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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF PALIPERIDONE

(57) Abstract: The present invention relates to a process for preparation and purification of 3-[2-[4-(6- fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H- pyrido[1,2-a]pyrimidin-4-one, also known as paliperidone or 9-hydroxy risperidone.

AN IMPROVED PROCESS FOR THE PREPARATION OF PALIPERIDONE

FIELD OF THE INVENTION

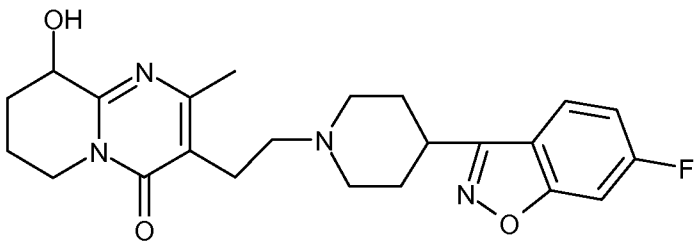
The present invention relates to a process for preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, also known as paliperidone or 9-hydroxy risperidone and intermediates useful in the process.

The present invention further relates to a process for the preparation of pure and highly pure paliperidone and a process for the preparation of pure and highly pure paliperidone that is free or substantially free of 3-[2-[4-(6-fluoro-1,2-benzisoxazole-3-yl)-1-piperdinyl]ethyl]-6,7,8,9-2-methyl-4H-pyrido[1,2-a]pyrimidin-4,9-dione (hereinafter "the 9-oxo impurity").

The present invention allows the preparation of pure and highly pure paliperidone without the need of tedious purification steps such as multiple solvent extractions or chromatographic purification such as column chromatography.

BACKGROUND OF THE INVENTION

The synthesis of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, also known as paliperidone (formula **I**), is disclosed in European Patent No. EP 368388.



I

Paliperidone is an atypical antipsychotic drug developed by Janssen Pharmaceuticals. Chemically, paliperidone is a primary active metabolite of the antipsychotic drug risperidone. Paliperidone is approved by the FDA for treatment of schizophrenia. It is also effective in the treatment of bipolar mania.

A number of methods for preparing paliperidone have been described in the art. For example:

U.S. Patent No. 5,688,799 discloses preparation of a precursor of paliperidone, namely, 3-(2-hydroxyethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, by using 2-amino-3-pyridinol, 2-acetyl butyrolactone and p-toluene sulfonic acid.

U.S. Publication No. 2007/0260061 A1 discloses preparation of a starting material of paliperidone, namely, crystalline 3-(2-hydroxyethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, substantially free of 2-acetylbutyrolactone.

U.S. Publication No. 2009/0247553 A1 discloses preparation of pure paliperidone or pharmaceutically acceptable salts thereof substantially free of the 9-oxo impurity wherein crude paliperidone or a pharmaceutically acceptable salt of crude paliperidone is dissolved or suspended in a first organic solvent. Solid paliperidone is recovered from the first organic solvent and dissolved in a second organic solvent. The dissolved paliperidone and second organic solvent are then combined with a reducing agent, and the pure paliperidone is isolated from the reaction mass.

WO 2008/024415 A2 discloses preparation of intermediates useful in preparing paliperidone such as 3-benzyloxy-2-amino-pyridine ("BOPA"), 3-(2-hydroxyethyl)-6,7,8,9-tetrahydro-9-benzyloxy-2-methyl-4H-pyrrido[1,2-a]-pyrimidine-4-one ("HMBP"), 3-(2-chloroethyl)-2-methyl-9-benzyloxy-4H-pyrrido[1,2-a]-pyrimidine-4-one ("CMBP"), 3-(2-chloroethyl)-2-methyl-9-hydroxy-4H-pyrrido[1,2-a]-pyrimidine-4-one ("CMHP"), 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]-pyrimidine-4-one ("CMHTP"). This patent also discloses preparation of 9-hydroxy risperidone (paliperidone) and reports the XRD pattern of CMHTP.

WO 2008/021342 A2 discloses preparation of amorphous and crystalline forms of paliperidone. XRD patterns and solid state ^{13}CNMR spectrum are also reported.

WO 2008/021345 A2 discloses preparation of paliperidone from CMHTP in a variety of solvents under different reaction conditions.

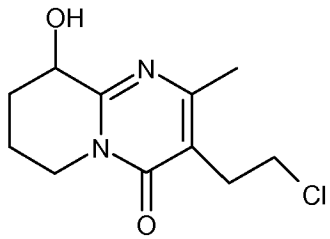
WO 2008/021346 A2 discloses a purification process to obtain paliperidone free of impurities.

WO 2008/087557 A2 discloses preparation of intermediates of paliperidone such as 9-hydroxy-3-(2-chloroethyl)-2-methyl-4H-pyrrido[1,2-a]-pyrimidine-4-one and 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrrido[1,2-a]-pyrimidine-4-one.

WO 2009/060297 discloses preparation of paliperidone which includes the steps of reacting paliperidone free base with an acid in the presence of an organic solvent, isolating the paliperidone acid addition salt and converting the paliperidone salt to paliperidone free base. The identified acids are hydrochloric, hydrobromic, hydroiodic, ortho phosphoric acid, fumaric acid, and oxalic acid.

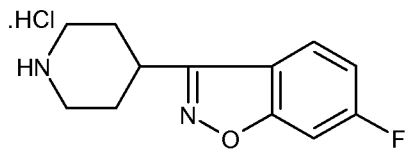
The above identified processes for preparing paliperidone exhibit problems which the present invention overcomes. One of the problems with some of the identified processes is the requirement for large volumes of solvents, many of which are costly and potentially dangerous. Another problem associated with some of the above identified processes is the requirement for long and tedious techniques such as distillation, solvent extractions and chromatographic purification.

EP 368388 B1 also discloses preparation of paliperidone (formula **I**) by condensation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (hereinafter referred to as "formula **II**" or "**II**")



II

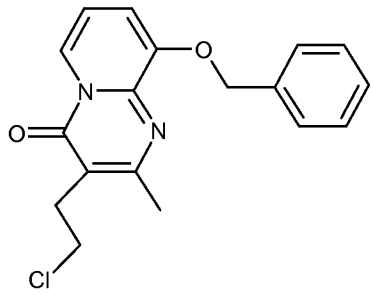
with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole·HCl (hereinafter referred to as "formula **III**" or "**III**"),



III

in the presence of an amine in methanol at 60°C, which is followed by its purification to obtain pure paliperidone. Pharmaceutical formulations containing paliperidone are also disclosed.

The intermediate of formula II in the synthesis of paliperidone can be obtained by hydrogenation of 3-(2-Chloroethyl)-2-methyl-9-(phenylmethoxy)-4H-pyrido[1,2-a]pyrimidin-4-one (hereinafter referred to as "formula **IV**" or "**IV**"):

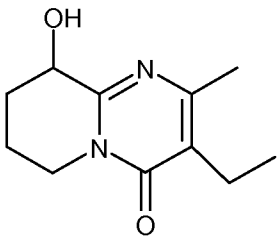


IV

in methanol at normal pressure and at room temperature over Pd/C catalysts to obtain the oily residue of formula II.

EP 368388 B1 further discloses that the compound of formula II is condensed with the compound of formula III in the presence of an amine and methanol to obtain crude paliperidone (I). The crude paliperidone is purified by subjecting the crude paliperidone to two column chromatographic separations using a mixture of methanol and chloroform saturated with ammonia. The paliperidone obtained from the column chromatographic separations is further crystallized by using 2-propanone and finally recrystallized from 2-propanol.

There are a number of problems with the process described in EP 368388 B1. One problem is that the hydrogenation of the compound of formula IV as described in EP 368388 may produce dechlorinated product, i.e., ethyl tetrahydro pyridopyrimidine (hereinafter referred to as "formula **V**" or "**V**"), as a by-product. This may result in lower yield and inferior quality, which is undesirable.



V

For example, when hydrogenation of the compound of formula IV was done in methanol as per EP 368388 B1, a significant quantity of undesired by-product of the compound of formula V was formed (more than 50% by HPLC) during this reaction.

An additional problem with the process described in EP 368388 B1 is the purification of crude paliperidone by column chromatography. This purification process is laborious, renders the process industrially undesirable and causes low yield.

OBJECT OF THE INVENTION

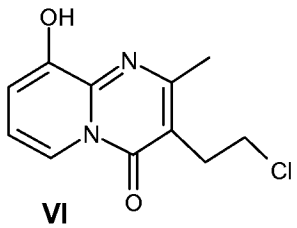
The object of the present invention is to provide a simple and efficient process for the preparation of paliperidone.

Another object of the present invention is to provide a simple and efficient process for purifying paliperidone that avoids the use of column chromatography and/or eliminates the necessity of column chromatography for separation and/or purification.

A further object of the present invention is to provide a simple and efficient process for preparation of intermediates useful in the preparation of paliperidone.

It is a still further object of the present invention to provide a process for the preparation of pure paliperidone by direct filtration without the need for tedious techniques such as distillation, solvent extraction and/or chromatographic purification.

An additional object of the present invention is to provide a process for preparation of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (formula VI) which can be used in the preparation of paliperidone.



VI

It is also an object of the present invention to provide a process for the preparation of a compound of formula II which can be used in the preparation of paliperidone wherein the process for preparation of the compound of formula II results in the production of small amounts of the compound of formula V, preferably less than 25% of the compound of formula V, more preferably less than 20% of the compound of formula V and most preferably less than 15% of the compound of formula V as determined by HPLC.

SUMMARY OF THE INVENTION

The present invention relates to a process for preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, also referred to as paliperidone, 9-hydroxy risperidone or formula I. The process comprises reacting the compound of formula II with the compound of formula III in inert solvents. The reaction is conducted in the presence of a base or a buffer and at a suitable temperature that avoids and/or eliminates the use of column chromatography.

The present invention also relates to processes for the preparation of pure and highly pure paliperidone by means of simple purification techniques. As used herein, "highly pure paliperidone" refers to paliperidone that is at least 99.5% paliperidone, preferably at least 99.75% paliperidone and most preferably at least 99.8% paliperidone as determined by HPLC. The amount of 9-oxo impurity should be less than 0.5%, preferably less than 0.3% and most preferably less than 0.1% as determined by HPLC.

One embodiment of the invention comprises the preparation of the compound of formula II by hydrogenation of the compound of formulas IV or VI in the presence of a hydrogenation catalyst and hydrogen in an acidic medium. A further aspect of this embodiment produces the compound of formula II with less than 25% of the compound of formula V, preferably less than 20% of the compound of formula V and most preferably less than 15% of the compound of formula V as determined by HPLC.

Another embodiment of the invention comprises the preparation of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (formula VI) by reacting 3-benzyloxy-2-amino pyridine with 2-acetyl butyrolactone and phosphorus oxychloride in the presence of a solvent. This aspect of the invention may also include quenching of the reaction with water or a mixture of water and an organic solvent, adjusting the pH of the reaction and isolation of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (formula VI). A further aspect of this embodiment may include the step of extracting the compound of formula VI from the quenched reaction mass by use of a suitable extraction solvent such as methylene chloride prior to isolating the compound of formula VI. Alternatively, the compound for formula VI may be isolated without an extraction solvent by adding a suitable base to the quenched reaction mass. Once the compound of formula VI is isolated, it may be crystallized using an appropriate solvent system.

A further embodiment of the present invention is a process for the preparation of pure paliperidone that comprises reacting the compound of formula II with the compound of formula III in inert solvents and in the presence of a base or a buffer at a suitable temperature to obtain crude paliperidone. Crude paliperidone refers to paliperidone than is less than 99.3% pure as determined by HPLC. The crude paliperidone is purified into pure or highly pure paliperidone by a process that does not require the use of column chromatography and preferably by direct filtration.

An alternative embodiment of the present invention is a process for the purification of the crude paliperidone by reacting the crude paliperidone with an acid to prepare an acid addition salt of paliperidone, isolating the acid addition salt of paliperidone, preferably in a solid form, dissolving or suspending the acid addition salt of paliperidone in a suitable solvent, adding a base to the dissolved or suspended reaction mass of the acid addition salt of paliperidone and isolating pure or highly pure paliperidone from the pH adjusted reaction mass. The pure or highly pure paliperidone may be isolated by direct filtration and without the need for column chromatography.

A still further embodiment of the invention further comprises preparing the compound of formula II by hydrogenation of the compound of formula IV or VI in the presence of a hydrogenation catalyst and hydrogen in an acidic medium to produce the compound of formula II with less than 25% of the compound of formula V, preferably less than 20% of the compound of formula V and most preferably less than 15% of the compound of formula V as determined by HPLC. The compound of formula VI when used in this embodiment is prepared by reacting 3-benzyloxy-2-amino pyridine with 2-acetyl butyrolactone and phosphorus oxychloride in the presence of a solvent.

DESCRIPTION OF THE DRAWINGS

Figure 1 is a representative XRD pattern of the paliperidone prepared in accordance with one embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-

a]pyrimidin-4-one, also referred to as paliperidone, 9-hydroxy risperidone or formula I comprising:

i) reacting the compound of formula II with the compound of formula III in inert solvents selected from the group consisting of alcohols, ketones, esters, ethers, hydrocarbons and mixtures thereof in the presence of a base or a buffer at a suitable temperature; and

ii) isolating the compound of formula I from the reaction mass of step (i).

Suitable solvents for the reaction described in step (i) include alcohols, ketones, esters, ethers, hydrocarbons and mixtures thereof. In one embodiment of the invention, the solvent is an alcohol or mixture of alcohols, preferably C_1 to C_4 alcohols such as methanol or IPA. In another embodiment of the present invention, the solvent for the reaction in step (i) is a ketone or mixture of ketones, preferably a C_3 to C_8 ketone, and most preferably acetone.

If a base is employed is step (i) of this process, it may be an organic base, an inorganic base or a mixture thereof. Examples of organic bases that may be used are tertiary amines such as triethylamine or N-(1-methylethyl)-2-propanamine. Examples of inorganic bases that may be used are alkali metal or alkaline earth metal carbonates, bicarbonates or hydroxides such as sodium carbonate, potassium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide, ammonium hydroxide. When a base is employed in step (i), the solvent for the reaction described in step (i) is a mixture of solvents selected from the group consisting of alcohols, ketones, esters, ethers and hydrocarbons. Preferably, the mixture of solvents is a mixture of ketones and alcohols, most preferably a mixture of ketones and C_1 to C_4 alcohols, such as an acetone/methanol mixture. The ratio of ketone to alcohol is preferably about 1:9 to about 1:1, more preferably about 1:4 to about 1:2 and most preferably about 3:7.

When a base is employed in step (i), the reaction temperature is typically between 25-64°C. When an alcohol such as methanol is used as the solvent in step (i), the preferred reaction temperature is about 60°C to about 63°C. When a mixture of solvents is used in step (i), the reaction is preferably conducted at reflux temperature. When a ketone such as acetone is used as the solvent in step (i), the reaction is preferably carried out at reflux temperature.

When a base is employed in step (i), the process may further employ the step of removing the solvent prior to isolating the compound of formula I. The solvent can be removed by any means known in the art such as vacuum or distillation.

Isolating the compound of formula I in step (ii) when a base is employed may be performed with a solvent selected from water, alcohols, ketones and mixtures thereof. A preferred solvent is alcohols such as methanol, water or a mixture of a C_1 to C_4 alcohol and water, such as a methanol/water mixture. The ratio of alcohol to water used for the isolation is preferably between about 5:95 to about 50:50, most preferably between about 5:95 to about 65:35.

In an alternate embodiment of the invention, isolating the compound of formula I in step (ii) when a base is employed may be performed with a solvent selected from water, alcohols, ketones and mixtures thereof. A preferred solvent is a ketone such as acetone, water or a mixture of a ketone and water, such as an acetone/water mixture. The ratio of ketone to water used for the isolation is preferably between about 5:95 to about 50:50, most preferably between about 5:95 to about 65:35.

If a buffer is employed in step (i) of this process, it may be selected from any known buffer, preferably an inorganic buffer and most preferably an inorganic phosphate buffer such as potassium hydrogen phosphate, dipotassium hydrogen phosphate, potassium phosphate or mixtures thereof. The amount of the buffer present in the reaction mass may range from about 1 mole to about 5 moles of buffer for each mole of the compound of formula II present in the reaction, preferably about 1.5 moles to about 4 moles of buffer for each mole of the compound of formula II present and most preferably about 2 moles to about 3 moles of buffer for each mole of the compound of formula II present in the reaction.

When a buffer is employed in step (i), it may also be necessary to include an initiator for the reaction. Suitable initiators may include inorganic salts of a halide and an alkali metal or alkali earth metal such as sodium or potassium iodide. The amount of the initiator present in the reaction mass may range from about 0.01 mole to about 0.5 moles of initiator for each mole of the compound of formula II present in the reaction, preferably about 0.05 moles to about 0.25 moles of initiator for each mole of the compound of formula II present and most preferably about 0.075 moles to about 0.2 moles of initiator for each mole of the compound of formula II present in the reaction.

When a buffer is employed in step (i), the solvent for the reaction described in step (i) is a mixture of solvents selected from the group consisting of alcohols, ketones, esters, ethers and hydrocarbons. Preferably, the solvent is a C_3 to C_8 ketone or mixture thereof and most preferably

the solvent is acetone. Water may also be present in the reaction of step (i). If water is employed with a buffer in step (i) the ratio of water to solvent should be about 10:90 to about 0.5:99.5, preferably about 5:95 to about 0.75:99.25 and most preferably about 3:97 to about 1:99. In one embodiment of the present invention wherein a buffer is employed in step (i) and actone is employed as a solvent, water may optionally be present in a ratio of water:acetone of about 5:95 to about 0.5:99.5, preferably about 2:98 to about 0.75:99.25 and most preferably about 1:99.

When a buffer is employed, the reaction temperature for step (i) is preferably between 25-75°C, and if a ketone such as acetone is used as the solvent in step (i), the reaction is preferably conducted at reflux temperature.

When a buffer is employed in step (i), the reaction should be allowed to proceed to completion which generally means the amount of compound of formula II in the reaction mass is not more than 10% as determined by HPLC. Once the reaction of step (i) employing a buffer is completed, the reaction mass is cooled to about 0° to about 35°C, preferably about 20° to about 30°C, and the crude paliperidone is isolated from the reaction mass by known techniques such as filtration and may be washed with a suitable solvent such as water, a C_3 to C_8 ketone or mixture thereof. The crude paliperidone may also be dried by conventional methods.

If the compound of formula I, when isolated in step (ii), does not exhibit sufficient purity, it may be further processed according to the present invention to increase the purity level.

The crude paliperidone obtained from step (ii) above, or any other method, may be purified without the use of column chromatography by a purification process comprising:

a) reacting the crude paliperidone with an acid in water to form an aqueous reaction mixture;

b) extracting the aqueous reaction mixture with an organic solvent wherein the organic solvent is selected from the group consisting of esters, chlorinated solvents, hydrocarbons and mixtures thereof and creating an aqueous layer and an organic layer;

c) separating the aqueous layer and organic layer of step (b);

d) adjusting the pH of the aqueous layer with a base to a pH of about 8 to about 10;

e) extracting the pH adjusted aqueous layer with a chlorinated solvent;

f) separating the aqueous layer and the chlorinated solvent;

g) removing the chlorinated solvent to create a reaction mass; and

h) isolating the paliperidone from the reaction mass with a solvent selected from the group consisting of ketones, alcohols, water and mixtures thereof.

The acid employed in step (a) may be an organic acid, a mineral acid or mixtures thereof. Preferably, the acid is an organic acid such as acetic acid. The amount of acid employed should impart a pH to the reaction mixture of about 3 to about 5, preferably about 3.5 to about 4.5.

The organic solvent employed in step (b) can be selected from the group consisting of esters, chlorinated solvents, hydrocarbons and mixtures. A preferred solvent is a chlorinated solvent such as methylene chloride.

The pH of the aqueous layer in step (d) may be adjusted with an organic base, an inorganic base or mixtures thereof. Examples of possible bases are described above. Some of the preferred bases that may be used include liquid ammonium or ammonium hydroxide. The pH of the aqueous layer in step (d) should be adjusted to a pH of about 8 to about 10, and preferably a pH of about 8.5 to about 9.5.

The isolation of the paliperidone in step (h) is preferably performed with solvents selected from ketones, alcohols, water and mixtures thereof, more preferably water, C_1 to C_4 alcohols such as methanol, acetone, isopropyl alcohol and mixtures thereof.

The crude paliperidone obtained from step (ii) above or any other method, may alternatively be purified without the use of column chromatography by a purification process comprising:

A) reacting the crude paliperidone with an acid in a suitable solvent to form an acid addition salt of paliperidone;

B) isolating the addition salt of paliperidone in a solid form, preferably by filtration;

C) dissolving or suspending the solid acid addition salt of paliperidone in a suitable solvent;

D) adjusting the pH of the reaction mass of step (C) with a base to form the free base form of the compound of formula I; and

E) isolating the free base of the compound of formula I formed in step (D).

The acid employed in step (A) may be an organic acid, a mineral acid or mixtures thereof. Preferably, the acid is an organic acid, preferably a mono-carboxylic acid such as acetic acid. The amount of acid employed in step (A) should be at least present in equal molar amounts to the amount of crude paliperidone present in step (A). Preferably, the amount of acid should be

about 1 mole to about 3 moles for every mole of crude paliperidone and most preferably about 1 mole to about 2 moles of acid for every mole of crude paliperidone employed in step (A).

The solvent employed in step (A) can be selected from the group consisting of alcohols, ketones, ethers, hydrocarbons or mixtures thereof. In one embodiment, the solvent employed in step (A) is a C_1 to C_4 alcohol, a mixture of C_1 to C_4 alcohols, a C_3 to C_8 ketone, a mixture of C_3 to C_8 ketones, a C_2 to C_8 ether, a mixture of C_2 to C_8 ethers, a C_3 to C_6 amide, a mixture of C_3 to C_6 amides, a C_2 to C_6 alkyl acetates, a mixture of C_2 to C_6 alkyl acetates, a C_6 to C_{12} aromatic hydrocarbon, a mixture of C_6 to C_{12} aromatic hydrocarbons, acetonitrile, propylene glycol, dimethyl sulphoxide and mixtures thereof. Preferably, the solvent for step (A) is a C_3 to C_8 ketone or mixture thereof, and most preferably the solvent is acetone. Water may also be present in the reaction of step (A).

The reaction temperature of step (A) is preferably about 25°C to about 110°C. If the solvent for step (A) is acetone, ethyl acetate or tetrahydrofuran, the reaction temperature is preferably conducted at reflux temperature. If an aromatic solvent such as toluene is used in step (A), the reaction temperature is preferably about 60° to about 90°C, most preferably about 70°C to about 80°C.

Once the reaction of step (A) is completed, the reaction mass may be cooled to about 0°C to about 20°C, preferably about 0°C to about 15°C, prior to isolating the solid acid addition salt of paliperidone.

The solvents suitable for dissolving or suspending the solid acid addition salt of the paliperidone in step (C) include alcohols, ketones, ethers, hydrocarbons, chlorinated hydrocarbons, water or mixtures thereof. In one embodiment of the present invention the solvent is water, a C_1 to C_4 alcohol, a mixture of C_1 to C_4 alcohols, a C_3 to C_8 ketone, a mixture of C_3 to C_8 ketones, a C_2 to C_8 ether, a mixture of C_2 to C_8 ethers, a C_3 to C_6 amide, a mixture of C_3 to C_6 amides, a C_2 to C_6 alkyl acetates, a mixture of C_2 to C_6 alkyl acetates, a C_6 to C_{12} aromatic hydrocarbon, a mixture of C_6 to C_{12} aromatic hydrocarbons, acetonitrile, propylene glycol, dimethyl sulphoxide and mixtures thereof. A preferred solvent for step (C) is water and a C_3 to C_8 ketone such as acetone.

The pH of the reaction mass of step (D) may be adjusted with an organic base, an inorganic base or mixtures thereof. Examples of possible bases are described above. Some of the preferred bases are nitrogen containing bases such as liquid ammonium, ammonium hydroxide,

triethylamine, N-(1-methylethyl)-2-propanamine or mixtures thereof. The pH of the aqueous layer should be adjusted to a pH of about 8 to about 10, and preferably a pH of about 9.0 to about 10.0. The amount of base employed should at least be present in at least equal molar amounts to the amount of acid addition salt paliperidone present in step (D). Preferably, the amount of acid should be about 1.1 moles to about 3 moles for every mole of crude paliperidone and most preferably about 1.2 mole to about 2 moles of acid for every mole of crude paliperidone employed in step (D).

The isolation of the paliperidone in step (E) is preferably performed by filtration, and the filtrate may be washed and dried using conventional techniques. The final paliperidone should be pure with the amount of 9-oxo impurity being less than 0.5%, preferably less than 0.3% and most preferably less than 0.1% as determined by HPLC. The final paliperidone should also be "highly pure paliperidone" meaning the paliperidone is at least 99.5% paliperidone, preferably at least 99.75% paliperidone and most preferably at least 99.8% paliperidone as determined by HPLC.

The paliperidone obtained in accordance with embodiments of the present invention was subjected to recrystallization and precipitation in a variety of solvents and mixtures of solvents. The x-ray diffraction data revealed a nearly identical pattern regardless of the solvent or solvent system utilized. For example, samples of paliperidone obtained from Examples 13 and 14 below, as well as samples prepared by recrystallization/leaching of paliperidone in a variety of solvents such as acetone, isopropyl alcohol, ethyl acetate, DMF, methanol, acetonitrile, toluene, methanol/isopropyl ether, methanol/water, DMF/water and toluene/hexane exhibited nearly identical XRD patterns to the representative pattern shown in Figure 1.

The present invention further relates to processes for the preparation of the compound of formula II comprising:

1) reacting 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (formula VI) or 3-(2-Chloroethyl)-2-methyl-9-(phenylmethoxy)-4H-pyrido[1,2-a]pyrimidin-4-one (formula IV) [prepared as per EP 368388] with hydrogen and hydrogenation catalyst in an acidic medium to form 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (formula II);

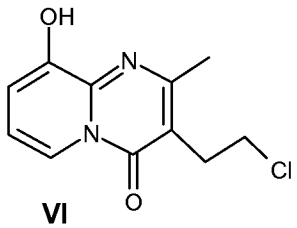
2) removing the acidic media from step (i); and

3) isolating the compound of formula II from a solvent selected from a group consisting of ketones, alcohols, water, hydrocarbons and mixtures thereof.

The catalyst used in step (1) is preferably Pd/C. Catalyst loading is 10-50% w/w of the wet catalyst, more preferably 10-20%. The hydrogen pressure applied during the reaction is in the range of 1-4 kg/cm^2, most preferably between 2-3 kg/cm^2. The reaction is performed at 25-60°C, more preferably at 30-40°C. The reaction medium used for the hydrogenation is selected from organic acids, aqueous mineral acids or mineral acids absorbed in alcoholic solvents. The preferred acids are organic acids such as acetic acid. The product is isolated in step (2) using a solvent selected from ketones, alcohols, water, hydrocarbons and mixtures thereof. Preferred solvents are a mixture of ketones and hydrocarbons such as acetone/hexane mixtures and/or water. When the product is isolated in step (2) using a mixture of ketones and hydrocarbons, the ratio of ketone to hydrocarbon is preferably about 10:90 to about 90:10, most preferably about 25:75 to about 50:50.

When the product is isolated in step (2) using water, the isolating step may further comprise adjusting the pH of the reaction mass with a base such as those previously described. The preferred base is an inorganic base such as sodium hydroxide. The pH of the reaction mass should be adjusted to about 4.5 to about 7, preferably about 5 to about 6.5, and most preferably about 5.5 to about 6. Isolation in water makes the process attractive industrially in terms of environmental friendliness and ease of operation.

3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one, also referred to herein as the compound of formula VI and depicted below:



VI

may be prepared in accordance with the present invention by a process comprising:

(1) reacting 2-amino-3-benzyloxy pyridine with 2-acetyl butyrolactone and $POCl_3$ in toluene at a suitable temperature to form a reaction mixture;

(2) quenching the reaction mixture by addition of water;

(3) adjusting the pH of the quenched reaction mixture with a base; and

(4) isolating compound of formula VI.

Preferably, the temperature of the reaction in step (1) is maintained between 50-110°C, more preferably 90-95°C.

The base added to the quenched reaction mixture in step (3) may be an organic base, an inorganic base or mixtures of the foregoing. Examples of possible inorganic bases include alkali metal or alkaline earth metal carbonates, bicarbonates or hydroxides such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate. Examples of possible organic bases include amines such as ammonium or tertiary amines such as triethylamine. The base should be added to the quenched reaction mixture in an amount that adjusts the pH to about 3.5 to about 7, preferably about 4 to about 5.

One embodiment for preparing the compound of formula VI may further comprise the use of an extraction solvent to assist in removing and isolating the compound of formula VI from the reaction mass. Preferably, the extraction solvent is an organic solvent or a mixture of water and organic solvent. A preferred organic solvent is a chlorinated solvent such as methylene chloride. The extraction solvent may be added during the quenching step or subsequent to the quenching step. If an extraction solvent such as methylene chloride is employed in the process, the extraction solvent should be removed or substantially reduced after the addition of the base and prior to the isolation of the compound of formula VI. Once the extraction solvent has been removed or reduced, the compound of formula VI may be isolated by the addition of an alcohol. Exemplary alcohols for use in step (4) of this embodiment are C_1 to C_4 alcohols such as methanol, isopropyl alcohol or mixtures thereof.

In an alternative embodiment of the present invention, the compound of formula VI can be isolated from the quenched reaction (step (2)) without the addition of solvents for the extraction. In this alternative embodiment, the compound is isolated from the aqueous layer of the quenching step by neutralizing the aqueous layer with a base, preferably an inorganic base such as sodium hydroxide as described above. The compound isolated from the aqueous layer may then be crystallized from a suitable solvent selected from alcohols, ketones, esters, ethers, hydrocarbons and mixtures thereof. Preferred solvents are alcohols, most preferably C_1 to C_4 alcohols such as methanol, isopropyl alcohol or mixtures thereof.

The pure or highly pure paliperidone prepared in accordance with the present invention may be combined with at least one or more pharmaceutically acceptable excipients to prepare a dosage form for administration to a patient. The dosage form may be a solid, liquid, powder,

aerosol, syrup or injectable solution for oral, buccal, parental, ophthalmic, rectal, vaginal or transdermal routes of administration. Pharmaceutically acceptable excipients that may be used to prepare the dosage forms are know in the art and include binders, fillers, diluents, lubricants, glidants, disintegrants, buffering agents, sweetening agents, stabilizers, solubilizers, surfactants and coating agents. A preferred dosage form is a solid dosage form for oral administration such as a tablet or capsule.

The following examples are intended to illustrate and not to limit the scope of the present invention.

EXAMPLES

EXAMPLE 1

Preparation of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one (compound of formula VI)

35 ml of phosphorus oxychloride and 50 ml of toluene were charged in a reaction vessel. 50 g of 2-amino-3-benzyloxy pyridine was added to the above mixture at 25-30°C. The temperature of the reaction mass was raised to 50°C and 48 g of 2-acetyl butyrolactone was added to the mass. The temperature of the mass was raised to 90-95°C and maintained for 5 hours. 16 g of additional 2-acetyl butyrolactone was added to the reaction mass at 90-95°C and the mixture was slowly stirred at 90-95°C for an additional 1 hour to achieve the desired conversion (monitored by HPLC). 250 ml of water was then added to the reaction mass, which was stirred at 90°C for 1 hour. It was then cooled to 25-30°C. Layers were separated. The toluene layer was further re-extracted with 50 ml of water. The combined aqueous layer was washed with 50 ml toluene. The layers were separated and 250 ml of methylene chloride was added to the aqueous layer, and the pH of the solution was adjusted to 4.7-5.0 with 50% sodium hydroxide solution. The reaction mass was allowed to settle. Aqueous layer was extracted with 150 ml of methylene chloride. Both organic layers were combined and washed twice with 150 ml of water, then concentrated under vacuum. 50 ml of methanol was added to the mass and distilled under vacuum. Again, 50 ml of methanol was added, and the reaction mass was cooled to 0-5°C. The solid mass was further stirred at 0-5°C for 30 minutes. The mass was then filtered and washed twice with (2x50 ml) chilled methanol. Finally, the resultant solid was dried at 70°C to obtain 28 g of formula VI.

Similarly, the compound of formula VI can be isolated from water by neutralizing the aqueous layer followed by its purification from methanol or isopropyl alcohol.

EXAMPLE 2

Preparation of 3-(2-Chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Compound of formula II)

50 g of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a] pyrimidin-4-one (IV) was charged to a hydrogenation apparatus, and 250 ml acetic acid was added to obtain a solution. 10 g of 10% Pd/C (wet) was charged to the solution. A hydrogen pressure of 3 kg/cm^2 was applied, and the mass was stirred at 25-30°C for 4-5 hours until the reaction was complete. The reaction mass was filtered to remove Pd/C and then subjected to vacuum distillation at 65-70°C to remove acetic acid. After distillation, an oily mass was obtained to which 150 ml of water and 250 ml of methylene chloride were added. The pH of the reaction mass was adjusted to 5.5-6.0 with 20% NaOH at 25-30°C. The reaction mass was stirred for 15-20 minutes at 25-30°C. The reaction mass was allowed to settle, and the layers were separated. The aqueous layer was extracted with 150 ml of methylene chloride. The organic layers were combined and washed with 250 ml of water. The combined organic layers were then subjected to vacuum distillation at 35°C. To the resulting oily mass was added 50 ml acetone, and the resulting solution was distilled atmospherically. Again, 50 ml acetone was added, and the reaction mixture was heated to reflux for 15-20 minutes. While at reflux, 50 ml of hexane was added to the mass and the resulting mixture was then chilled to 0-5°C. The temperature was maintained for a further 30-45 minutes. The reaction mass was filtered, and the solid was washed twice with (2x25 ml) chilled hexane/acetone mixture. The resulting solid was dried under vacuum at 50°C to obtain compound II. Dry wt. = 30 g (compound of formula V, < 10 % by HPLC analysis, Purity of compound of formula II > 85 %).

EXAMPLE 3

The process of Example 2 was followed using the compound of formula IV instead of the compound of formula VI to obtain the compound of formula II (compound of formula V, < 10% by HPLC analysis, Purity of compound of formula II > 85%).

Example 4

Preparation of 3-(2-Chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Compound of formula II)

60 g of 3-(2-Chloroethyl)-2-methyl-9-hydroxy-4H-pyrido[1,2-a] pyrimidin-4-one (VI) was charged to a hydrogenation apparatus and 300 ml acetic acid was added to obtain a solution. 12 g of 10% Pd/C (wet) was charged to the solution. A hydrogen pressure of 3 kg/cm^2 was applied, and the mass was stirred at 25-30°C for 4-5 hours until the reaction was complete. The reaction mass was filtered to remove Pd/C and then subjected to vacuum distillation below 60°C to remove acetic acid. After distillation, an oily mass was obtained to which 180 ml of water was added. The reaction mixture was stirred for 30-45 minutes. The pH of the slurry was adjusted to 5.5-6.0 with 20% NaOH at 25-30°C and stirred for 15-20 minutes at 25-30°C. The solid was filtered and washed twice with 60 ml water to obtain 36.5 g of compound of formula II.

Example 5

Preparation of Crude Paliperidone

79 g of 6-Fluoro-3,4-(piperidinyl)-1,2-benzisoxazole hydrochloride, 750 ml of methanol, and 78.2 g of triethyl amine were charged in a reaction vessel at 25-30°C. 75 g of the compound of formula II was added to the above mass. The reaction mixture was heated to 60-63°C and then maintained at 60-63°C to achieve desired conversion. The reaction mixture was then cooled to 40-45°C. Methanol was distilled off under reduced pressure to obtain a thick mass. 375 ml of methylene chloride was added to the reaction mass followed by 375 ml of water. The reaction mixture was stirred for 10-15 minutes and then filtered to obtain a clear solution. The layers were separated, and the aqueous layer was extracted twice with (2x190 ml) methylene chloride. Organic layers were combined and washed thrice with (3x190 ml) water. The organic layers were subjected to distillation under vacuum at 35°C to remove methylene chloride. 75 ml of acetone was added to the thick mass and distilled to strip off methylene chloride. 750 ml of acetone was charged to the reaction mass, which was then heated to achieve reflux. The reflux was maintained for 30 minutes and then cooled to 0-5°C and maintained for 45-60 minutes. The

reaction mass was filtered, and the solid was washed twice with chilled (2x75 ml) acetone. The solid was dried at 70°C to obtain crude paliperidone. Dry wt. = 60 g (Purity of compound of formula I = 99.07%).

Example 6

Preparation of Crude Paliperidone

79 g of 6-Fluoro-3-(4- piperidinyl)-1,2-benzisoxazole hydrochloride, 375 ml of methanol, and 78.2 g of triethyl amine were charged in a reaction vessel at 25-30°C. The reaction mixture was stirred for 5 minutes. 75 g of the compound of formula II and 375 ml methanol were added to the above mass. The reaction mixture was heated to 60-63°C and then maintained at 60-63°C to achieve the desired conversion. The reaction mixture was then cooled to 40-45°C. Methanol was distilled off under reduced pressure up to two volumes. 375 ml of water was added to the reaction mixture and stirred for 20-30 minutes at 25-30°C. The solid was filtered and washed twice with 150 ml water followed by 2x150 ml acetone to obtain 87 g crude paliperidone. (Purity of compound of formula I >97%).

Example 7

Preparation of Crude Paliperidone

5.3 g of 6-Fluoro-3 -(4-piperidinyl)-1,2-benzisoxazole hydrochloride, 35 ml of methanol, and 5.2 g of triethyl amine were charged in a reaction vessel at 25-30°C. The reaction mixture was stirred for 5 minutes. 5 g of the compound of formula II and 15 ml acetone were added to the above mass. The reaction mixture was heated to reflux and then maintained at reflux temperature to achieve the desired conversion. The reaction mixture was then cooled to 40-45°C. The solvent was completely distilled off from the reaction mixture under reduced pressure. 10 ml of methanol was added to the reaction mixture and heated to 50-55°C for 15-20 minutes. 25 ml water was added, and the reaction mixture was cooled to 25-30°C and maintained for 20-30 minutes. The solid was filtered and washed twice with 10 ml water followed by 2x10 ml acetone to obtain 6.3 g crude paliperidone. (Purity of compound of formula I >97%).

EXAMPLE 8

Preparation of Pure Paliperidone

60 g of the crude paliperidone prepared in Example 5 and 900 ml of water were added to a reaction vessel. The pH of the reaction mixture was adjusted to 3.5-4.5 with acetic acid at 25-30°C. The reaction mass was stirred for 15-20 minutes at 25-30°C. The reaction mixture was extracted with 180 ml methylene chloride. The layers were separated, and the organic layer was discarded. The aqueous layer was again extracted with 120 ml methylene chloride. Then, 600 ml of methylene chloride was added to the reaction mass, and the pH was adjusted to 9.0-9.5 with liquor ammonia at 25-30°C. The reaction mass was then stirred for 15-20 minutes. The layers were separated, and the aqueous layer was extracted with 120 ml of methylene chloride. The organic layers were combined and washed thrice with 180 ml water. The washed organic layer was treated with 15 g silica. The treated organic layer was subjected to atmospheric distillation to remove methylene chloride at 25-30°C. Acetone (2x60 ml) was added to the concentrated mass and distilled off atmospherically. Finally, 300 ml of acetone was added to the reaction mass. Acetone was distilled up to 150 ml at atmospheric pressure. The slurry was cooled to 0-5°C and maintained for 45-60 minutes. The reaction mass was filtered, and the solid was washed twice with (2x60 ml) chilled acetone. The solid was dried under vacuum at 80°C to obtain pure paliperidone. Dry wt. = 45 g (Purity of compound of formula I = 99.81%).

EXAMPLE 9

Preparation of Pure Paliperidone

14 g of crude paliperidone and 210 ml of water were added to a reaction vessel. The pH of the reaction mixture was adjusted to 3.5- 4.5 with acetic acid at 25-30°C. The reaction mass was stirred for 15-20 minutes at 25-30°C. The reaction mixture was extracted with methylene chloride 42 ml. The layers were separated, and the organic layer was discarded. The aqueous layer was again extracted with 28 ml methylene chloride. 140 ml of methylene chloride was added to the reaction mass, and the pH of the aqueous layer was adjusted to 9.0-9.5 with liquor ammonia at 25-30°C. The reaction mass was then stirred for 15-20 minutes. The layers were again separated, and the aqueous layer was extracted with 28 ml of methylene chloride. The organic layers were combined and washed thrice with 42 ml water. The washed organic layer

was treated with 3.5 g silica. The treated organic layer was subjected to atmospheric distillation to remove methylene chloride at 25-30°C. Methanol (280 ml) was added to the concentrated mass and distilled off atmospherically. Acetone (70 ml) was added to the slurry and distilled off atmospherically. Acetone was distilled up to 35 ml at atmospheric pressure. The slurry was cooled to 0-5°C and maintained for 45-60 minutes. The reaction mass was filtered, and the solid was washed twice with (2x14 ml) chilled acetone. The solid was dried under vacuum at 80°C to obtain pure paliperidone. Dry wt. = 10 g.

Example 10

Preparation of Pure Paliperidone

15 g of the crude paliperidone and 75 ml of water were added to a reaction vessel. The pH of the reaction mixture was adjusted to 3.5-4.5 with acetic acid at 25-30°C, and the reaction mass was stirred for 15-20 minutes at 25-30°C. The reaction mixture was extracted twice with methylene chloride (15 ml). The layers were separated, and the organic layer was discarded. The aqueous layer was treated with charcoal for 30 minutes. The pH of the aqueous layer was adjusted to 9.0-9.5 with liquor ammonia at 25-30°C. The reaction mass was stirred for 1 hour at 25-30°C. The solid was then filtered and washed twice with 30 ml of water followed with 15 ml acetone. The solid was transferred to a flask and refluxed with 75 ml acetone for 20-30 minutes. The reaction mixture was cooled to 25-30°C and maintained for 30 minutes. The solid was filtered and washed twice with 15 ml acetone to obtain 11.5 g pure paliperidone.

Similarly, crude paliperidone prepared as in Example 7 was purified as per the process followed in Example 10 to obtain a pure paliperidone. (Purity of compound of formula I = 99.86%).

EXAMPLE 11

Preparation of Pure Paliperidone

14 g of crude paliperidone and 70 ml of water were added to a reaction vessel. The pH of the reaction mixture was adjusted to 3.5-4.5 with acetic acid at 25-30°C, and the reaction mass was stirred for 15-20 minutes at 25-30°C. The reaction mixture was extracted twice with methylene chloride (14 ml). The layers were separated, and the organic layer was discarded. 140 ml of methylene chloride was added to the reaction mass, and the pH of the aqueous layer was adjusted to 9.0-9.5 with liquor ammonia at 25-30°C. The reaction mass was then stirred for 15-20 minutes. The layers were again separated, and the aqueous layer was extracted with 28 ml of methylene chloride. The organic layers were combined and washed thrice with 42 ml of water. The washed organic layer was treated with 3.5 g silica. The treated organic layer was subjected to atmospheric distillation to remove methylene chloride at 25-30°C. Isopropanol (280 ml) was added to the concentrated mass and distilled off atmospherically. Acetone (70 ml) was added to the slurry, and 35 ml of solvent was distilled off atmospherically. The slurry was cooled to 0-5°C and maintained for 45-60 minutes. The reaction mass was filtered, and the solid was washed twice with (2x14 ml) chilled acetone. The solid was dried under vacuum at 80°C to obtain pure paliperidone. Dry wt. = 11 g.

Example 12

Paliperidone (5 g) obtained from Example 10 was dissolved in isopropanol (400 ml) at reflux temperature. The clear mass was concentrated up to 4 volumes. Acetone (25 ml) was added to the slurry, and 13 ml of solvent was distilled off atmospherically. The slurry was cooled to 0-5°C and maintained for 45-60 minutes. The reaction mass was filtered, and the solid was washed twice with (2x5 ml) chilled acetone. The solid was dried under vacuum at 80°C to obtain pure paliperidone. Dry wt. = 4.5 g.

Example 13

Paliperidone (2 g) was slurried in acetone (80 ml). The temperature was raised to 55-57°C and maintained for 1 hour. The suspension was cooled to 25-30°C. The product was filtered and dried at 70°C.

Example 14

Paliperidone (1.5 g) was dissolved in toluene (45 ml) at 90-95°C. Hexane (90 ml) was added to the solution. The suspension was cooled to 25-30°C and stirred for 30 minutes. The product was filtered and dried at 70°C.

Example 15

Preparation of paliperidone:

375 ml of acetone, 95.2 g of 6-fluoro-3-(4-piperidinyl)1,2-benzisoxazole hydrochloride and 134.5 g of dipotassium hydrogen phosphate were charged in a reaction vessel and stirred for 5-10 minutes. To the above suspension, 75 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]Pyrimidin-4-one and 5.13 g of potassium iodide were added. The resulting reaction mixture was heated to reflux. After reaction completion, the reaction mixture was cooled to 20-30°C, stirred for 30 minutes and then filtered. The solid filtrate was collected, combined with 375 ml water and stirred for 30 minutes, filtered and washed twice with water (2 x 150 ml) followed by acetone (75ml) to obtain 92.3 g paliperidone with an HPLC purity of 98.97% and a 9-oxo impurity level of 0.03%.

Example 16

248 ml of acetone, 63.4 g of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride and 89.7 g of dipotassium hydrogen phosphate were charged in a reaction vessel and stirred for 5-10 minutes. To the above suspension, 50 g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]Pyrimidin-4-one, 3.48 g of potassium iodide and 2.5 ml of water were added. The resulting reaction mixture was heated to reflux. After reaction completion, the

reaction mixture was cooled to 20-30°C, stirred for 30 minutes and then filtered. The solid filtrate was collected, combined with 250 ml of water and stirred for 30 minutes, filtered and washed twice with water (2 x 100 ml) followed by acetone (50ml) to obtain 59.6 g. paliperidone with an HPLC purity of 98.04% and 9-oxo impurity level of 0.04%.

Example 17

Purification of paliperidone:

90 g of paliperidone from Example 15 and 900 ml of acetone were charged to a reaction vessel and heated to reflux. To the above slurry, 90 ml of acetic acid was added at reflux temperature. Reflux was maintained for 30 minutes. The reaction mass was then cooled to 0-5°C and stirred for 3-4 hrs. The resulting solid was filtered and then washed twice with acetone (2x90 ml) to obtain paliperidone acetate (wet cake 117 g). The paliperidone acetate (wet cake) was then dissolved in 450 ml of water followed by addition of 900 ml of acetone. The pH of the resulting reaction mass was adjusted to 9-10 using ammonia solution. The slurry obtained was cooled to 0-5°C and stirred for 30 mins. The resulting solid was filtered, washed twice with water (2 x 180 ml) followed by acetone (90 ml) to obtain 70 g of pure paliperidone with an HPLC purity of 99.93% and a 9-oxo impurity level of 0.04%

Example 18

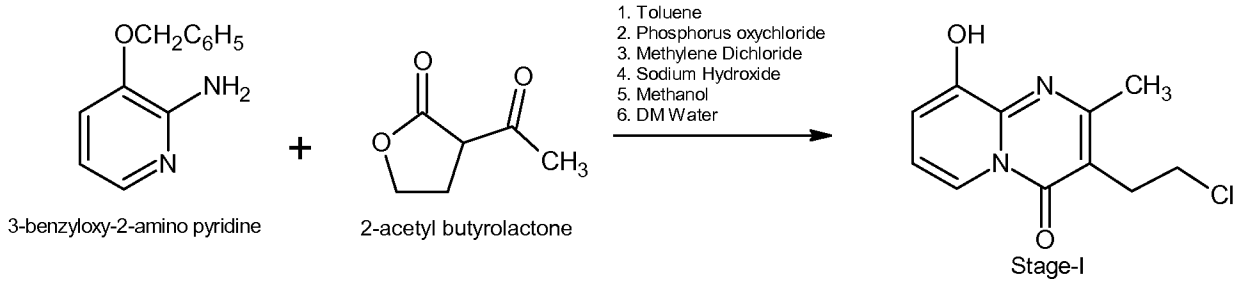
Purification of paliperidone:

50 g of paliperidone from Example 16 and 500 ml of acetone were heated to reflux. To the above slurry, 50 ml of acetic acid was added at reflux temperature. Reflux was maintained for 30 minutes. The reaction mass was then cooled to 0-5°C and stirred for 3-4 hrs. The resulting solid was filtered and then washed twice with acetone (2 x 50 ml) to obtain paliperidone acetate (wet cake 63 g). The paliperidone acetate (wet cake) was then dissolved in 250 ml of water followed by addition 500 ml of acetone. The pH of the resulting reaction mass was adjusted to 9-10 using ammonia solution. The slurry obtained was cooled to 0-5°C and maintained at that temperature for 30 minutes. The resulting solid was filtered, washed twice with water (2 x 100 ml) followed by acetone (50 ml). Wet cake was then refluxed in 500 ml of acetone for 1 hr. The solid was filtered and washed twice with acetone (2 x 50 ml) to obtain 41 g of pure paliperidone with an HPLC purity of 99.98% and a 9-oxo impurity level that was undetectable.

Example 19

The following is a detailed description of one embodiment of the present invention for preparing highly pure paliperidone

Stage – I: Preparation of 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one from 2-amino-3-benzyloxy pyridine



3-benzyloxy-2-amino pyridine 2-acetyl butyrolactone Stage-I

Raw-material:

Sr. No.	Input	Quantity	Unit	Mol Wt.	Moles	Mole ratio
1	2-Amino-3-benzyloxy pyridine	400	gm	200	2.0	1
2	Toluene	400	ml	-	-	1 V
3	2-Acetyl butyrolactone	384	gm	128	3.0	1.5
4	Phosphorus Oxychloride (d – 1.645)	460	gm	153.33	3.0	1.5
		276	ml			
5	Water	4800	ml	-	-	12 V
6	Dichloromethane (MDC)	3200	ml	-	-	8 V
7	50% NaOH soln.	480	ml	-	-	1.2 V
8	Methanol	1200	ml	-	-	3 V
9	Toluene	400	ml	-	-	1V

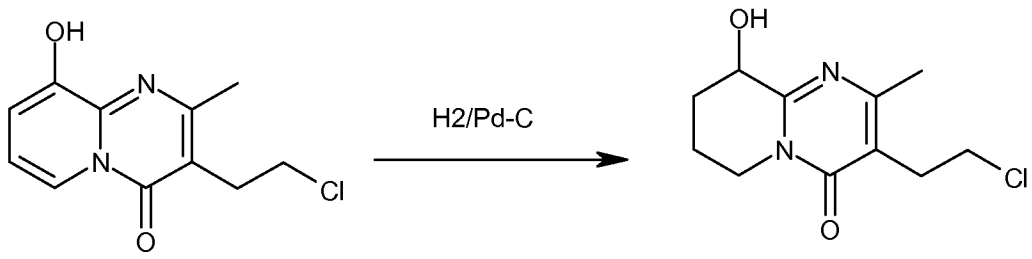
Process:

1. Charge $POCl_3$ (276 ml), Toluene (400 ml), 2-Amino-3-benzyloxy pyridine (400 g) to clean dry reactor with a guard tube and stir for 5-10 minutes.
2. Charge 2-Acetyl butyrolactone (320g).
3. Heat the reaction mass to 90-95°C and maintain for 5 hrs.
4. Charge 2-Acetyl butyrolactone (64g), and stir for 2 hrs at 90-95°C.
5. Give sample for HPLC analysis (SM NMT 6% by HPLC).
6. After completion of reaction, charge water (2.0 L) at 90-95°C slowly.
7. Maintain reaction mass at 90-95°C for 1 hr.

8. Cool reaction mass to 25-30°C.
9. Separate the layers.
10. Extract toluene layer with water (400 ml).
11. Separate the layers.
12. Mix both the aqueous layers and wash it with toluene (400 ml).
13. Separate the layers.
14. Charge MDC (2.0 L) to aqueous layer, and adjust the pH to 4.60-5.2 slowly by addition of 50% NaOH solution below 30°C.
15. Separate the layers.
16. Extract the aqueous layer with 1200 ml MDC.
17. Separate the layers.
18. Mix the organic layers and wash it with 2 x 1200 ml water.
19. Separate the layers.
20. Distill the organic layer under vacuum below 40°C.
21. Charge methanol (400 ml) to the concentrated mass, heat to reflux for 10-15 minutes and continue distillation under vacuum below 50°C to remove traces of MDC.
22. Charge methanol (400 ml) to the concentrated mass, and heat to reflux until clear solution is obtained.
23. Cool to 0-5°C.
24. Stir at 0-5°C for 2 hr.
25. Filter solid, and wash with 2x200ml chilled methanol.
26. Dry at 60-70°C under vacuum until LOD NMT 1%.

Final Dry Wt. = 209.0 gm

Stage – II: Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one from 3-(2-chloroethyl)-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one



Stage - I **Stage - I I**

Raw-material:

Sr. No.	Input	Quantity	Unit	Mol Wt.	Moles	Mole ratio
1	Stage-I	200	g	242.5	0.8248	1
2	Acetic acid	1200	ml	-	-	6 V
3	10% Pd-C	42	g	-	-	21%
4	Charcoal	10	g	-	-	5%
5	Acetic acid (washing)	200	ml	-	-	1 V
6	MDC	1600	ml	-	-	8 V
7	Water	1200	ml	-	-	6 V
8	20% NaOH soln.	360	ml	-	-	1.8V
9	Acetone	500	ml	-	-	2.5V
10	Hexane	300	ml	-	-	1.5V

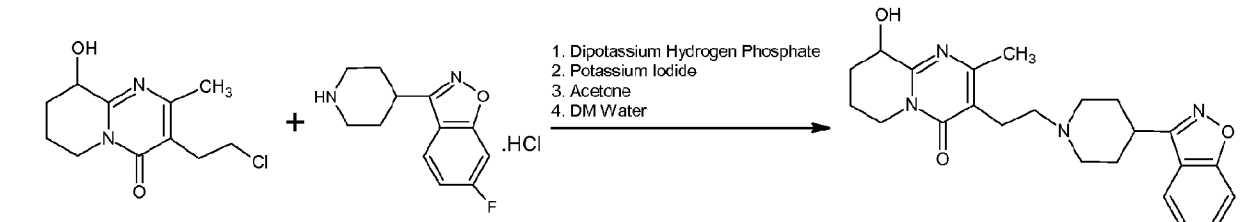
Process:

1. Charge (100 ml) acetic acid, charcoal (10 gm) and stir for 60 minutes (for de-poisoning).
2. Charge (100 ml) acetic acid, 10%Pd-C (2 gm) and stir for 60 minutes (for depoisoning).
3. Charge Stage-I (200 gm), acetic acid (1000 ml), 10% Pd-C (40 gm) to the clean hydrogenator.
4. Apply hydrogen pressure and maintain it at 1-3kg/cm^2 below 35°C.
5. Continue hydrogenation till stage-I content NMT 5% by HPLC.
6. After completion of reaction, filter RM through hyflow bed and wash the bed with acetic acid (200 ml).
7. Distill off acetic acid under vacuum below 70°C and degas for 30 minutes.
8. Charge water (600 ml) and MDC (1000 ml) to the concentrated mass.
9. Adjust pH slowly to 5.5-6.5 using 20% NaOH solution below 30°C
10. Separate the layers.
11. Extract aqueous layer with MDC (600 ml).
12. Separate the layers.
13. Wash organic layer with (600 ml) water.
14. Separate the layers.
15. Distill off organic layer under vacuum below 40°C.
16. Charge (200 ml) acetone to the concentrated mass, and heat to reflux until reaction mass becomes clear.
17. Distill off acetone under vacuum below 50°C and degas for 30 minutes.
18. Charge again (200 ml) acetone, and heat to reflux.
19. Maintain reflux until reaction mass becomes clear.
20. Charge (200 ml) hexane slowly to the reaction mass.

21. Cool the mass to 0-5°C.
22. Maintain it at 0-5°C for 45-60 minutes.
23. Filter the solid and wash it with (2x100 ml) chilled (0-5°C) acetone-hexane mixture (1:1).
24. Dry the solid at 50-60°C under vacuum.

Final Dry Wt. = 82.1 gm

Stage III: Preparation of 3-[2-[4-(6-fluoro-1, 2-benxisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one from 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H- pyrido[1,2-a] pyrimidin-4-one.



3-(2-chloroethyl)-6,7,8,9-tetra hydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one (Stage - II)

6-fluoro-3-(4-piperidinyl) -1,2-benzisoxazole hydrochloride

Stage III

Raw-material:

Sr. No.	Input	Quantity	Unit	Mol Wt.	Moles	Mole ratio
1	3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one (Stage II)	50.0	gm	242.5	0.2062	1.0
2	Acetone	247.5	ml	-	-	4.95 V
3	Dipotassium hydrogen phosphate	89.7	gm	174	0.7759	2.5
4	6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole HCl	63.4	gm	256.5	0.3704	1.2
5	Potassium iodide	3.48	gm	166	0.0310	0.1
6	DM Water	2.5	ml	-	-	0.05 V
7	DM Water (washing)	450.0	ml	-	-	9.0 V

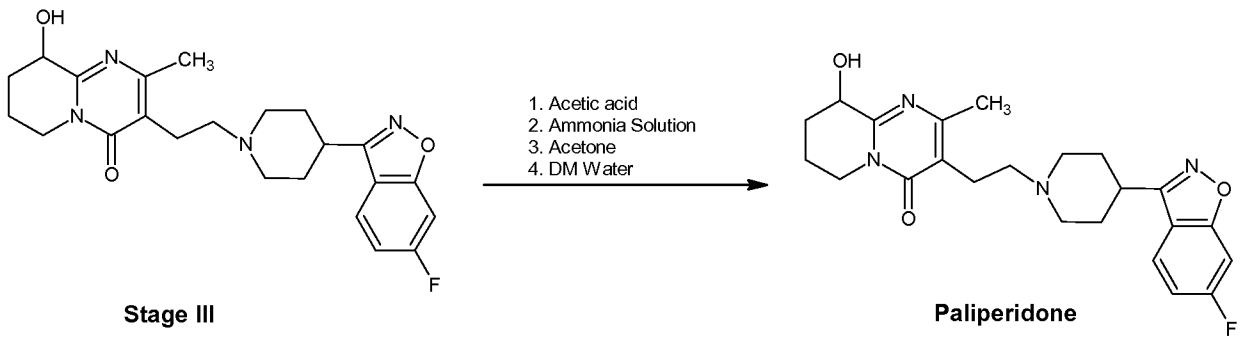
8	Acetone (washing)	100.0	ml	-	-	2.0 V

Process:

1. Charge 6-Fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride (63.4 g), Dipotassium hydrogen phosphate (89.7 g), acetone (125.0 ml) at 25-35°C to clean reactor, and stir for 5-10 minutes.
2. Charge 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one (Stage II) (50 g), Acetone (122.5 ml), potassium iodide (3.48 g) and DM Water (2.5 ml) to the mass below 35°C.
3. Heat to reflux.
4. Continue the reaction at reflux until 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido [1,2-a] pyrimidin-4-one (Stage II) is NMT 10% by HPLC.
5. After completion of reaction, cool the reaction mass to 25-30°C.
6. Maintain reaction mass at 25-30°C for 30 minutes.
7. Filter the solid mass.
8. Charge the solid in a reactor, add water (250 ml) to it and stir for 30 minutes.
9. Filter the solid, and wash it with water (2x100 ml) followed by acetone (2x50 ml).
10. Dry the wet product at 60-70°C.

Final Dry Wt. = 55.0 gm

Stage IV: Purification of crude 3-[2-[4-(6-fluoro-1, 2-benxisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a] pyrimidin-4-one



Stage III Paliperidone

Raw-material:

Sr. No.	Input	Quantity	Unit	Mol Wt.	Moles	Mole ratio
1	Crude Stage-III	50	gm	426.5	0.1172	1.0
2	Acetone	1800	ml	-	-	36.0 V
3	Acetic acid	50	ml	-	-	1.0 V
4	Ammonia solution	67.5	ml	-	-	1.25 V
5	Water	450	ml	-	-	9.0 V

Process:

1. Charge crude stage-III (50g), Acetone (500 ml) and heat to reflux.
2. Charge acetic acid (50 ml) slowly to the mass at reflux.
3. Stir the reaction mixture at reflux for 30 minutes.
4. Cool the mass to 0-5°C.
5. Maintain the reaction mass at 0-5°C for 3-4 hrs.
6. Filter the solid, and wash wet cake with acetone (2x50 ml).
7. Dissolve the wet cake in (250 ml) water and charge acetone (250 ml).
8. Filter the reaction mass, wash the bed with acetone (250 ml).
9. Collect all the filtrate, and adjust pH of the mass to 9.0-10.0 with ammonia solution below 30°C
10. Cool the reaction mass to 0-5°C.
11. Maintain for 30 minutes.
12. Filter the solid, and wash with (2x100 ml) water followed by acetone (2x50 ml).
13. Charge wet cake, Acetone (500 ml) and heat to reflux.
14. Stir the reaction mixture at reflux for 60 minutes.
15. Cool the mass to 20-30°C.
16. Maintain the reaction mass at 20-30°C for 30 minutes.
17. Filter the solid, and wash wet cake with acetone (2x50 ml).
18. Dry the wet product at 65-70°C.

Final Dry Wt. = 37.0 gm.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein, any of the terms "comprising," "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

What is claimed is:

1. A process for purifying paliperidone comprising:

A) reacting crude paliperidone with an acid in a suitable solvent to form an acid addition salt of paliperidone;

B) isolating the acid addition salt of paliperidone formed in step (A) in a solid form;

C) dissolving or suspending the solid acid addition salt of paliperidone of step (B) in a suitable solvent;

D) adjusting the pH of the reaction mass of step (C) with a base to form the free base form of paliperidone; and

E) isolating the free base of paliperidone formed in step (D).

2. The process of claim 1, wherein the acid is a mono-carboxylic acid.

3. The process of claim 2, wherein the acid is acetic acid.

4. The process of claim 1, wherein the solvent of step (A) comprises a C_3 to C_8 ketone.

5. The process of claim 4, wherein the solvent of step (A) comprises acetone.

6. The process of claim 1, further comprising the step of cooling the reaction mixture of step (A) to about 0°C to about 20°C prior to isolating the acid addition salt of paliperidone in step (B).

7. The process of claim 1, wherein the solvent for step (C) is a mixture of water and a C_3 to C_8 ketone.

8. The process of claim 7, wherein the solvent of step (C) comprises a mixture of water and acetone.

9. The process of claim 1, wherein the base employed in step (D) is a nitrogen containing base.

10. The process of claim 9, wherein the nitrogen base is selected from the group consisting of liquid ammonium, ammonium hydroxide, triethylamine, N-(1-methylethyl)-2-propanamine or mixtures thereof.

11. The process of claim 1, wherein the pH of the reaction mass in step (D) is adjusted to about 8 to about 10.

12. The process of claim 11, wherein the pH of the reaction mass in step (D) is adjusted to about 9 to about 10.

13. The process of claim 1, wherein the free base paliperidone is isolated in step (E) by filtration.

14. A solid oral dosage form comprising at least one pharmaceutically acceptable excipient and the paliperidone prepared according to the process of claim 1.

15. A process for preparing paliperidone comprising:

(i) reacting 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one with 6-fluoro-3 -(4-piperidinyl)-1,2-benzisoxazole hydrochloride in inert solvents selected from the group consisting of alcohols, ketones, esters, ethers, hydrocarbons and mixtures thereof in the presence of a buffer ; and
(ii) isolating paliperidone from the reaction mass of step (i).

16. The process of claim 15 wherein the buffer of step (i) is an inorganic buffer.

17. The process of claim 16 wherein inorganic buffer is a phosphate buffer.

18. The process of claim 17 wherein the phosphate buffer is selected from the group consisting of potassium hydrogen phosphate, dipotassium hydrogen phosphate, potassium phosphate or mixtures thereof.

19. The process of claim 15 wherein the buffer present step (i) is about 1 mole to about 5 moles of buffer for each mole of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

20. The process of claim 19 wherein the buffer present step (i) is about 1.5 moles to about 4 moles of buffer for each mole of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

21. The process of claim 20 wherein the buffer present step (i) is about 2 moles to about 3 moles of buffer for each mole of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one.

22. The process of claim 15 wherein the solvent for step (i) comprises C_3 to C_8 ketone.

23. The process of claim 22, wherein the solvent comprises a mixture of water and acetone.

24. A process for preparing highly pure paliperidone comprising:

(i) reacting 3-(2-chloroethyl)-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one with 6-fluoro-3 -(4-piperidinyl)-1,2-benzisoxazole hydrochloride in inert solvents selected from the group consisting of alcohols, ketones, esters, ethers, hydrocarbons and mixtures thereof in the presence of an inorganic buffer is a phosphate buffer to form paliperidone;
(ii) isolating paliperidone from the reaction mass of step (i);
(iii) reacting the paliperidone of step (ii) with an acid in a suitable solvent to form an acid addition salt of paliperidone;
(iv) isolating the acid addition salt of paliperidone formed in step (iii) in a solid form;
(v) dissolving or suspending the solid acid addition salt of paliperidone of step (iv) in a suitable solvent;
(vi) adjusting the pH of the reaction mass of step (v) with a base to form the free base form of paliperidone; and
(vii) isolating the free base of paliperidone formed in step (vi).

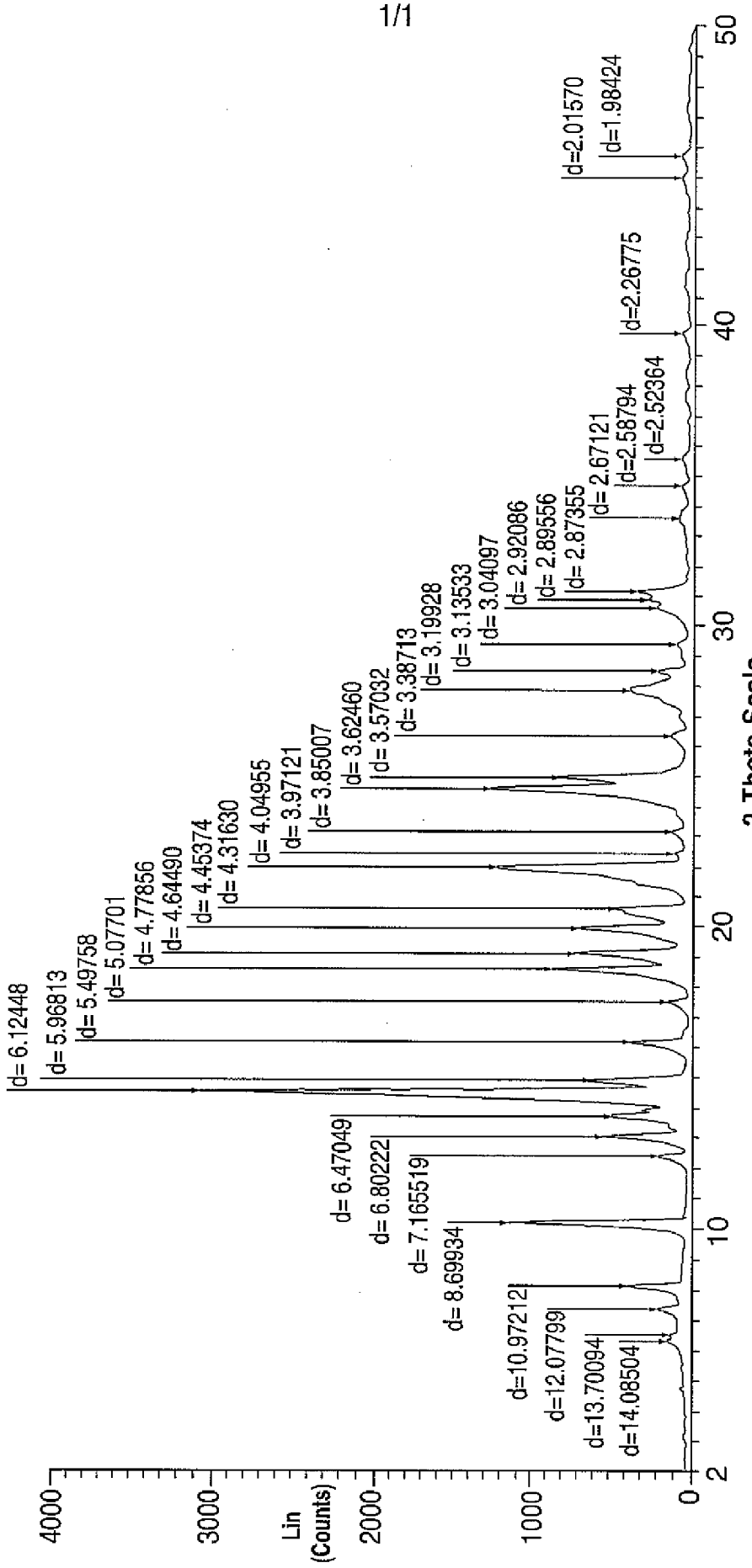
25. The process of claim 24 wherein the phosphate buffer is selected from the group consisting of potassium hydrogen phosphate, dipotassium hydrogen phosphate, potassium phosphate or mixtures thereof.

26. The process of claim 24 wherein the solvent for step (i) comprises C_3 to C_8 ketone.

27. The process of claim 26, wherein the solvent comprises a mixture of water and acetone.

28. The process of claim 24 wherein the acid of step (iii) is a mono-carboxylic acid.

29. The process of claim 28, wherein the acid is acetic acid.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1000
0
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2
10
20
30
40
50
2-Theta-Scale

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/030302

A. CLASSIFICATION OF SUBJECT MATTER

C07D 471/04(2006.01)i, C07D 413/14(2006.01)i, A61K 31/519(2006.01)i, A61K 31/506(2006.01)i, A61P 25/18(2006.01)i

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 471/04

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), Google, PubMed

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009-130710 A2 (GLENMARK GENERICS LIMITED) 29 October 2009 See claims 9-10, 16-18, p.15 lines 16-22.	1-29
A	US 2010-0311969 A1 (CHAVAN, A. A. et al.) 09 December 2010 See claims 12, 18-19, 27-31, paragraph 18.	1-29
A	US 2010-0267954 A1 (MANTEGAZZA, S. et al.) 21 October 2010 See claims 1, 3-4, 7-8, paragraph 64.	1-29

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 DECEMBER 2011 (26.12.2011)	**27 DECEMBER 2011 (27.12.2011)**

Name and mailing address of the ISA/KR
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Facsimile No. 82-42-472-7140

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Telephone No. 82-42-481-8163

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2011/030302

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2011-0087024 A1	14.04.2011
		WO 2009-130710 A3	17.12.2009
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		JP 2010-254692 A	11.11.2010