Title: NILOTINIB DIHYDROCHLORIDE SALT

Abstract: The present invention relates to nilotinib dihydrochloride and its hydrates, to methods for preparing nilotinib dihydrochloride and its hydrates, pharmaceutical compositions comprising nilotinib dihydrochloride and its hydrates, and methods of treatment using the same.
NILOTINIB DIHYDROCHLORIDE SALT

Field of the invention

The present invention relates to a novel salt of 4-methyl-N-[3-(4-methyl-imidazol-1-yl)-5-(trifluoromethyl)-phenyl]-3-[(4-pyridin-3-yl-pyrimidin-2-yl)amino] benzamide and hydrates thereof, to methods for preparing the novel salt and its hydrates, pharmaceutical compositions comprising the novel salt and its hydrates, and methods of treatment using the same.

Background of the invention

4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-(trifluoromethyl)-phenyl]-3-[(4-pyridin-3-yl-pyrimidin-2-yl)amino] benzamide having formula (I) was first disclosed in WO 2004/005281. This compound, known genetically as nilotinib, is a tyrosine kinase inhibitor and is indicated in the treatment of drug-resistant chronic myelogenous leukemia (CML). However, WO 2004/005281 does not disclose any salts or hydrates of nilotinib.

WO 2007/015871 is directed to various salts of nilotinib. Preferred embodiments include the hydrochloride, monophosphate, diphosphate, sulfate, methane sulfonate, ethane sulfonate, benzene sulfonate and p-toluene sulfonate salts of nilotinib. In relation to the hydrochloride salt in particular, the application only discloses forms A and B and further specifically discloses the preparation of the nilotinib monohydrate monohydrochloride by adding nilotinib free base to methanol and hydrochloric acid and recovering the
hydrochloride salt after seeding. There are further references to the hydrochloride salt that
do not specify the monohydrate monohydrochloride form, but taking the specification as a
whole the skilled person could only be led to the conclusion that all references to the
hydrochloride salt refer to either form A or B of the monohydrochloride monohydrate salt
prepared as described above.

The marketed product, Tasigna®, is the monohydrochloride monohydrate salt described
above. There is always a need to prepare alternate salts or salt forms which can either
match or better the pharmacokinetic properties of such marketed products. These
alternative salts and salt forms must also pass the quality and safety criteria set out by the
various health authorities worldwide and can themselves be marketed as equally efficacious
and often more cost effective alternatives to patient groups and healthcare services.

**Summary of the invention**

The inventors have succeeded in preparing a novel nilotinib salt and different forms of said
novel salt. Accordingly, there is provided in a first aspect of the invention nilotinib
dihydrochloride. Preferably the nilotinib dihydrochloride of the first aspect of the invention
is crystalline. A second aspect of the invention provides hydrates of nilotinib
dihydrochloride, which in a particularly preferred embodiment is nilotinib dihydrochloride
dihydrate. Preferably the hydrate of nilotinib dihydrochloride of the second aspect of the
invention is crystalline. A third aspect of the invention provides anhydrous nilotinib
dihydrochloride.

One embodiment of the second aspect of the invention provides crystalline nilotinib
dihydrochloride dihydrate, preferably having an X-ray diffraction pattern comprising peaks
at 7.18, 14.32, 23.34 and 27.62 ± 0.2 degrees 2-theta. A particularly preferred embodiment
provides nilotinib dihydrochloride dihydrate having an X-ray diffraction pattern comprising
further peaks at 8.47, 10.25, 11.61, 12.34, 12.62, 17.15, 17.84, 19.34, 21.55, 21.93, 22.18,
24.17, 24.5, 25.56, 26.22 and 29.49 ± 0.2 degrees 2-theta. Preferably the nilotinib
dihydrochloride dihydrate of the second aspect of the invention has an X-ray diffraction
pattern substantially as shown in Figure 1.
In another embodiment of the second aspect of the invention nilotinib dihydrochloride dihydrate is provided having a differential scanning calorimetry thermogram with endothermic peaks at about 107°C ± 2°C and 251°C ± 2°C. Preferably the nilotinib dihydrochloride dihydrate of the second aspect of the invention has a differential scanning calorimetry thermogram substantially as shown in Figure 2.

Yet another embodiment of the second aspect of the invention provides nilotinib dihydrochloride dihydrate having a thermogravimetric analysis thermogram substantially as shown in Figure 3.

Preferably the nilotinib dihydrochloride of the first aspect of the invention, the nilotinib dihydrochloride dihydrate of the second aspect of the invention, and the anhydrous nilotinib dihydrochloride of the third aspect of the invention have a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A fourth aspect according to the invention provides a process for preparing nilotinib dihydrochloride comprising:

(i) mixing nilotinib free base in an organic solvent system;
(ii) adding either concentrated HCl or an organic solution of HCl to the mixture from step (i) or adding the mixture from step (i) to either concentrated HCl or an organic solution of HCl; and
(iii) isolating the nilotinib dihydrochloride salt.

In certain embodiments of the fourth aspect the organic solvent system comprises N,N-dimethylacetamide, methanol, methanol-water, acetone, ethanol, acetonitrile, isopropyl alcohol, n-butanol, N-methyl-pyrrolidine, tetrahydrofuran, dimethyl sulfoxide or N,N-dimethylformamide or mixtures thereof.

In step (ii) of the process of the fourth aspect, preferably either concentrated HCl or an organic solution of HCl is added to the mixture from step (i).

Preferably about 1 to about 4 equivalents of HCl are used in step (ii) relative to the nilotinib free base, preferably about 2 to about 4 equivalents of HCl.
Preferably the organic solution of HC1 in step (ii) is prepared by passing HC1 gas through the organic solvent. In preferred embodiments the organic solvent used in preparing the organic solution of HC1 is selected from the group comprising a C_{1-4} alcohol, ethyl acetate and acetonitrile or mixtures thereof. Most preferably, the C_{1-4} alcohol is one or more of methanol, ethanol, isopropanol and n-butanol or mixtures thereof.

In certain preferred embodiments an anti-solvent is added to the mixture from step (ii) in order to help precipitate the desired nilotinib dihydrochloride salt. In particularly preferred embodiments the solvent/anti-solvent combination is as defined in table 1.

The present invention also provides a process according to the fourth aspect and embodiments thereof, for preparing anhydrous nilotinib dihydrochloride wherein the nilotinib free base, the organic solvent system, and the concentrated HC1 or the organic solution of HC1 are all anhydrous and the process is carried out under anhydrous conditions. A particularly preferred alternative embodiment according to the fourth aspect of the present invention provides a process for preparing nilotinib dihydrochloride dihydrate.

A fifth aspect of the invention provides nilotinib dihydrochloride having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A sixth aspect of the invention provides nilotinib dihydrochloride dihydrate having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A seventh aspect of the invention provides anhydrous nilotinib dihydrochloride having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

Preferably the nilotinib dihydrochloride of the first and fifth aspects of the invention, the nilotinib dihydrochloride dihydrate of the second and sixth aspects of the invention, and the anhydrous nilotinib dihydrochloride of the third and seventh aspects of the invention are suitable for use in medicine, preferably for treating cancer, preferably for treating adults
with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

In an eighth aspect of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of nilotinib dihydrochloride and at least one pharmaceutically acceptable excipient. In a most preferred embodiment of the eighth aspect of the present invention, the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or may in alternative embodiments be anhydrous nilotinib dihydrochloride.

Further preferred embodiments of the eighth aspect of the invention provide a composition for use in the treatment of cancer, most preferably for use in the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A ninth aspect of the invention provides the use of nilotinib dihydrochloride in the manufacture of a medicament for treating cancer. Preferably the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or alternatively the nilotinib dihydrochloride may be anhydrous nilotinib dihydrochloride. Preferably the medicament is for treating adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A tenth aspect of the invention provides a method of treating cancer comprising administering a therapeutically effective amount of nilotinib dihydrochloride to a patient in need thereof. Preferably the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or alternatively the nilotinib dihydrochloride may be anhydrous nilotinib dihydrochloride. Preferably the patient is a mammal, preferably a human. Preferably the patient is an adult with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.
Brief description of the accompanying drawings

Figure 1 is a representative X-ray diffraction pattern of nilotinib dihydrochloride dihydrate according to the invention.

Figure 2 is a representative differential scanning calorimetry thermogram of nilotinib dihydrochloride dihydrate according to the invention.

Figure 3 is a representative thermogravimetry curve of nilotinib dihydrochloride dihydrate according to the invention.

Detailed description of the invention

The term "nilotinib dihydrochloride" as used herein throughout the description and claims is intended to mean nilotinib dihydrochloride and/or any hydrates, solvates, anhydrates or polymorphs unless otherwise specified or stated.

The term "purity" as used herein throughout the description and claims refers to chemical purity and/or polymorphic purity. Chemical purity may be determined for example by HPLC and polymorphic purity may be determined by XRPD analysis.

The inventors have succeeded in preparing an alternative salt and polymorphs thereof to those disclosed in the prior art. Alternative salts and salt forms are desirable for a number of reasons. Preparing novel salts and salt forms is always desirable as it widens the repertoire available to the medicinal chemist or the pharmaceutical formulator. Cancer medication is traditionally very expensive. Any means by which the cost of such medication can be reduced is particularly advantageous to individuals and to healthcare providers. Providing alternative but equally efficacious salts or salt forms that may be formulated into significantly cheaper drug products is a particularly advantageous and desirable goal.

However preparing such alternative salts or salt forms is not routine. There are a huge number of possible alternative salts, hydrates, polymorphs and pseudopolymorphs for any given drug, all, none or any proportion of which may be a suitable candidate. The present inventors have found that despite utilising similar solvents as disclosed in the prior art for
preparing nilotinib monohydrate monohydrochloride an alternative hydrochloride salt of nilotinib may be prepared.

Accordingly, there is provided in a first aspect of the present invention nilotinib dihydrochloride. Preferably the nilotinib dihydrochloride of the first aspect of the invention is crystalline. A second aspect of the invention provides hydrates of nilotinib dihydrochloride, which in a particularly preferred embodiment is nilotinib dihydrochloride dihydrate. Preferably the hydrate of nilotinib dihydrochloride of the second aspect of the invention is crystalline. A third aspect of the invention provides anhydrous nilotinib dihydrochloride.

One embodiment of the second aspect of the invention provides crystalline nilotinib dihydrochloride dehydrate, preferably having an X-ray diffraction pattern comprising peaks at 7.18, 14.32, 23.34 and 27.62 ± 0.2 degrees 2-theta. A particularly preferred embodiment provides nilotinib dihydrochloride dihydrate having an X-ray diffraction pattern comprising further peaks at 8.47, 10.25, 11.61, 12.34, 12.62, 17.15, 17.84, 19.34, 21.55, 21.93, 22.18, 24.17, 24.5, 25.56, 26.22 and 29.49 ± 0.2 degrees 2-theta. Preferably the nilotinib dihydrochloride dihydrate of the second aspect of the invention has an X-ray diffraction pattern substantially as shown in Figure 1.

In another embodiment of the second aspect of the invention nilotinib dihydrochloride dihydrate is provided having a differential scanning calorimetry thermogram with endothermic peaks at about 107°C ± 2°C and 251°C ± 2°C. Preferably the nilotinib dihydrochloride dihydrate of the second aspect of the invention has a differential scanning calorimetry thermogram substantially as shown in Figure 2.

A further embodiment of the second aspect of the invention provides nilotinib dihydrochloride dihydrate having a thermogravimetric analysis thermogram substantially as shown in Figure 3.

Preferably the nilotinib dihydrochloride of the first aspect of the invention, the nilotinib dihydrochloride dihydrate of the second aspect of the invention, and the anhydrous
nilotinib dihydrochloride of the third aspect of the invention have a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A fourth aspect according to the invention provides a process for preparing nilotinib dihydrochloride comprising:

(i) mixing nilotinib free base in an organic solvent system;

(ii) adding either concentrated HCl or an organic solution of HCl to the mixture from step (i) or adding the mixture from step (i) to either concentrated HCl or an organic solution of HCl; and

(iii) isolating the nilotinib dihydrochloride salt.

For the purposes of the invention, particularly the fourth aspect, the term "mixing" is meant to include any addition of nilotinib free base to an organic solvent system, this may include dissolving or suspending all or any proportion of the nilotinib free base in the solvent system. In certain embodiments the addition of the nilotinib free base to the solvent system may result in a suspension or the free base may be dissolved completely or partially in the solvent system.

In certain embodiments of the fourth aspect the organic solvent system comprises a C\textsubscript{1-4} alcohol (such as methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol, t-butanol), a C\textsubscript{1-4} alcohol-water mixture (such as methanol-water), an amide (such as N,N-dimethylacetamide, N,N-dimethylformamide), a ketone (such as acetone), a nitrile (such as acetonitrile), an amine (such as N-methyl-pyrrolidine), an ether (such as tetrahydrofuran), a sulfoxide (such as dimethyl sulfoxide) or mixtures thereof. Preferably the organic solvent system comprises N,N-dimethylacetanide, methanol, methanol-water, acetone, ethanol, acetonitrile, n-propanol, isopropyl alcohol, n-butanol, isobutanol, t-butanol, N-methylpyrrolidine, tetrahydrofuran, dimethyl sulfoxide or N,N-dimethylformamide or mixtures thereof. Preferably the organic solvent system comprises N,N-dimethylacetamide, methanol, methanol-water, acetone, ethanol, acetonitrile, isopropyl alcohol, n-butanol, N-methyl-pyrrolidine, tetrahydrofuran, dimethyl sulfoxide or N,N-dimethylformamide or mixtures thereof.
In step (ii) of the process of the fourth aspect, preferably either concentrated HCl or an organic solution of HCl is added to the mixture from step (i).

Preferably about 1 to about 4 equivalents of HQ are used in step (ii) relative to the nilotinib free base, preferably about 2 to about 4 equivalents of HCl.

The inventors have found that addition of concentrated hydrochloric acid or an organic solution of hydrochloric acid to the reaction mixture obtained in step (i) or addition of the reaction mixture obtained in step (i) to concentrated hydrochloric acid or an organic solution of hydrochloric acid, results in the nilotinib dihydrochloride salt according to the invention, in particular the nilotinib dihydrochloride dihydrate of the second aspect of the invention. Preferably the organic solution of HCl in step (ii) is prepared by passing HCl gas through the organic solvent. In preferred embodiments the organic solvent used in preparing the organic solution of HCl is selected from the group comprising a C_{1-4} alcohol, ethyl acetate and acetonitrile or mixtures thereof. Preferably the C_{1-4} alcohol is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol and t-butanol or mixtures thereof. Most preferably, the C_{1-4} alcohol is selected from methanol, ethanol, isopropanol and n-butanol or mixtures thereof.

The desired nilotinib dihydrochloride salt is obtained from the reaction mixture in step (ii) by precipitation. In certain preferred embodiments an anti-solvent is added to the mixture from step (ii) in order to help precipitate the desired nilotinib dihydrochloride salt. An anti-solvent can be added to a solvent system in order to reduce the solubility of a solute, in this case the nilotinib dihydrochloride salt, in that solvent system thus causing the solute to precipitate out of solution. The inventors have found for example that when N,N-dimethylacetamide is used as the organic solvent system and concentrated HCl is used as the source of HCl, an anti-solvent is not needed.

Examples of anti-solvents are acetone, acetonitrile, dichloromethane, ethyl acetate, tetrahydrofuran, toluene and acetone-toluene. In particularly preferred embodiments the solvent/ anti-solvent combination is as defined in table 1.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>Anti-solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Methanol-Water</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>not needed when cone. HCl is used</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Acetone</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>N-Methyl-pyroUdine</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>N-Methyl-pyroHdine</td>
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</tr>
<tr>
<td>N-Methyl-pyrildidine</td>
<td>Toluene</td>
</tr>
<tr>
<td>Methanol</td>
<td>Acetone-Toluene</td>
</tr>
</tbody>
</table>

Table 1

In certain embodiments the reaction mixture is stirred until the precipitate forms. In alternate embodiments the precipitate may form spontaneously or the reaction mixture may be cooled to facilitate the formation of the desired precipitate. The inventors have found stirring the reaction mixture to form the precipitate to be particularly advantageous.

In certain embodiments the formation of the desired precipitate may cause the reaction mixture to become increasingly viscous. In these embodiments additional solvent may be added to loosen the mixture. Most preferably the same solvent system utilised in step (i) is added to "loosen" the mixture. It will be apparent to the skilled person that in those embodiments where an anti-solvent is utilised the addition of solvent may cause the nilotinib dihydrochloride salt to re-dissolve. In such situations the skilled person would realise that additional anti-solvent may be added to cause the desired nilotinib dihydrochloride salt to precipitate from the solution.

The precipitated solid may then be isolated by any means available to the skilled person. Most advantageously the precipitated nilotinib dihydrochloride salt is isolated by filtration. Most preferably the filtered nilotinib dihydrochloride salt is dried in conditions of reduced pressure. The inventors have found that drying under vacuum or near vacuum until a
constant weight is achieved is particularly preferred. Accordingly, in particularly advantageous embodiments the filtered nilotinib dihydrochloride salt is dried in a vacuum oven, preferably at temperatures that do not cause dissociation or degradation of the nilotinib dihydrochloride salt. The inventors have found drying between about 55-65°C, most preferably between about 60-65°C to be particularly advantageous. Further preferred embodiments provide drying in the vacuum oven at between about 500-600 mmHg pressure.

The inventors have found that the process of the fourth aspect of the invention is particularly advantageous in preparing nilotinib dihydrochloride dihydrate. Accordingly, there is provided a process for preparing nilotinib dihydrochloride dihydrate comprising:

(i) mixing nilotinib free base in an organic solvent system;
(ii) adding either concentrated HC1 or an organic solution of HC1 to the mixture from step (i) or adding the mixture from step (i) to either concentrated HC1 or an organic solution of HC1; and
(iii) isolating the nilotinib dihydrochloride dihydrate.

The present invention also provides a process according to the fourth aspect and embodiments thereof, for preparing anhydrous nilotinib dihydrochloride wherein the nilotinib free base, the organic solvent system, and the concentrated HC1 or the organic solution of HC1 are all anhydrous and the process is carried out under anhydrous conditions.

A fifth aspect of the invention provides nilotinib dihydrochloride having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A sixth aspect of the invention provides nilotinib dihydrochloride dihydrate having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.

A seventh aspect of the invention provides anhydrous nilotinib dihydrochloride having a purity of greater than 95%, preferably greater than 99%, most preferably greater than 99.5%.
Preferably the nilotinib dihydrochloride of the first and fifth aspects of the invention, the nilotinib dihydrochloride dihydrate of the second and sixth aspects of the invention, and the anhydrous nilotinib dihydrochloride of the third and seventh aspects of the invention are suitable for use in medicine, preferably for treating cancer, preferably for treating adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

In an eighth aspect of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of nilotinib dihydrochloride and at least one pharmaceutically acceptable excipient. In a most preferred embodiment of the eighth aspect of the present invention, the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or may in alternative embodiments be anhydrous nilotinib dihydrochloride. Further preferred embodiments of the eighth aspect of the invention provide a composition for use in the treatment of cancer, most preferably for use in the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A ninth aspect of the invention provides the use of nilotinib dihydrochloride in the manufacture of a medicament for treating cancer. Preferably the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or alternatively the nilotinib dihydrochloride may be anhydrous nilotinib dihydrochloride. Preferably the medicament is for treating adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

A tenth aspect of the invention provides a method of treating cancer comprising administering a therapeutically effective amount of nilotinib dihydrochloride to a patient in need thereof. Preferably the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or alternatively the nilotinib dihydrochloride may be anhydrous nilotinib dihydrochloride. Preferably the patient is a mammal, preferably a human. Preferably the patient is an adult with chronic phase and accelerated phase Philadelphia chromosome positive chronic
myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

**Examples**

The following non-limiting examples illustrate specific embodiments of the present invention. They are not intended to limit the scope of the present invention in any way.

**Example 1**

Nilotinib free base (2 g, 3.76 mmol) was completely dissolved in N,N-dimethylacetamide (30 ml). Concentrated hydrochloric acid (34.7% w/v, 3.76 mmol) at 24-30°C was added to the solution and the reaction mixture was stirred for about 30 minutes until a precipitate formed. The stirring was continued for about 1 hour. The precipitated solid was then filtered through a Buchner funnel and washed with N,N-dimethylacetamide (20 ml). The precipitated solid was initially suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, all of which confirmed that the obtained solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.16 g (96%)

Chemical purity: 98.72% (measured by HPLC)

**Example 2**

Nilotinib free base (1 g, 1.88 mmol) was suspended in acetone (20 ml). Ethanol-HCl (10.7% w/v, 5.64 mmol) was added at 24-30°C and the reaction mixture was stirred until a clear solution was obtained. The solution was stirred for a further 10 minutes at the same temperature. A thick, viscous mass was observed as the precipitate formed and acetone (30 ml) was added to loosen the mass. The mixture was stirred for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and further washed with acetone (10 ml). The precipitated solid was initially suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA,
KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.72 g (60%)
Chemical purity: 99.46% (measured by HPLC)

Example 3
Nilotinib free base (1 g, 1.88 mmol) was suspended in n-butanol (20 ml). Ethanol-HCl (10.7% w/v, 5.64 mmol) was added at 24-30°C. The slurry was stirred for a further 10 minutes at the same temperature. A thick, viscous mass was observed as the precipitate formed and n-butanol (30 ml) was added to loosen the mass. The mixture was stirred for a further 5 hours. The precipitated solid was then filtered though a Buchner funnel and further washed with n-butanol (10 ml). The precipitated solid was initially suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.68 g (56%)
Chemical purity: 95.42% (measured by HPLC)

Example 4
Nilotinib free base (1 g, 1.88 mmol) was suspended in methanol (20 ml). Ethanol-HCl (10.7% w/v, 5.64 mmol) was added at 24-30°C and the reaction mixture was stirred until a clear solution was obtained. Methanol (10 ml) was then added to the reaction mixture and stirred for a further 5 hours. Ethyl acetate (70 ml) was added as an anti-solvent. A thick slurry formed which was further stirred for about 1 hour. The precipitated solid was then filtered though a Buchner funnel and initially suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.62 g (51%)
Chemical purity: 98.47% (measured by HPLC)
Example 5
Nilotinib free base (1 g, 1.88 mmol) was suspended in acetonitrile (25 ml). Acetonitrile-HCl (11.32% w/v, 5.64 mmol) was then added and the reaction mixture maintained at 24-30°C. The reaction mixture was stirred until a thick slurry formed. The reaction mixture was stirred for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and further washed with acetonitrile (10 ml). The precipitated solid was initially suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.87 g (72%)
Chemical purity: 96.47% (measured by HPLC)

Example 6
Nilotinib free base (2 g, 3.76 mmol) was suspended in methanol (40 ml). Methanol-HCl (7.7% w/v, 7.52 mmol) was added at 24-30°C under stirring to obtain a clear solution and the reaction mixture was stirred for 5 hours. Ethyl acetate (100 ml) was added as an anti-solvent. A thick slurry formed which was further stirred for about 1 hour. The precipitated solid was then filtered through a Buchner funnel and washed with ethyl acetate (20 ml). The washed precipitate was suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.1 g (46%)
Chemical purity: 96.6% (measured by HPLC)

Example 7
Nilotinib free base (2 g, 3.76 mmol) was suspended in methanol (40 ml). To this suspension was added water (20 ml) and concentrated HCl (34.75% w/v, 11.3 mmol). The reaction mixture was maintained at 24-30°C and stirred for approximately 5 hours until a clear solution was obtained. Ethyl acetate (130 ml) was added as an anti-solvent. A slurry was formed and the reaction mixture was stirred for a further 16-18 hours. The precipitated
solid was then filtered through a Buchner funnel and washed with ethyl acetate (20 ml). The washed precipitate was suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dibydrate.

Yield (% molar): 1.3 g (54%)
Chemical purity: 96.81% (measured by HPLC)

Example 8
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N,N-dimethylacetamide (30 ml). Ethyl acetate-HCl (12.98% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C for about 48 hours. After this time no precipitation was observed. Ethyl acetate (100 ml) was then added as an anti-solvent and the mixture stirred for about 1 hour until a precipitate formed. The resulting precipitated solid was then filtered through a Buchner funnel and washed with ethyl acetate (20 ml). The washed precipitate was suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dibydrate.

Yield (% molar): 0.62 g (51%)
Chemical purity: 95.94% (measured by HPLC)

Example 9
Nilotinib free base (5 g, 9.44 mmol) was suspended in ethanol (100 ml). Ethanol-HCl (10.7% w/v, 18.88 mmol) was added to this suspension and the reaction mixture was stirred whilst being maintained at 24-30°C until a clear solution formed. The stirring continued for approximately 55 minutes until a precipitate formed and then for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with ethanol (25 ml). The washed precipitate was suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA,
KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 3.71 g (62%)
Chemical purity: 97.09% (measured by HPLC)

Example 10

Nilotinib free base (5 g, 9.44 mmol) was dissolved in N,N-dimethylacetamide (75 ml). Concentrated HCl (34.7% w/v, 28.32 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 30 minutes until a precipitate formed and then for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with N,N-dimethylacetamide (100 ml). The washed precipitate was suction dried for 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 3.6 g (60%)
Chemical purity: 98.25% (measured by HPLC)

Example 11

Nilotinib free base (1 g, 1.88 mmol) was dissolved in N,N-dimethylacetamide (15 ml). Concentrated HCl (34.7% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 30 minutes until a precipitate formed and then for a further 2.5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with N,N-dimethylacetamide (5 ml). The washed precipitate was suction dried for 2 hours, followed by drying in a vacuum oven at 50°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.69 g (57%)
Chemical purity: 99.5% (measured by HPLC)
Example 12
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N,N-dimethylacetamide (30 ml). Concentrated HCl (34.7% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 30 minutes until a precipitate formed and then for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with N,N-dimethylacetamide (20 ml). The washed precipitate was suction dried for 20 minutes, followed by drying in a vacuum oven at 50°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.14 g (95%)
Chemical purity: 98.12% (measured by HPLC)

Example 13
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N,N-dimethylacetamide (30 ml). Concentrated HCl (34.7% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 30 minutes until a precipitate formed and then for a further 2 hours. The precipitated solid was then filtered through a Buchner funnel and washed with N,N-dimethylacetamide (20 ml). The washed precipitate was suction dried for 1 hour, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.218 g (100%)
Chemical purity: 97.8% (measured by HPLC)

Example 14
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N,N-dimethylacetamide (30 ml). Concentrated HCl (34.7% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 1 hour until a precipitate formed and then for a further 5 hours. The
precipitated solid was then filtered through a Buchner funnel and washed with N,N-
dimethylacetamide (20 ml). The washed precipitate was suction dried for about 30 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.987 g (82%)
Chemical purity: 98.23% (measured by HPLC)

Example 15
Nilotinib free base (5 g, 9.44 mmol) was dissolved in N-methyl-pyrrolidine (75 ml). Concentrated HCl (34.7% w/v, 28.32 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 30 minutes until a precipitate formed and then for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with N-methyl-
pyrrolidine (50 ml). The washed precipitate was suction dried for about 30 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 3.169 g (53%)
Chemical purity: 95.8% (measured by HPLC)

Example 16
Nilotinib free base (15 g, 28.35 mmol) was dissolved in N,N-dimethylacetamide (150 ml). Concentrated HCl (34.7% w/v, 56.71 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 3 minutes until a precipitate formed and then for a further 2 hours. The precipitated solid was then filtered through a Buchner funnel and initially suction dried for about 45 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.
Yield (% molar): 14.8 g (82%)
Chemical purity: 95.90% (measured by HPLC)

Example 17
Nilotinib free base (1 g, 1.88 mmol) was suspended in n-butanol (25 ml). n-Butanol-HCl (13.65% w/v, 5.64 mmol) was added to this suspension and the reaction mixture was stirred whilst being maintained at 24-30°C. The stirring continued for approximately 25 minutes until a precipitate formed and then for a further 5 hours. The precipitated solid was then filtered through a Buchner funnel and washed with n-butanol (10 ml). The washed precipitate was initially suction dried for about 45 minutes, followed by drying in a vacuum oven at 60-65°C for 6 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.0 g (83%)
Chemical purity: 96.06% (measured by HPLC)

Example 18
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N-methyl-pyrroHdine (30 ml). Ethyl acetate-HCl (12.98% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C for about 24 hours. After this time no precipitation was observed. Ethyl acetate (100 ml) was then added to this clear solution as an anti-solvent. A precipitate formed immediately and the mixture stirred for about 1 hour. The resulting precipitated solid was then filtered through a Buchner funnel and washed with ethyl acetate (20 ml). The washed precipitate was suction dried for 15 minutes, followed by drying in a vacuum oven at 60-65°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.72 g (60%)
Chemical purity: 98.8% (measured by HPLC)

Example 19
Nilotinib free base (2 g, 3.76 mmol) was dissolved in N-methyl-pyrrolidine (30 ml). Acetonitrile-HCl (11.32% w/v, 3.76 mmol) was added to this solution and the reaction mixture was stirred whilst being maintained at 24-30°C for about 24 hours. After this time no precipitation was observed. Ethyl acetate (100 ml) was then added to this clear solution as an anti-solvent and the mixture stirred for about 30 minutes until a precipitate formed. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 15 minutes, which was then dried in an oven at 60-65°C for 4 hours. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.41 g (34%)
Chemical purity: 98.50% (measured by HPLC)

Example 20
Nilotinib free base (2 g, 3.76 mmol) was suspended in ethanol (40 ml) at 25-30°C. Ethanol-HCl (10.7% w/v, 7.52 mmol) at 24-30°C was added to the suspension. The reaction mixture was stirred for 24 hours, during which time a precipitate had formed. The precipitated solid was then filtered through a Buchner funnel and washed with ethanol (20 ml). The washed solid was dried in a vacuum oven at 60-65°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the obtained solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.7 g (70%)
Chemical purity: 92.13% (measured by HPLC)

Example 21
Nilotinib free base (2 g, 3.76 mmol) was suspended in methanol (40 ml) at 25-30°C. Ethanol-HCl (10.7% w/v, 7.52 mmol) at 24-30°C was added to the suspension. The reaction mixture was stirred initially for 5 minutes until a clear solution was observed. Ethyl acetate (100 ml) was then added to this clear solution as an anti-solvent and the mixture was stirred for about 30 minutes until a precipitate formed. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 15 minutes,
followed by drying in a vacuum oven at 60-65°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 1.5 g (62%)
Chemical purity: 95.64% (measured by HPLC)

Example 22
Nilotinib free base (1 g, 1.88 mmol) was dissolved in N,N-dimethylacetamide (10 ml) at 25-30°C. This solution was added to a mixture of concentrated HCl (34.7% w/v, 7.52 mmol) in N,N-dimethylacetamide (10 ml) and stirred at 25-30°C for about 40 minutes until a precipitate was observed and then for a further 5 hours. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 15 minutes, followed by drying in a vacuum oven at 60-65°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.715 g (59%)
Chemical purity: 96.7% (measured by HPLC)

Example 23
Nilotinib free base (3 g, 5.64 mmol) was suspended in dimethyl sulfoxide (24 ml) to obtain a light brown coloured slurry. Concentrated HCl (34.7% w/v, 11.28 mmol) was added at 24-30°C whilst stirring and a clear solution was obtained. This reaction mixture was maintained at 24-30°C for 5 hours. A precipitate did not form. Acetone (24 ml) was then added as an anti-solvent and a precipitate formed after 5-10 minutes. The slurry was stirred for a further hour at 24-30°C. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 60-65°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 3.1 g (86%)
Chemical purity: 98.2% (measured by HPLC)

Example 24
Nilotinib free base (3 g, 5.64 mmol) was suspended in dimethyl sulfoxide (24 ml) at 24-30°C resulting in an off-white coloured slurry. Concentrated HCl (34.7% w/v, 11.28 mmol) was added and the reaction mixture stirred for about 5 hours. Dichloromethane (24 ml) was added as an anti-solvent and precipitation was observed after 20-25 minutes, the slurry was stirred for a further hour at 24-30°C. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 3.21 g (89%)

Chemical purity: 98.3% (measured by HPLC)

Example 25
Nilotinib free base (2 g, 3.76 mmol) was suspended in dimethyl sulfoxide (16 ml) under stirring at 24-30°C resulting in a slurry. Concentrated HCl (34.7% w/v, 7.52 mmol) was added and the slurry stirred for about 5 hours. Acetonitrile (30 ml) was added as an anti-solvent and precipitation was observed after 20-25 minutes, the slurry was stirred for a further hour at 24-30°C. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 2.1 g (87%)

Chemical purity: 97.7% (measured by HPLC)

Example 26
Nilotinib free base (2 g, 3.76 mmol) was suspended in dimethyl sulfoxide (24 ml) at 24-30°C resulting in an off-white coloured slurry. Concentrated HCl (34.7% w/v, 7.52 mmol)
was added and the slurry stirred for about 5 hours. Tetrahydrofuran (30ml) was added as an anti-solvent and precipitation was observed after 20-25 minutes, the slurry was stirred for a further 30 minutes at 24-30°C. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 1 hour, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate yellow solid.

Yield (% molar): 1.9 g (79%)

Chemical purity: 98.8% (measured by HPLC)

Example 27

Nilotinib free base (1 g, 1.88 mmol) was suspended in N,N-dimethylformamide (15 ml) whilst stirring resulting in a light brown coloured slurry. Concentrated HCl (34.7% w/v, 1.88 mmol) was added at 24-30°C whilst stirring and a clear solution was obtained. This reaction mixture was maintained at 24-30°C for 10-15 minutes. A precipitate formed after about 20 minutes. The slurry was stirred for a further hour at 24-30°C. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 60-65°C for 15 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, TCF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.58 g (96%)

Chemical purity: 97.1% (measured by HPLC)

Example 28

Nilotinib free base (1 g, 1.88 mmol) was suspended in tetrahydrofuran (25 ml) under stirring at 24-30°C resulting in the formation of a light yellow coloured slurry. Concentrated HCl (34.7% w/v, 1.88 mmol) was added and the slurry stirred for about 5 hours. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.
analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.42 g (70%)
Chemical purity: 97.5% (measured by HPLC)

Example 29
Nilotinib free base (1 g, 1.88 mmol) was suspended in acetonitrile (25 ml) under stirring at 24-30°C resulting in the formation of a light yellow coloured slurry. Concentrated HCl (34.7% w/V, 5.64 mmol) was added and the slurry stirred for about 5 hours. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.69 g (57%)
Chemical purity: 98.7% (measured by HPLC)

Example 30
Nilotinib free base (1 g, 1.88 mmol) was suspended in N-methyl-pyrrolidine (20 ml) under stirring at 24-30°C resulting in a transparent orange reaction mixture. Concentrated HCl (34.7% w/V, 5.64 mmol) was added and the slurry stirred for about 4 hours. Ethyl acetate (20 ml) was added as an anti-solvent and precipitation was observed. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 5 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.64 g (53%)
Chemical purity: 98.8% (measured by HPLC)

Example 31
Nilotinib free base (1 g, 1.88 mmol) was suspended in N-methyl-pyrrolidine (20 ml) under stirring at 24-30°C resulting in a transparent orange reaction mixture. Concentrated HCl
(34.7% w/v, 5.64 mmol) was added and the slurry stirred for about 4 hours. Acetone (20 ml) was added as an anti-solvent and precipitation was observed. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 5 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.65 g (54%)
Chemical purity: 95.5% (measured by HPLC)

Example 32
Nilotinib free base (1 g, 1.88 mmol) was suspended in N-methyl-pyrrolidine (20 ml) under stirring at 24-30°C resulting in a transparent orange reaction mixture. Concentrated HCl (34.7% w/v, 5.64 mmol) was added and the slurry stirred for about 4 hours. Toluene (30 ml) was added as an anti-solvent and precipitation was observed. The resulting precipitated solid was then filtered through a Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 5 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.67 g (56%)
Chemical purity: 96.8% (measured by HPLC)

Example 33
Nilotinib free base (1 g, 1.88 mmol) was suspended in methanol (20 ml) at 24-30°C. The suspension was stirred and maintained at this temperature until a slurry was obtained. The reaction mixture was then heated to 45-50°C and concentrated HCl (34.75% w/v, 5.64 mmol) was added whilst stirring the slurry until a clear solution was observed. The solution was further heated and maintained at about 65°C for 3 hours. Precipitation was not observed during the cooling of the solution. A mixture of acetone (40 ml) and toluene (20 ml) was added when the mixture was cooled to 24-30°C and further stirred for 15 minutes. A yellow coloured solid precipitated from the solution and the slurry was stirred for a further 20 minutes at 24-30°C. The resulting precipitated solid was then filtered through a
Buchner funnel and initially suction dried for 30 minutes, followed by drying in a vacuum oven at 50-55°C for 12 hours at approximately 600 mmHg pressure to yield a light yellow coloured solid. The dried solid was subjected to XRPD, DSC, TGA, KF, HCl content and chloride content analyses, which all confirmed that the precipitated solid was nilotinib dihydrochloride dihydrate.

Yield (% molar): 0.69 g (57%)
Chemical purity: 99.1% (measured by HPLC)

The XRPDs were recorded on a Bruker D8 Advance (BRUKER AXS) Instrument, using Cu Kα-radiation as the X-ray source and LynxEye as the detector, with a 2Θ range of from 3° to 50°, a step-size of 0.05° and a time/step of 1 sec. Samples were placed on a silica background holder.

The DSCs were recorded on a Perkin Elmer Pyris 1, over a temperature range of from 25°C to 350°C and at a rate of heating of 10°C/min. The DSC sample/cell chamber was purged with 40ml/min of ultra high purity indium. The accuracy of the measured sample temperature with this method is within about ±1°C. The sample was placed into a closed aluminium DSC pan with pinhole. At least 2mg of sample powder was placed in the pan and sealed.

The TGAs were recorded on a Perkin Elmer Pyris 1. Samples of at least 10mg were analysed at a heating rate of 10°C/min in the temperature range of from 25°C to 350°C.

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.
Claims

1. Nilotinib dihydrochloride.

2. Crystalline nilotinib dihydrochloride.

3. A hydrate of nilotinib dihydrochloride.

4. A hydrate of nilotinib dihydrochloride according to claim 3, wherein the hydrate is nilotinib dihydrochloride dihydrate.

5. Nilotinib dihydrochloride dihydrate according to claim 4, having an X-ray diffraction pattern comprising peaks at 7.18, 14.32, 23.34 and 27.62 ± 0.2 degrees 2-theta.

6. Nilotinib dihydrochloride dihydrate according to claim 5, having an X-ray diffraction pattern comprising further peaks at 8.47, 10.25, 11.61, 12.34, 12.62, 17.15, 17.84, 19.34, 21.55, 21.93, 22.18, 24.17, 24.5, 25.56, 26.22 and 29.49 ± 0.2 degrees 2-theta.

7. Nilotinib dihydrochloride dihydrate according to any one of claims 4 to 6, having an X-ray diffraction pattern substantially as shown in Figure 1.

8. Nilotinib dihydrochloride dihydrate according to any one of claims 4 to 7, having a differential scanning calorimetry thermogram substantially as shown in Figure 2.

9. Nilotinib dihydrochloride diliydrate according to any one of claims 4 to 8, having a thermogravimetric analysis thermogram substantially as shown in Figure 3.

10. Anhydrous nilotinib dihydrochloride.

11. A process for preparing nilotinib dihydrochloride comprising:

(i) mixing nilotinib free base in an organic solvent system;
adding either concentrated HCl or an organic solution of HCl to the mixture from step (i) or adding the mixture from step (i) to either concentrated HCl or an organic solution of HCl; and

(iii) isolating the nilotinib hydrochloride salt.

12. A process according to claim 11, wherein the organic solution of HCl in step (ii) is prepared by passing HCl gas through the organic solvent.

13. A process according to claim 12, wherein the organic solvent used in preparing the organic solution of HCl is selected from the group comprising a C₄ alcohol, ethyl acetate and acetonitrile or mixtures thereof.

14. A process according to claim 13, wherein the C₄ alcohol is selected from methanol, ethanol, isopropanol and n-butanol or mixtures thereof.

15. A process according to any one of claims 11 to 14, wherein the organic solvent system comprises N,N-dimethylacetamide, methanol, methanol-water, acetone, ethanol, acetonitrile, isopropyl alcohol, n-butanol, N-methyl-pyrrolidine, tetrahydrofuran, dimethyl sulfoxide or N,N-dimethylformamide or mixtures thereof.

16. A process according to any one of claims 11 to 15, wherein an anti-solvent is added to the mixture from step (ii) in order to help precipitate the desired nilotinib dihydrochloride salt.

17. A process according to claim 16, wherein the solvent/anti-solvent combination is as defined in table 1.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Anti-solvent</th>
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</thead>
<tbody>
<tr>
<td>Methanol</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>Methanol-Water</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>not needed when cone. HCl is used</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Acetone</td>
</tr>
<tr>
<td>Dimethyl sulfoxide</td>
<td>Dichloromethane</td>
</tr>
</tbody>
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Dimethyl sulfoxide & Acetonitrile  
Dimethyl sulfoxide & Tetrahydrofuran  
N-Methyl-pyrrolidine & Ethyl acetate  
N-Methyl-pyrrolidine & Acetone  
N-Methyl-pyrrolidine & Toluene  
Methanol & Acetone-Toluene  

Table 1

18. A process according to any one of claims 11 to 17, for preparing nilotinib dihydrochloride dihydrate.
19. A process according to any one of claims 11 to 17, for preparing anhydrous nilotinib dihydrochloride, wherein the nilotinib free base, the organic solvent system, and the concentrated HCl or the organic solution of HCl are all anhydrous and the process is carried out under anhydrous conditions.
20. Nilotinib dihydrochloride having a purity of greater than 95%.
22. Nilotinib dihydrochloride for treating cancer.
23. Nilotinib dihydrochloride according to any one of claims 20 to 22, wherein the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or anhydrous nilotinib dihydrochloride.
24. A pharmaceutical composition comprising nilotinib dihydrochloride and at least one pharmaceutically acceptable excipient.
25. A composition according to claim 24, wherein the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or anhydrous nilotinib dihydrochloride.
26. A composition according to claim 24 or 25, for use in the treatment of cancer.
27. A composition according to claim 26, for use in the treatment of an adult with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

28. Use of nilotinib dihydrochloride in the manufacture of a medicament for treating cancer.

29. The use according to claim 28, wherein the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or anhydrous nilotinib dihydrochloride.

30. The use according to claim 28 or 29, wherein the medicament is for treating an adult with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.

31. A method of treating cancer comprising administering a therapeutically effective amount of nilotinib dihydrochloride to a patient in need thereof.

32. The method according to claim 31, wherein the nilotinib dihydrochloride is nilotinib dihydrochloride dihydrate or anhydrous nilotinib dihydrochloride.

33. The method according to claim 31 or 32, wherein the patient is an adult with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib.
Figure 3

Delta Y = 5.963 %
X1 = 25.00 °C
Y1 = 99.931 %
X2 = 112.43 °C
Y2 = 93.968 %

Delta Y = 7.103 %
X1 = 129.86 °C
Y1 = 93.785 %
X2 = 234.09 °C
Y2 = 89.662 %
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2007/015871 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; MANLEY PAUL W [CH]; SHIEH) 8 February 2007 (2007-02-08) paragraph [0024]; claims 1-3, 11-12, 16-17; examples 1, 6</td>
<td>1-33</td>
</tr>
</tbody>
</table>

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 document but published on or after the international filing date
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