POLYMORPHS OF BENDAMUSTINE HCL AND PROCESSES FOR PREPARATION THEREOF

Novel polymorphs of Bendamustine HCl have been prepared and characterized. These polymorphs and pharmaceutical compositions containing them are useful, for example, in treating patients with various cancers.
POLYMORPHS OF BENDAMUSTINE HCL
AND PROCESSES FOR PREPARATION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial Nos. 61/185,646, filed June 10, 2009; 61/221,272, filed June 29, 2009; 61/244,122, filed September 21, 2009; 61/245,375, filed September 24, 2009; 61/302,356, filed February 8, 2010, which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to polymorphs of Bendamustine HCl, processes for preparing said polymorphs, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

[0003] Bendamustine HCl, 4-{5-[Bis(2-chloroethyl)amino]-l-methyl-lH-benimidazol-2-yl}butanoic acid HCl, having the following formula I, belongs to the family of drugs named alkylating agents. Bendamustine HCl (BEM) of formula I

\[
\begin{align*}
\text{Cl} & \text{C} & \text{N} \\
\text{Cl} & \text{C} & \text{N} & \text{H} \\
\text{N} & \text{C} & \text{H} & \text{Cl} \\
\text{O} & \text{C} & \text{Cl} & \text{OH} \\
\end{align*}
\]

Formula I

is used in the treatment of leukemia, chronic lymphocytic leukemia (CLL) and also being studied for the treatment of sarcoma. One of the advantages of Bendamustine HCl is that it is not cross resistant with other alkylating agents.

[0004] Bendamustine HCl received first marketing approval in Germany under the trade name Ribomustin, by Astellas Pharma GmbH's licensee, Mundipharma International Corporation Limited, in which it is indicated as a single-agent or in
combination with other anticancer agents for indolent Non-Hodgkin's Lymphoma and multiple myeloma, as well as CLL.

[0005] DD 34727 discloses synthesis of Bendamustine HCl from 4-nitro-2-amino-N-methylaniline, and the recrystallization of the product from water. US 2006/159713, US 2006/128777 and WO 2010036702 disclose formulations of Bendamustine HCl. These patent applications also include impurities of bendamustine.

[0006] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Bendamustine HCl, 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 Bendamustine HCl.

**SUMMARY OF THE INVENTION**

[0008] In one embodiment, the present invention encompasses a crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof.
In yet another embodiment, the present invention provides a process for preparing Bendamustine HCl characterized by data selected from the group consisting of:

a powder XRD pattern with peaks at 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4, a solid-state $^{13}$C NMR spectrum having signals at 150.3 and 130.8 ± 0.2 ppm; a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift (at 109.6 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of 40.7 and 21.2 ± 0.1 ppm; and a combination thereof, by preparing the above Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof according to the process of the present invention, and converting it to Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4, a solid-state $^{13}$C NMR spectrum having signals at 150.3 and 130.8 ± 0.2 ppm; a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift (at 109.6 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of 40.7 and 21.2 ± 0.1 ppm; and a combination thereof.

In one embodiment, the present invention refers to the use of the above described polymorphic form of Bendamustine HCl for the preparation of a formulation.

In yet another embodiment, the present invention refers to a pharmaceutical composition comprising polymorphic form of Bendamustine HCl and at least one pharmaceutically acceptable excipient.

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 shows a powder XRD pattern of crystalline Bendamustine HCl form A.

Figure 2 shows a DSC thermogram of crystalline Bendamustine HCl form A.
Figure 3 shows a TGA thermogram of crystalline Bendamustine HCl form A.

Figure 4 shows a powder XRD pattern of crystalline Bendamustine HCl form B (the peak marked with "Si" belongs to silicon internal standard).

Figure 5 shows a powder XRD pattern of crystalline Bendamustine HCl form C (the peak marked with "Si" belongs to silicon internal standard).

Figure 6 shows a full-width solid state $^{13}$C NMR spectrum of Bendamustine HCl form A.

Figure 7 shows a detailed solid state $^{13}$C NMR spectrum of Bendamustine HCl form A.

Figure 8 shows a full-width solid state $^{13}$C NMR spectrum of Bendamustine HCl form B.

Figure 9 shows a detailed solid state $^{13}$C NMR spectrum of Bendamustine HCl form B.

Figure 10 shows a powder XRD pattern of crystalline Bendamustine HCl form D (the peak marked with "Si" belongs to silicon internal standard; the amorphous bump is a result of presence of n-dodecane used for sample preparation).

Figure 11 shows a powder XRD pattern of crystalline Bendamustine HCl form E (the peak marked with "Si" belongs to silicon internal standard; the amorphous bump is a result of presence of n-dodecane used for sample preparation).

Figure 12 shows a powder XRD pattern of crystalline Bendamustine HCl form F (the peak marked with "Si" belongs to silicon internal standard; the amorphous bump is a result of presence of n-dodecane used for sample preparation).

Figure 13 illustrates an optical microscope photo of Bendamustine HCl form E.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to polymorphs of Bendamustine HCl process for preparing said polymorphs, and pharmaceutical compositions thereof.

A thing, e.g., a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature.” This expression means that the temperature
of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room temperature is from about 20° C to about 30° C, or about 25° C.

[0027] A process or portion thereof may be referred to herein as being carried out "overnight." This term refers to a time interval, *e.g.*, for carrying out the process portion thereof, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, typically about 16 hours.

[0028] A crystal form may be referred to herein as being characterized by graphical data substantially "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 graphical data are characterizing the same crystal form or two different crystal forms.

[0029] In one embodiment, the present invention encompasses a crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof. This form can be designated as form E.

[0030] The above crystalline form of Bendamustine HCl designated Form E may be further characterized by data selected from the group consisting of: a powder XRD pattern with additional peaks at 9.9, 13.3, 19.7, 19.9 and 26.0 ± 0.1 degrees 2-theta.

[0031] The above crystalline Bendamustine HCl form E is a formamide solvate.

[0032] Also, the crystalline Bendamustine HCl creates columnar particles of length between about 50 and 80 µm, which distinguishes it from all other forms of Bendamustine HCl as shown in Fig. 13. Therefore, it is expected to have an excellent flowability. Thus, this form is exceptionally attractive for formulations.
Preferably, the polymorph form E is substantially free of any other polymorph forms. By "substantially free" is meant 20% or less, preferably 10% or less, more preferably 5% or less, most preferably 2% or less, particularly 1% or less, more particularly 0.5% or less and most particularly 0.2% or less, for example, between about 0.01 and about 5% or between about 0.1 and about 1%.

Preferably, the polymorph form E is substantially free of Bendamustine HCl form A. By "substantially free" is meant 20% or less, preferably 10% or less, more preferably 5% or less, most preferably 2% or less, particularly 1% or less, more particularly 0.5% or less and most particularly 0.2% or less, for example, between about 0.01 and about 5% or between about 0.1 and about 1%. Typically, the content of the crystalline Bendamustine HCl having an X-ray powder diffraction pattern with peaks at about 8.4, 14.0, 17.5, 20.9 degrees two-theta ± 0.2 degrees two-theta is measured by PXRD.

The above crystalline form of Bendamustine HCl can be prepared by a process comprising crystallizing Bendamustine HCl from formamide and ethylacetate. This process may comprise dissolving Bendamustine HCl in formamide and ethylacetate to obtain a solution comprising the crystalline form. The volume ratio of formamide and ethylacetate is preferably between 1:1 and 1:10, more preferably between 1:1.5 and 1:9, yet more preferably between 1:2 and 1:7, for example, 1:3, 1:4, and 1:6.25 and 1:7.5.

In one embodiment, the Bendamustine HCl is dissolved in the formamide and then ethylacetate added, optionally, slowly (e.g. over a period of about 2 minutes to about 10 minutes) or drop wise.

Preferably, the dissolution is done at a temperature that is in a range from about room temperature to about 70°C, preferably about 40°C to about 60°C, preferably about 50°C. Then, the solution may be stirred for a period of between about 5 minutes to about 5 days, preferably, about 30 minutes to about 1 day, more preferably about 1 hour to about 20 hours, yet more preferably about 2 hours to about 4 hours, most preferably about 3 hours at preferably about room temperature, during which a precipitation occurred forming a suspension. The above crystalline form can be recovered from the suspension. Recovery can be done by filtering, washing and drying. Preferably, drying is done under nitrogen at room temperature.
In yet another embodiment, the present invention provides a process for preparing Bendamustine HCl, designated form B, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4, a solid-state 13C NMR spectrum having signals at 150.3 and 130.8 ± 0.2 ppm; a solid-state 13C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift (at 109.6 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of 40.7 and 21.2 ± 0.1 ppm; and a combination thereof, by preparing the above Bendamustine HCl form E according to the process of the present invention, and converting it to Bendamustine HCl form B.

The conversion of Bendamustine HCl form E to Bendamustine HCl form B may be carried out, for example, by crystallization from HCl and water or by washing form E with ethylacetate and water and drying in a flow of wet nitrogen.

The present invention also provides a polymorphically pure crystalline Bendamustine HCl. This polymorph is a monohydrate form of Bendamustine HCl. This polymorph is also preferably chemically pure. In a preferred embodiment, it is free of a by-product where one Cl group is substituted by OH.

One embodiment is polymorphically pure crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4, a solid-state 13C NMR spectrum having signals at 150.3 and 130.8 ± 0.2 ppm; a solid-state 13C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift (at 109.6 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of 40.7 and 21.2 ± 0.1 ppm; and a combination thereof, wherein the polymorphically pure crystalline Bendamustine HCl contains less than about 15% by weight of Bendamustine HCl, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.7, 10.2, 15.4, 19.4 and 25.5 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 5; and a combination thereof. This form can be designated as form B, which is a monohydrate form.
The above crystalline form of Bendamustine HCl designated Form B may be further characterized by data selected from the group consisting of: a powder XRD pattern with additional peaks at 10.6, 13.6, 15.0, 22.9 and 26.4 ± 0.1 degrees 2-theta; a water content of about 4.7% by weight as determined by Karl-Fischer titration; and a combination thereof.

In addition, crystalline Bendamustine HCl Form B contains less than about 10% by weight, preferably, less than about 5% by weight (for example, between about 0.01% and about 9%, between about 0.05% and about 5%, or between about 0.1% and 1%) of crystalline Bendamustine HCl, designated Form C, characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.7, 10.2, 15.4, 19.4 and 25.5 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 5; and a combination thereof. Typically, the amount of form C in form B is measured by PXRD using any peak from the group of peaks at: 7.7, 10.2, 15.4, 19.4 and 25.5 deg ± 0.1 degrees 2-theta.

The above form B is preferably polymorphically pure Bendamustine HCl. This polymorph is a monohydrate form of Bendamustine HCl. This polymorph is also preferably chemically pure; especially free of a by product where one Cl group is substituted by OH.

Crude Bendamustine HCl form B can be prepared according to example 20 infra.

During its preparation several impurities, described herein, can be formed. One impurity that has been observed is dioxazaphosphocan HCl, 4-[5-(2-hydroxy-2-oxido-1,3,6,2-dioxazaphosphocan-6-yl)-1-methyl-1H-benzimidazol-2-yl]butanoic acid hydrochloride (BEMN07);
Another is hydroxybendamustine HCl, 4- \{5-[(2-Chloroethyl)(2-hydroxyethyl)amino]-1-methyl-1H-benzimidazol-2-yl\}butanoic acid hydrochloride (BEMN03);

Another is ethyl bendamustine HCl, Ethyl 4- \{5-[bis(2-chloroethyl)amino]-1-methyl-1H-benzimidazol-2-yl\}butanoate hydrochloride (BEMMO1);

and another impurity has an HPLC elution time 12.8 of min., but has not been identified. The crystallization from formamide-ethylacetate has high purification efficiency for removal of the ethyl bendamustine impurity. The crystallization from diluted hydrochloric acid is efficient in removal of the polar impurities BEMN03 and BEMN07.

Also described is a crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.0, 9.8, 14.8, 19.7 and 21.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 10; and a combination thereof. This form can be designated as form D.

The above crystalline form of Bendamustine HCl designated Form D may be further characterized by a powder XRD pattern with additional peaks at 10.2, 10.6, 12.4, 22.0 and 30.1 ± 0.1 degrees 2-theta.
Described herein a crystalline form of Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 8.4, 16.8, 17.5, 18.4 and 28.2 ± 0.2 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 1; a solid-state 13C NMR spectrum having signals at 152.8 and 132.4 ± 0.2 ppm; a solid-state 13C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift (at 109.7 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of 43.1 and 22.7 ± 0.1 ppm; and a combination thereof. This form can be designated as form A.

The above crystalline form of Bendamustine HCl designated Form A may be further characterized by a powder XRD pattern with additional peaks at 8.7, 14.0, 22.0, 24.8 and 25.1 ± 0.2 degrees 2-theta; a DSC thermogram substantially as depicted in figure 2; a TGA thermogram substantially as depicted in figure 3; and combinations thereof.

The above crystalline form of Bendamustine HCl can be prepared by a process comprising crystallizing Bendamustine HCl from a solvent mixture that is selected from the group consisting of: dimethylsulfoxide and toluene, dimethylsulfoxide and tetrahydrofuran, N,N-dimethylformamide and toluene, N,N-dimethylformamide and tetrahydrofuran, N,N-dimethylacetamide and tetrahydrofuran, N-methyl-2-pyrrolidone and toluene and mixtures thereof.

The above process may comprise dissolving Bendamustine HCl in a first solvent selected from a group consisting of dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone or mixtures thereof, and combining the solution with a second solvent (antisolvent) selected from a group consisting of toluene, tetrahydrofuran or mixtures thereof, to obtain a suspension comprising said crystalline form. Preferably, the dissolution is done at about 10°C to about 100°C, preferably about 15°C to about 90°C, yet more preferably at about room temperature to about 80°C.

The solution can be mixed with the second solvent; preferably the second solvent is added to the solution. Preferably, the combination of the solution with the second solvent, such as toluene, tetrahydrofuran or mixtures thereof provides a suspension. Preferably, the addition of the second solvent, such as toluene, tetrahydrofuran or mixtures thereof is done over a period of about 2 minutes to about 10 minutes.
Then, the suspension is stirred for a period of about 30 minutes to about 24 hours, preferably about 1 hour to about overnight. Optionally, additional amount of toluene, tetrahydrofuran or mixtures thereof can be added to the suspension to increase the amount of precipitated product. To further increase the yield, the above suspension is further stirred for an additional amount of time. Preferably, stirring is done for a period of about 30 minutes to about 24 hours, preferably about 2 hours to about overnight.

[0057] The above crystalline form can be recovered from the suspension. Recovery can be done by filtering, washing and drying. Preferably, drying is done at a temperature of about room temperature to about 50°C. Preferably, drying is done under vacuum.

[0058] In a another process, the above crystalline form of Bendamustine HCl form A can be prepared by a process comprising crystallizing Bendamustine HCl from acetonitrile. Typically, the crystallization comprises dissolving a Bendamustine HCl in acetonitrile and precipitating the crystalline form to obtain a suspension.

[0059] The solution of Bendamustine HCl and acetonitrile is provided, preferably, by combining Bendamustine HCl and acetonitrile, and heating the combination. Optionally, the combination can also contain formamide, for example from the starting material, which can be a solvate, like form E. Preferably, the combination is heated to a temperature of about 70°C to about 90°C, more preferably about 75°C to about 82°C, more preferably about 80°C to about 82°C, more preferably about 85°C.

After the solution is formed, it is cooled to provide a suspension in which Bendamustine HCl form A precipitates. Preferably, cooling is to a temperature of about 15°C to about 25°C, more preferably about 15°C to about 20°C.

[0060] Preferably, the suspension is maintained prior to the recovering of Bendamustine HCl form A, e.g., at a temperature of about room temperature, preferably for a period of about 15 minutes to about 24 hours, more preferably about 30 minutes to about 20 hours, more preferably about 30 minutes to about 2 hours.

[0061] The process for preparing Bendamustine HCl form A can further comprise recovery of the polymorph from the suspension. The recovery process may comprise, for example, filtering the crystalline form and drying, preferably, air drying. Preferably, drying is done at a temperature of about 40°C to about 60°C, more preferably about 50°C.
Preferably, drying is done for a period of about 10 hours to about 24 hours, more preferably about 12 hours to about 20 hours, more preferably about 15 hours to about 17 hours.

[0062] The above crystalline form A of Bendamustine HCl can also be prepared from crystalline Bendamustine HCl form E. In one embodiment, for example, Bendamustine HCl form E is heated at a temperature of at least about 100°C, more preferably at least about 105°C under atmospheric pressure, for example between about 100°C and about 150°C. Preferably, the heating is done for a period of about 15 minutes to about 120 minutes, preferably about 30 minutes to about 60 minutes.

[0063] In another embodiment, Bendamustine HCl form E is slurried in acetonitrile, acetone or propylacetate. Preferably, slurrying is done at a temperature about reflux temperature, preferably about 75°C to about 82°C, more preferably about 80°C to about 82°C. Preferably slurrying is done for a period of about 15 minutes to about 24 hours, more preferably about 30 minutes to about 24 hours, more preferably about 1 hour. This process can further comprise recovering Bendamustine HCl form A from the slurry. The recovery can comprise, for example, filtering the crystal form and drying, preferably, on air. Preferably, drying is done at a temperature of about 70°C to about 80°C, more preferably 75°C. Preferably, drying is done for a period of about 10 hours to about 24 hours, more preferably about 12 hours.

[0064] Further described is a polymorphically pure crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.7, 10.2, 15.4, 19.4 and 25.5 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 5; and a combination thereof, wherein the polymorphically pure crystalline Bendamustine HCl contains less than about 15% by weight Bendamustine HCl Form B, preferably less than about 10%, more preferably less than about 10%, for example between about 0.5% and about 12% or between about 2% and about 8%. This form can be designated as form C, which is an anhydrous form.

[0065] The above crystalline form of Bendamustine HCl designated Form C can be further characterized by data selected from the group consisting of: a powder XRD pattern with additional peaks at 3.9, 10.2, 10.7, 15.4 and 20.3 ± 0.1 degrees 2-theta; a water content of less than 0.5% by weight, preferably less than 0.3% by weight, more
preferably less than 0.1% by weight as determined by Karl-Fischer titration, for example between about 0.01% and about 0.4% or between about 0.02 and about 0.05%, and combinations thereof.

[0066] In addition, crystalline Bendamustine HCl Form C contains less than about 10% by weight, preferably, less than about 5% by weight of crystalline Bendamustine HCl Form B, for example between about 0.1% and about 8% or between about 2% and about 3%. Typically, the amount of form B in form C is measured by PXRD using any peak from the group of peaks at: 7.4, 13.6, 15.0 and 32.1 deg ± 0.1 degrees 2-theta.

[0067] Form C of Bendamustine HCl can be prepared by a process comprising slurrying Bendamustine HCl (preferably, Form B) in tetrahydrofuran. Preferably, the slurrying is performed for about 2 hours to about 8 hours, preferably about 4 hours at preferably room temperature.

[0068] The process for preparing form C of Bendamustine HCl may further comprise recovering the crystalline form. The recovery can be done, for example, by filtering the suspension and drying. Preferably, drying is performed on a filter at room temperature under dry (relative humidity below 10 %) nitrogen flow and atmospheric pressure. Preferably, drying is performed at room temperature.

[0069] Further described is a crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.9, 10.5, 15.9, 21.3 and 27.8 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 12; and a combination thereof. This form can be designated as form F.

[0070] The above crystalline form of Bendamustine HCl designated Form F can be further characterized by data selected from the group consisting of: a powder XRD pattern with additional peaks at 19.5, 23.4, 25.4, 25.7 and 33.6 ± 0.1 degrees 2-theta.

[0071] The above described forms of Bendamustine HCl can be used to prepare formulations by any method known in the art.

[0072] The present invention also includes a pharmaceutical composition comprising a crystalline form of Bendamustine HCl (preferably form E) and at least one pharmaceutically acceptable excipient, and optionally another active agent, preferably an anti-cancer agent.
Crystalline forms of Bendamustine HCl (preferably form E) and pharmaceutical compositions comprising them may be used for treating leukemia, chronic lymphocytic leukemia, sarcoma, indolent Non-Hodgkin's Lymphoma or multiple myeloma.

**EXAMPLES**

**PXRD**

XRD diffraction was performed on X-Ray powder diffractometer: Philips X'pert Pro powder diffractometer, CuKa radiation, \( \lambda = 1.5418 \) A. X'Celerator detector active length (2 theta) = 2.122°, laboratory temperature 22-25° C. Zero background sample holders. Prior to analysis the samples were gently ground by means of mortar and pestle in order to obtain a fine powder. The sample might be mixed with n-dodecane in order to avoid the environmental contamination by airborne particles coming from the powder. The ground sample or its suspension with n-dodecane was adjusted into a cavity of the sample holder and the surface of the sample was smoothed by means of a cover glass. The presence of n-dodecane when used for a sample preparation usually causes an amorphous bump in the middle of the diffractogram.

A silicon internal standard can be used to calibrate peak positions and to eliminate an effect of sample preparation. The internal standard possesses a diffraction with defined position at 28.44 degrees 2-theta. The internal standard can be mixed with a sample, PXRD is then acquired and the current position of the aforementioned internal standard diffraction peak is determined. The difference between the current position of the diffraction and its nominal value of 28.44 degrees 2-theta is calculated. The current positions of all relevant sample peaks are then re-calculated by means of the above difference to obtain the true positions of the sample diffractions.

Measurement parameters:
Scan range: at least 3 - 40° 2-theta;
Scan mode: continuous;
Step size: 0.0167 °;
Time per step: 2 1 s; or 400 s for more sensitive measurements;
Sample spin: 16 rpm;
Sample holder: quartz plate.
DSC

[0077] DSC measurements were performed on Differential Scanning Calorimeter DSC823e (Mettler Toledo). Aluminum crucibles 40 µl with PIN were used for sample preparation. Usual weight of sample was 1.5 - 3.5 mg.

[0078] Program: temperature range at least 30 - 250°C, heating rate 10°C/min, nitrogen flow 50 ml/min.

Water content by KF

[0079] Water content was determined by Karl Fischer titrator TITRANO 841, software Tiamo 1.1 (Metrohm). Solution used for determination: Hydranal Composite 2 (Riedel de Haen). Sampling: 100 mg, 2 repeats.

TGA

[0080] TGA measurements were performed on Thermo gravimetric analyzer TGA851e (Mettler Toledo). Alumina crucibles 70 µl were used for sample preparation. Usual weight of sample was 7 - 13 mg.

[0081] Program: temperature range at least 30 - 250°C, heating rate 10°C/min, nitrogen flow 50°C/min.

[0082] HPLC method:

Instrument: Water Alliance;
Column: Zorbax SB-C18, 150 x 3 mm, 3.5 µm, 30°C;
Mobile phase:

Solvent A: 1 ml/1 TFA in water-acetonitrile v/v 9:1;
Solvent B: 1 ml/1 TFA in water-acetonitrile v/v 5:5;

Gradient:

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</tr>
<tr>
<td>11.0</td>
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<td>45</td>
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</table>
Sample solvent: DMSO-acetonitrile v/v 1:3
Injection volume: 5 µl;
Flow rate: 0.9 ml/min;
Detection: UV 330 nm.

Example 1: Preparation of form A
[B0083] Bendamustine HCl (BEM.HCl) form C (1.18 g) was dissolved in DMSO (10 ml) at room temperature. Toluene (5x5 ml) was added to this solution over 10 minutes, and the solution was then stirred overnight to obtain crystals. The crystals were filtered off and dried on the filter overnight at 50 °C.

Example 2: Preparation of form A
[B0084] BEM.HCl (1.0 g) was dissolved in 2 ml DMSO at 24-25°C. Then 6 ml toluene was added to the solution over 5 minutes. Crystallization occurred after 2 hours of stirring. Toluene (1ml) was added into the consistent mixture, and then the mixture was further stirred overnight. The precipitated crystals were then separated by filtration. After filtration the white crystalline product that was obtained was washed with 3 ml toluene and dried under vacuum at 50 °C.

Example 3: Preparation of form A
[B0085] BEM.HCl (1.0 g) was dissolved in 2 ml DMSO at 24-25°C. Then 6 ml of THF was added and the resulting mixture was stirred. After 2 hours of stirring, 1 ml of THF was added to the consistent mixture and then the mixture was further stirred overnight. White crystals precipitated during this time. The white crystals were filtered and washed with 3 ml THF and dried under vacuum at 50° C overnight.
Example 4: Preparation of form A
[0086] BEM.HCl (1.0 g) was dissolved in 4 ml DMF at 60°C. The solution was then cooled to room temperature. Then 9 ml toluene was added over 5 minutes. A crystalline precipitate formed and this mixture was stirred overnight. The white product was then filtered, washed with 1 ml toluene and dried under vacuum at 50°C overnight.

Example 5: Preparation of form A
[0087] BEM.HCl (1.0 g) was dissolved in 4 ml DMF at 60°C. The solution was cooled to room temperature, and then 9 ml of THF was added over 5 minutes. A crystalline precipitate formed and this mixture was stirred overnight. The white product was then filtered, washed with 1 ml THF and dried under vacuum at 50°C.

Example 6: Preparation of form B
[0088] BEM.HCl (2.2 g) was dissolved in 4.0 ml of concentrated HCl at room temperature. Then 30 ml distilled water was added to the solution. A crystalline precipitate formed and this mixture was stirred for 15 min. The precipitate was then separated by filtration. After filtration, the white product was washed with water, then with 4 ml THF, and then it was dried on the filter at room temperature.

Example 7: Preparation of form C
[0089] BEM.HCl (form B) (1 g) was stirred with THF for 4 hours to obtain a slurry comprising crystals. The crystals were filtered off and dried on the filter for 1 hour at room temperature under nitrogen flow and at atmospheric pressure.

Example 8: Preparation of form A
[0090] BEM.HCl (Form A) (3.3 g) was dissolved in 20 ml N,N-dimethylacetamide at 50°C. Then 30 ml THF was added to the solution. The solution was stirred at room temperature for 2 hours to form a suspension of crystalline material. The suspension was stirred for another 2 hours and then filtered. After filtration, the white crystalline product was washed with THF and dried on the filter at room temperature under nitrogen.
Example 9: Preparation of form A

[0091] BEM.HC1 (1 g) was dissolved in 8 ml N-methyl-2-pyrrolidone (NMP) at 80°C. Then 10 ml toluene was added to the solution. This solution was stirred overnight at room temperature, during which time a solid precipitate formed. The precipitate was separated by filtration and dried overnight at 50°C in vacuo.

Example 10: Preparation of form D

[0092] A mixture of 1 g crude bendamustine hydrochloride and 20 ml of 1,4-dioxane was stirred and heated at 60°C. The solid part was dissolved after the addition of 680 µl water. Then, the clear solution was cooled in an ice bath and white crystals were formed slowly. The mixture was stirred for 1 hour, and then 5 ml 1,4-dioxane was added, followed by further 2 hrs of stirring. The product was then filtered off and dried on the filter for 1 hour at room temperature under nitrogen.

Example 11: Preparation of form E

[0093] Bendamustine hydrochloride (2.2 g) was dissolved in 2 ml formamide at 50°C. Then 12.5 ml of ethyl acetate was slowly added. The resulting mixture was stirred for 30 minutes until crystallization occurred. The suspension of crystalline material was then stirred for another 2 hours at room temperature. The product was then filtered off and dried on the filter at room temperature under nitrogen.

Example 12: Preparation of form E

[0094] Bendamustine hydrochloride (5.0 g) was dissolved in 10 ml formamide at 50°C. Then 30 ml ethyl acetate was slowly added to the solution. The solution was stirred for 5 minutes until crystallization occurred. This suspension was then stirred for another 30 minutes at room temperature. The product was then filtered off, washed with ethyl acetate and dried on the filter at room temperature under nitrogen.

Example 13: Preparation of form E
Bendamustine hydrochloride (2.0 g) was dissolved in 2 ml formamide at 50 °C. Then 15 ml ethyl acetate was slowly added to the solution. The solution was stirred for 5 min until crystallization occurred. This suspension was then stirred for another 4 days at room temperature. The product was then filtered off, washed with ethyl acetate and dried on the filter at room temperature under nitrogen.

Example 14: Preparation of form A
Bendamustine hydrochloride form E (100 mg) was heated in a closed vial at 105 °C for 30 minutes under atmospheric pressure.

Example 15: Preparation of form F
A mixture of 1.0 g BEM.HCl (form E) and 25 ml ethylacetate was heated under reflux for 2 h to form a suspension. Then, the suspension was stirred at room temperature for 1 hour. The product was filtered off, washed with 5 ml ethyl acetate and dried on the filter at room temperature under nitrogen.

Example 16: Preparation of form F
BEM.HCl (crude bendamustine) (7.0 g) was dissolved in 7 ml formamide at 50 °C. Ethylacetate (13 ml) was slowly added to form a cloudy mixture. The mixture was stirred for 20 hrs at RT to form a suspension. The product was filtered off, washed with ethylacetate (3 x 10 ml), and dried on the filter. The product was Form E as determined by XRD analysis.

4.32 g of the above product (form E) was washed two times with 10 ml of hot (65 °C) ethyl acetate and dried on the filter. The product was a mixture of Form E and Form F as determined by XRD analysis. 3.0 g BEM.HCl of the above product was dried (vacuum, 110 °C, 20 h. The product was Form F as determined by XRD analysis.

Example 17: Preparation of form A
BEM HCl form E (7.0 g) was refluxed for 1 hour in a mixture of 600 ml of acetonitrile and 3 ml of formamide. The product was filtered off of this mixture at 75 °C, and dried on filter at room temperature under nitrogen.
Example 18: Preparation of form A

BEM HCl (form E) (500 mg) was suspended in 10 ml acetonitrile to form a slurry. The slurry was stirred at 80 °C for 20 h. The slurry was then stirred at ambient temperature for 1 hour. The crystals that were formed were filtered off and dried on the filter at room temperature under nitrogen. Yield 400 mg.

Example 19: Preparation of form A

BEM HCl form E (590 mg) was dissolved in 60 ml acetonitrile at 80 °C to form a clear solution. The solution was then stirred at room temperature for 20 hours (after 30 min crystallization occurred). The crystals were filtered off and dried on the filter at room temperature under nitrogen. Yield 430 mg.

Example 20: Preparation of crude Bendamustine hydrochloride (form B)

A 5 L bottle was charged with 197 g of phosphorus oxychloride. The contents of the bottle were heated to 50 °C and 150 g of ethyl 4-[5-[bis(2-hydroxyethyl)amino]-1 -methyl-1H-benzimidazol-2-yl]butanoate("BBOH") dissolved in 600 ml of dichloromethane was added. Reaction mixture was stirred at 75-85 °C for 4-5 hours. The reaction mixture was then cooled to room temperature and diluted with 450 ml dichloromethane to form a solution. Then the solution was decomposed with 900 ml of 21 % hydrochloric acid and then this reaction mixture was heated at 92 - 96 °C for 5-6 h. The resulting solution was then cooled, and its pH was adjusted with 50 % sodium hydroxide to a pH of 1.4 - 1.6 at 0 - 20°C. The product crystallized and the mixture was stirred 30 - 60 minutes at 0-10°C. The crude Bendamustine was separated by filtration and the filter cake was washed three times with 600 ml of cold dilute hydrochloric acid (1:20), then three times with 600 ml of cold water, and then three times with 600 ml of ethyl acetate. The filter cake was then dried in wet (relative humidity over 30 %) nitrogen to give 144 g of crude bendamustine hydrochloride.

Example 21: Preparation of form A through form E.
[00104] Bendamustine hydrochloride (crude) (2.5g) was dissolved in 3 ml of formamide at 70°C. Ethyl acetate (12 ml) was added and the resulting solution was stirred at ambient temperature for 3 hours. Crystals formed and were filtered off and washed with 10 ml of ethylacetate. The cake (form E) was dried in flow of nitrogen at room temperature for 1 hour.

[00105] Then the filter cake (form E) was washed with acetone (3 x 15 ml), and then dried at room temperature in a flow of nitrogen for 1 hour to give 1.5 g of bendamustine hydrochloride, form A

Example 22: Preparation of form B through form E.

[00106] Bendamustine hydrochloride (2.5g) was dissolved in 3 ml of formamide at 70°C. Ethyl acetate (12 ml) was added and the resulting solution was stirred at ambient temperature for 3 hours. Crystals formed and were filtered off and washed with 10 ml of ethyl acetate. The cake is dried in flow of nitrogen at room temperature for 2 hours. Then the filter cake (form E) was washed (3 x 15 ml) with ethylacetate saturated with water (3 % of water w/w). The filter cake was dried in a flow of wet nitrogen (relative humidity 32 - 56 %) for 4 hours to give 1.6 g of bendamustine hydrochloride, form B.

Example 23: HPLC results indicating purification effect of the crystallization system:

[00107] Step A) Recrystallization of crude bendamustine (Form B) from formamide-ethylacetate:

[00108] Crude bendamustine (prepared in Example 20) (100 g) was dissolved in 120 ml formamide at 70°C. Ethyl acetate (480 ml) was added and the mixture was stirred for 3 hours at room temperature. Crystals formed and were filtered off. The wet filter cake was then washed with 750 ml ethyl acetate (3 x 250 ml ethyl acetate) and then dried on the filter under a flow of nitrogen for 2 hours to give 85g of BEM.HCl (form E).

[00109] Step B) Recrystallization of Form E from HCl - water:

[00110] Bendamustine form E (the product of the above step A) (78 g of) was dissolved in 140 ml of 21% hydrochloric acid at 50°C. The solution was stirred in an ice bath for 30 minutes. Then 600 ml of distilled water was added. Crystallization
started after 2 minutes. The resulting suspension was stirred in an ice bath for 30 minutes (at +18 to +12 °C). The product was filtered off, washed twice with 250 ml ice water and dried on the filter. The filter cake was then washed twice with 250 ml cool acetone (-10 °C). The filter cake was then dried on the filter by a flow of wet nitrogen (relative humidity 35 - 60 %) for 4 hours.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Crude BEM</th>
<th>Form E (after Step A)</th>
<th>Final Form B (after step B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Area</td>
<td>% Area</td>
<td>% Area</td>
</tr>
<tr>
<td>BEMM01</td>
<td>0.34</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>OH-BEM</td>
<td>0.25</td>
<td>0.12</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>BEM</td>
<td>98.92</td>
<td>99.75</td>
<td>99.92</td>
</tr>
</tbody>
</table>

Legend:
BEMN03 = hydroxybendamustine
BEM = bendamustine
BEMMO1 = ethylbendamustine

Explanation:

[00112] Step A using formamide-ethylacetate crystallization purifies the material especially from BEMMO1 which non-polar impurity.

[00114] Step B using diluted HCl is then purifying the product from BEMN03 which is polar impurity.

[00115] The system in its entirety purifies crude bendamustine to excellent quality.

[00116] Drying parameters - especially nitrogen humidity - plays a role in the physical state of produced bendamustine hydrochloride. Polymorph C is formed on drying with dry nitrogen as it is evident from the next table.

[00117] Table - Drying of the wet bendamustine hydrochloride in the chamber at room temperature by nitrogen of various humidity for 7 days.
Comparative example and HPLC results:

Repetition of DD 34727 - Bendamustine hydrochloride 1.51 g was dissolved in distilled water (20 ml) at 85 °C to give clear solution in 10 min. The solution was stirring at room temperature for 60 minutes. The product was filtered off and dried on the filter.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Commercial API Bendamustine HCl by Conier (China)</th>
<th>Product of repetition DD 34727</th>
<th>Commercial product Ribomustine (Ribopharm, Germany)</th>
<th>Commercial product Treanda (Cephalon, USA)</th>
<th>Final Form B (after step B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Area</td>
<td>% Area</td>
<td>% Area</td>
<td>% Area</td>
<td>% Area</td>
</tr>
<tr>
<td>BEMN03</td>
<td>0.30</td>
<td>0.42</td>
<td>0.92</td>
<td>0.27</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>BEM</td>
<td>99.56</td>
<td>99.45</td>
<td>98.51</td>
<td>99.15</td>
<td>99.92</td>
</tr>
</tbody>
</table>

The non-inventive process gave a product with elevated concentration of the polar impurity BEMN03 (from 0.3 to 0.4 %) and thus less purity of the final material (99.56 down to 99.45 %).

Comparative example and HPLC results:

<table>
<thead>
<tr>
<th>BEM.HCl</th>
<th>BEMN07</th>
<th>BEMN03</th>
<th>12.8 min</th>
<th>BEM</th>
<th>BEMM01</th>
</tr>
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<tbody>
<tr>
<td>crude</td>
<td>0.26</td>
<td>0.13</td>
<td>0.17</td>
<td>98.59</td>
<td>0.533</td>
</tr>
<tr>
<td>Crystallized from diluted HCl</td>
<td>0.05</td>
<td>0.0</td>
<td>0.15</td>
<td>99.34</td>
<td>0.20</td>
</tr>
<tr>
<td>Crystallized from formamide/ethylacetate</td>
<td>0.12</td>
<td>0.07</td>
<td>0.01</td>
<td>99.53</td>
<td>0.04</td>
</tr>
</tbody>
</table>
What is claimed is:

1. A crystalline Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof.

2. The crystalline Bendamustine HCl of claim 1, characterized by a powder XRD pattern with peaks at 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta.

3. The crystalline Bendamustine HCl of claim 2, further characterized by a powder XRD pattern with additional peaks at 9.9, 13.3, 19.7, 19.9 and 26.0 ± 0.1 degrees 2-theta.

4. A process for preparing the Bendamustine HCl of claim 1, claim 2 or claim 3, comprising crystallizing Bendamustine HCl from formamide and ethylacetate.

5. A process for preparing Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4; a solid-state $^{13}$C NMR spectrum having signals at 150.3 and 130.8 ± 0.2 ppm; a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the lowest chemical shift, at 109.6 ± 1.0 ppm, and another in the chemical shift range of 100 to 180 ppm of 40.7 and 21.2 ± 0.1 ; and a combination thereof, said process comprising:
   - preparing Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at about 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof; and
   - converting it to Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at about 7.4, 13.6, 15.0, 22.9 and 32.1 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 4, a solid-state $^{13}$C NMR spectrum having signals at about 150.3 and 130.8 ± 0.2 ppm; a solid-state $^{13}$C NMR spectrum having chemical shifts differences between the signal exhibiting the
lowest chemical shift (at about 109.6 ± 1.0 ppm) and another in the chemical shift range of 100 to 180 ppm of about 40.7 and 21.2 ± 0.1 ppm; and a combination thereof.

6. The process according to claim 5, wherein the Bendamustine HCl characterized by data selected from the group consisting of: a powder XRD pattern with peaks at about 3.3, 11.1, 12.0, 16.0 and 16.6 ± 0.1 degrees 2-theta; a powder XRD pattern substantially as depicted in figure 11; and a combination thereof, is prepared by the method of claim 3.

7. A pharmaceutical composition comprising the crystalline form of Bendamustine HCl according to claim 1, claim 2 or claim 3, and at least one pharmaceutically acceptable excipient.

8. The composition of claim 7, further comprising another anti-cancer agent.

9. The use of the crystalline form of Bendamustine HCl of claim 1, claim 2 or claim 3 for treating leukemia, chronic lymphocytic leukemia, sarcoma, indolent Non-Hodgkin's Lymphoma or multiple myeloma.

10. The use of the crystalline form of bendamustine HCl of claim 1 for the manufacture of a medicament for treating a patient suffering from leukemia, chronic lymphocytic leukemia, sarcoma, indolent Non-Hodgkin's Lymphoma or multiple myeloma.

11. A method of treating a patient suffering from leukemia, chronic lymphocytic leukemia, sarcoma, indolent Non-Hodgkin's Lymphoma or multiple myeloma comprising administering to said patient a therapeutically effective amount of the crystalline form of bendamustine HCl of claim 1 or a pharmaceutical composition according to claim 7.
FIG. 6

Bendamustine, 13C CP/MAS, DR, 11kHz.
Bandamustine, 13C CP/MAS NMR, 11 kHz, RT.

109.59
114.38
125.14
130.75
144.80
150.26
174.39

197.05

FIG. 9

RECTIFIED SHEET (RULE 91)
ISA/EP
A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4184 C07D235/16 A61P35/00

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)
A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>DD 34 727 A1 (KREBS ET AL.) 28 December 1964 (1964-12-28) example 2</td>
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Further documents are listed in the continuation of Box C

See patent family annex

Date of the actual completion of the international search
20 July 2010

Date of mailing of the international search report
03/08/2010

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
Steendijk, Martin
<table>
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<td>ANON.: &quot;Crystalline form of 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazo[2,1-\textit{b}]pyrimidin-2-yl]butanoic acid hydrochloride&quot;</td>
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<td></td>
<td>IP.COM JOURNAL, 9(7A), 16 (NO. IPCOM000184385D), 23 JUN 2009 CODEN: IJPOBX; ISSN: 1533-0001, 2009, XP002592632</td>
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<td>Patent family member(s)</td>
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