (i) preparing a reaction mixture comprising compound (I) in free base form, L-tartaric acid, ethanol and water; and

(ii) isolating the crystalline L-tartrate salt (Form E) from the reaction mixture;

or

(B) (i) preparing a reaction mixture comprising compound (I) in free base form, L-tartaric acid and ethyl acetate; and

(ii) isolating the crystalline L-tartrate salt (Form D) from the reaction mixture; and

(iii) recrystallizing the crystalline L-tartrate salt (Form D) obtained in step (B)(ii) from a mixture of ethanol and acetonitrile; and

(iv) isolating the crystalline L-tartrate salt (Form E) from the reaction mixture;

or

(C) (i) preparing crystalline L-tartrate salt (Form D) by the process as defined above;

(ii) preparing crystalline L-tartrate salt (Form E) by the process of steps (A)(i)-(ii) or B(i)-(iv) above;

(iii) forming a slurry of L-tartrate salt (Form D) and L-tartrate salt (Form E) in a solvent selected from ethyl acetate, propan-2-ol, IMS and acetonitrile; and

(iv) isolating the crystalline L-tartrate salt (Form E) from the slurry; or

(D) (i) preparing crystalline L-tartrate salt (Form D) by the process as defined above;

(ii) preparing crystalline L-tartrate salt (Form E) by the process of steps (A)(i)-(ii) or B(i)-(iv) above;

(iii) dissolving the crystalline L-tartrate salt (Form D) obtained in step (D)(i) in a mixture of ethanol and acetonitrile and seeding with crystalline L-tartrate salt (Form E); and

(iv) isolating the crystalline L-tartrate salt (Form E) from the reaction mixture; or

(E) (i) preparing a reaction mixture comprising free base compound (I) in ethanol;

(ii) adding solution of tartaric acid in water/ethanol to the reaction mixture obtained in step (E)(i);

(iii) filtering the reaction mixture formed in step (E)(ii);

(iv) seeding the filtrate with crystalline L-tartrate salt (Form E) prepared in accordance with steps (A)(i)-(ii), (B)(i)-(iv) or (C)(i)-(iv) above; and

(v) isolating crystalline L-tartrate salt (Form E) from the reaction mixture.

DETAILED DESCRIPTION

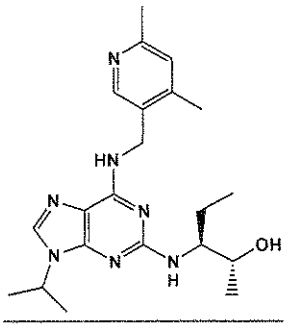
The crystalline forms of the invention may be characterised by a range of different analytical techniques, including x-ray powder diffraction and differential scanning calorimetry. Further details of these techniques and equipment are set forth in the accompanying examples section.

As used herein, the term "solvate" or "solvated form" refers to a crystal having one or more molecules of solvent associated therewith as an inherent part of the crystal structure. Preferably, the solvate or solvated form is the hydrate.

In general, different plural crystalline forms (polymorphs) of the same compound can be produced by varying the crystallisation conditions used. These different crystalline forms have different three-dimensional structures and different physicochemical properties. However, the existence of polymorphs is inherently unpredictable and theoretical calculations to predict polymorphs are extremely unreliable, with many more polymorphs predicted than can actually be isolated in practice.

Preferably, the crystalline forms of the invention are at least 95 % pure (in terms of the purity of the crystal form), more preferably, at least 97 % pure, even more preferably, at least 98 or 99 % pure (for example, as analysed by HPLC). More preferably still, the crystalline forms of the invention are at least 99.5 % pure.

2. A crystalline form of compound (I),



(I)

wherein said compound is in the form of an L-tartrate salt or a pharmaceutically acceptable solvate thereof, and ~~The crystalline form of claim 1 which~~ is characterized by:

(i) an x-ray powder diffraction pattern having two or more diffraction peaks at 2[theta] values selected from 3.82 ± 0.2, 7.57 ± 0.2, 8.12 ± 0.2, 10.53 ± 0.2, 11.39 ± 0.2, 12.00 ± 0.2, 13.54 ± 0.2, 15.15 ± 0.2, 16.35 ± 0.2, 16.88 ± 0.2, 17.37 ± 0.2, 18.51 ± 0.2, 18.98 ± 0.2, 19.77± 0.2, 21.06 ± 0.2, 22.70 ± 0.2, 23.47 ± 0.2, 24.66 ± 0.2 and 28.73 ± 0.2 [Form D] when using Cu Kα radiation and a scan speed of 0.146°/s, more preferably having two or more diffraction peaks at 2[theta] values selected from 3.82 ± 0.2, 7.57 ± 0.2, 15.15 ± 0.2, 16.88 ± 0.2, 19.77± 0.2, 22.70 ± 0.2, 23.47 ± 0.2, 24.66 ± 0.2 and 28.73 ± 0.2 [Form D]; or

(ii) a differential scanning calorimetry trace recorded at a heating rate of 10°C per minute which shows a maximum endothermic peak at a temperature between 145°C and 154°C.

(iii) recrystallizing the crystalline L-tartrate salt (Form D) obtained in step (B)(ii) from a mixture of ethanol and acetonitrile; and

(iv) isolating the crystalline L-tartrate salt (Form E) from the reaction mixture; or

(C) (i) preparing crystalline L-tartrate salt (Form D) by the process of claim ~~209~~9;

(ii) preparing crystalline L-tartrate salt (Form E) by the process of steps (A)(i)-(ii) or B(i)-(iv) above;

(iii) forming a slurry of L-tartrate salt (Form D) and L-tartrate salt (Form E) in a solvent selected from ethyl acetate, propan-2-ol, IMS and acetonitrile; and

(iv) isolating the crystalline L-tartrate salt (Form E) from the slurry; or

(D) (i) preparing crystalline L-tartrate salt (Form D) by the process of claim ~~209~~9;

(ii) preparing crystalline L-tartrate salt (Form E) by the process of steps (A)(i)-(ii) or B(i)-(iv) above;

(iii) dissolving the crystalline L-tartrate salt (Form D) obtained in step (D)(i) in a mixture of ethanol and acetonitrile and seeding with crystalline L-tartrate salt (Form E); and

(iv) isolating the crystalline L-tartrate salt (Form E) from the reaction mixture; or

(E) (i) preparing a reaction mixture comprising free base compound (I) in ethanol;

(ii) adding solution of tartaric acid in water/ethanol to the reaction mixture obtained in step (E)(i);

(iii) filtering the reaction mixture formed in step (E)(ii);

(iv) seeding the filtrate with crystalline L-tartrate salt (Form E) prepared in accordance with steps (A)(i)-(ii), (B)(i)-(iv) or (C)(i)-(iv) above; and

(iv) isolating crystalline L-tartrate salt (Form E) from the reaction mixture.