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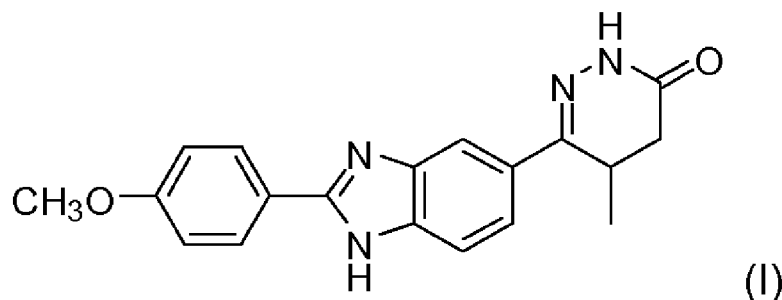
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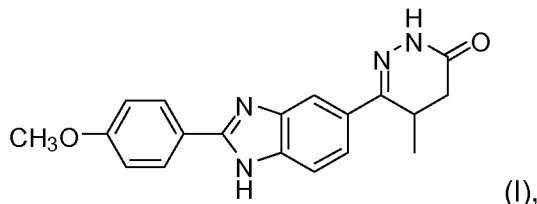
(54) Title: PIMOBENDAN MANUFACTURING PROCESS



(57) Abstract: The present invention generally relates to an improved process for the manufacture of a non-solvated crystalline compound of formula (I). The invention further relates to a new valuable intermediate compound for the commercial synthesis of pimobendan, which is a compound according to formula (I) in MeOH, wherein n is from 1 to 2 molar equivalents. Still further, the invention relates to the use of said intermediate compound or a compound according to formula (I) obtained by the process of the invention, for the manufacture of a pharmaceutical composition.

Pimobendan manufacturing process

The present invention generally relates to an improved process for the manufacture of a non-solvated crystalline compound of formula **(I)**.



The invention further relates to a new valuable intermediate compound for the commercial synthesis of pimobendan, which is a compound according to formula (I) • n MeOH, wherein n is from 1 to 2 molar equivalents. Still further, the invention relates to the use of said
10 intermediate compound or a compound according to formula (I) obtained by the process of the invention, for the manufacture of a pharmaceutical composition.

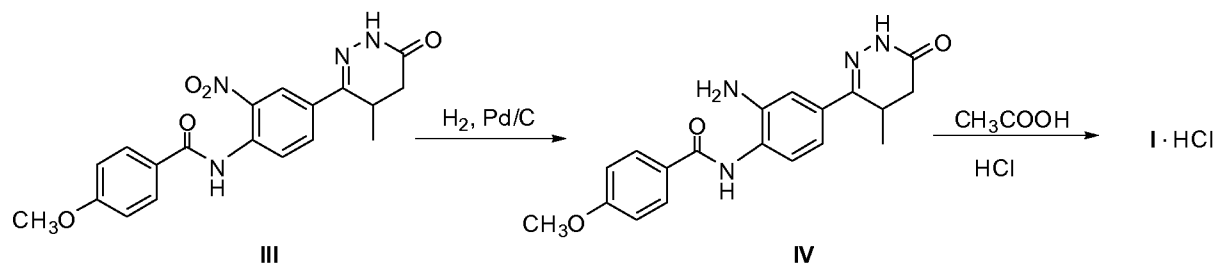
Background of the invention

15 Pimobendan (commercially available as Acardi[®] and Vetmedin[®]) is a calcium sensitizer with positive inotropic and vasodilatory effects and an inhibitor of phosphodiesterase (III) (PDE3).

Research has shown that pimobendan increases survival time and improves quality of life of patients with congestive heart failure when compared with benazepril, an angiotensin-
20 converting-enzyme (ACE) inhibitor. Pimobendan is further useful for the management of heart failure in dogs.

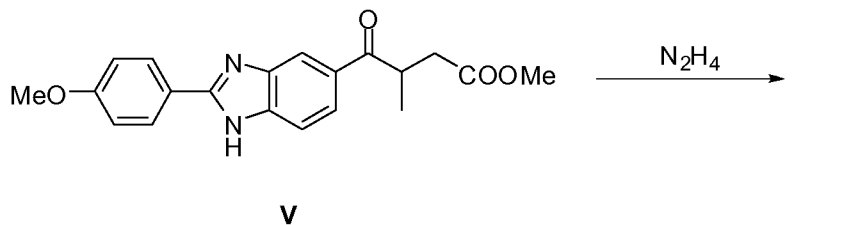
One synthetic route to obtain pimobendan, which is a compound according to formula **(I)**, in the form of a pharmaceutically acceptable salt thereof, is disclosed in **DE 2837161** as
25 follows:

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A compound of formula (III) is treated with hydrogen in the presence of Pd/C to form a compound of formula (IV), which then is cyclized in presence of acetic acid to obtain a compound of formula (I) in the form of the corresponding hydrochloride salt (I) • HCl. However, the yield of said synthetic route is only about 50 % for compound (I), based on compound (IV).

A compound of formula (I) is also accessible according to DE 2837161 by reacting benzimidazole of formula (V) with a large excess of highly toxic hydrazine hydrate in acetic acid. The yield of said synthetic route is only about 70 % for compound (I), which was isolated as its hydrochloride after chromatographic work up.



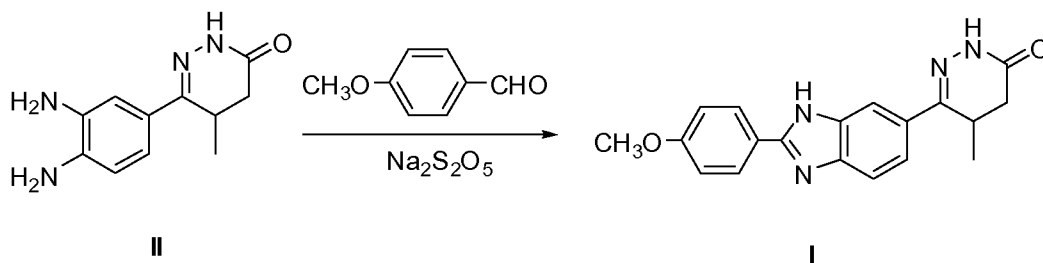
It is to be noted, that the acetic acid in DE 2837161 is used as a solvent, i.e. in large excess based on the amount of the compound of formula (IV) or (V), respectively.

An improvement to said synthetic route was reported in Hecheng Huaxue 1999, 7, 194, wherein the need for column chromatography is overcome by re-crystallization of crude pimobendan obtained according to the above, from a mixture of DMF and water, yielding compound (I) as a hydrate, which exhibited a melting range of 175 to 178 °C.

Further, as disclosed in Zhongguo Yaowu Huaxue Zazhi 1997, 7, 185, the compound of formula (I) can also be obtained by the reaction of a compound of formula (II) with 4-

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methoxybenzaldehyde in the presence of sodium metabisulfite in a mixture of methanol and water to obtain the compound of formula (I) in yields of about 90 % after chromatographic purification over silica gel, in a crystalline form (melting range of 240 to 242 °C).

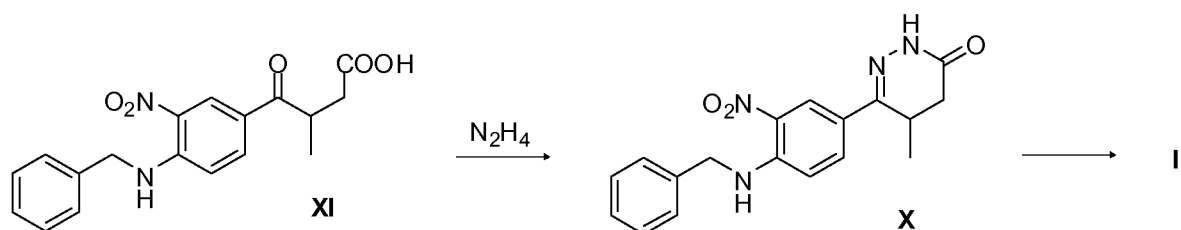


Said synthesis however, has some major disadvantages, in particular for the manufacture of pimobendan on a commercial scale. The process requires not only a chromatographic purification procedure for the compound of formula (I). Moreover the conversion according to the above reaction scheme is exothermic. During the initial heating of the reaction mixture, a spontaneous reaction can be observed which releases a total energy of 130 kJ/mol with respect to compound (II). This corresponds to an adiabatic temperature increase of 55 K. It is to be noted, that an adiabatic increase of not more than 50 K is typically considered safe, provided that the boiling point of the reaction mixture is not exceeded and the reactants are thermodynamically stable. The synthesis as disclosed above therefore cannot be regarded as safe on an industrial scale.

Further, as disclosed in *Zhongguo Yaowu Huaxue Zazhi* **1997**, 7, 185, in order obtain the desired high yield for the synthetic route, the compound of formula (II) has to be purified by means of chromatography over silica gel prior to the reaction to compound of formula (I).

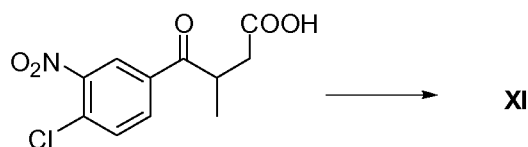
As disclosed in *Eur. J. Med. Chem.* **1993**, 28, 129, compounds of formula (II) are readily accessible by hydrogenation of 6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one of formula (X). However, the quality of (II) strongly depends on the purity of the corresponding precursor (X). Moreover, compounds of formula (II) proved to be unstable under general laboratory conditions.

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DE3129447 discloses the synthesis of said precursor (**X**) starting from 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoic acid of formula (**XI**).

5



The known processes for the preparation of compounds of formula (**X**) require a large excess (three to eleven molar equivalents) of hydrazine hydrate. According to the processes disclosed in the prior art, compounds of formula (**XI**) are usually dissolved in acetic acid and treated with excess hydrazine hydrate at reflux temperature for several hours. This again cannot be regarded as safe on an industrial scale.

It is therefore a general objective of the present invention to provide an improved process for the manufacture of a compound of formula (**I**), which is feasible on an industrial scale.

It is a further objective of the present invention to provide an improved process to obtain intermediates (**II**) and (**X**) in sufficient purity, which on an industrial scale is feasible to provide the compound of formula (**I**) in sufficient yield and purity.

20

It is still a further objective of the present invention to provide a defined, pure and stable compound of formula (**I**) in crystalline form, which is feasible for pharmaceutical use.

Summary of the invention

In one aspect the present invention relates to an improved process for the manufacture of a non-solvated crystalline compound of formula (**I**), wherein the obtained compound of formula (**I**) preferably is characterized by a purity of more than 99 %.

25

In another aspect the present invention relates to an improved process for the manufacture of compounds of formula (II), as an important intermediate for the manufacture of a compound of formula (I). The improved process provides highly pure 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one of formula (II) in a safe, viable and economic manner, wherein the obtained compound of formula (II) is characterized by a purity of more than 99 % and is further substantially free of inorganic salts, heavy metals and residual hydrazine.

Surprisingly it has been found that, starting from a compound of formula (XI) or (XII), and using from 1 to 2 molar equivalents of hydrazine, preferably hydrazine hydrate, a compound of formula (X) can be obtained in yields of more than 70% and purities of more than 99.7 % with no need for further purification.

Further, it has been found that, the conversion can be accelerated significantly by addition of sub-stoichiometric amounts of a proton donor, preferably an organic acid, more preferably acetic acid, as a catalyst. It is to be noted, that in related processes in the prior art, acetic acid is used as a solvent, i.e. in large excess, whereas in the present invention it has surprisingly been found, that sub-stoichiometric amounts, respectively catalytic amounts, of a proton donor, preferably an organic acid, more preferably acetic acid, are effective in reducing the total reaction time at comparably low temperatures, which leads to a significantly improved impurity profile and to improved yields.

Hydrogenation of the compound of formula (X) then provides the compound of formula (II).

In yet another aspect, the present invention relates to an improved process for the manufacture of a solvated compound of formula (I) from a compound of formula (II), wherein a crystalline hydrate of the compound of formula (I) is obtained and optionally converted to a crystalline solvate, other than the hydrate of the compound of formula (I).

In still another aspect, the present invention relates to a compound of formula (I) in the form of a crystalline methanol solvate of the formula (I) • *n* MeOH (wherein *n* is from 1 to 2 molar equivalents, preferably *n* is 0.125 to 1.25 molar equivalents).

In still a further aspect, the present invention relates to the use of a compound of formula (I) as described above for the manufacture of a pharmaceutical composition comprising the compound of formula (I) together with at least one pharmaceutically acceptable carrier, diluent, or excipient.

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Definitions

A "solvated" compound as used herein generally relates to a compound comprising a solvent as an adduct, e.g. of the general formula $A \cdot B$. In particular solvation occurs in that a solvent is incorporated in the crystal structure of the respective crystalline compound. Crystalline solvates of a compound may comprise the respective solvent in an amount of 1 to 10 % by weight, preferably 2 to 8 % by weight, more preferably 4 to 6 % by weight. In the general formula $A \cdot n B$, the solvent content is usually expressed in molar equivalents (n).

The term "solvate" *inter alia* comprises the term "hydrate" as a preferred meaning. Within the term "hydrated compounds", monohydrates are most preferred, e.g. corresponding to a general formula $A \cdot n H_2O$, wherein n is 1. Crystalline hydrates of a compound may comprise water in an amount of 1 to 10 % by weight, preferably 2 to 8 % by weight, more preferably 4 to 6 % by weight.

In a "non-solvated" compound as used herein the residual solvent is 1% or less, preferably 0.5 or less and more preferably 0.1% or less. Accordingly, the crystal structure is only little or undisturbed compared to a (theoretical) compound with no residual solvent at all.

Generally, crystalline compounds may exist in more than one "polymorphic form". The term "polymorphic form" refers to the ability of a solid material to exist in more than one form or crystal structure and covers all known forms of polymorphism, for example, polyamorphism, packing polymorphism, conformational polymorphism, as well as so-called pseudo-polymorphism, i.e. different crystal forms as a result of different solvation.

The term "solvent" as used herein refers to a polar or non-polar liquid or mixture of liquids that at least partially dissolve a solid, liquid, or gaseous solute, resulting in a solution, emulsion, or a suspension.

The terms "acid" and "base" as used herein refer to Brønsted acids and Brønsted bases, that is "proton donators" and "proton acceptors", respectively.

5 The term "oxidant" as employed herein means elements or compounds in reduction-oxidation (redox) reactions that oxidize another species, and are therefore the electron acceptors in the redox reaction.

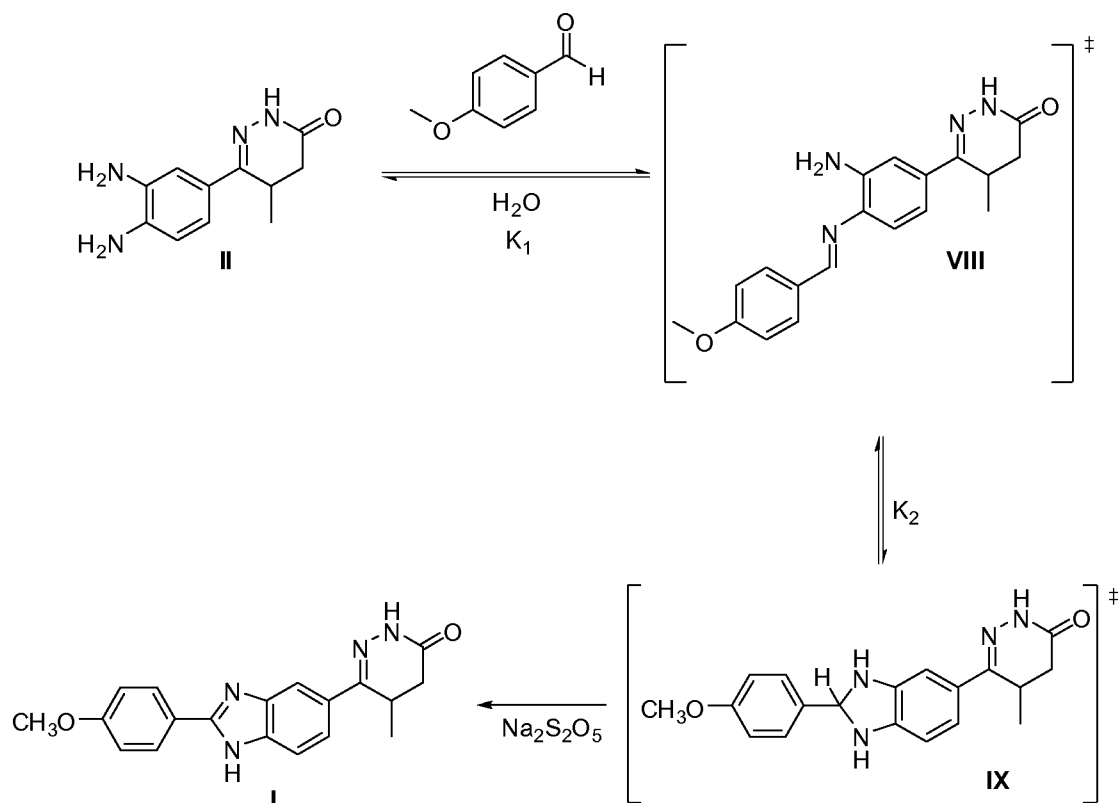
Preferred embodiments of the invention

10 The present invention provides a safe, viable and economic process to produce highly pure 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one of formula (II), characterized by purities of more than 99 %, which are substantially free of inorganic salts, heavy metals and residual hydrazine. In accordance with the present invention compounds of formula (II), are an important intermediate for the manufacture of a compound of formula (I).

15 Generally the present invention relates to an improved process for the manufacture of a solvated compound of formula (I), wherein the process comprises reacting the compound of formula (II) with 4-Methoxybenzaldehyde in a polar aprotic solvent, such as DMF to yield the hydrate of the compound of formula (I); and optionally converting the hydrate of the compound of formula (I) to a solvate, other than the hydrate of the compound of formula (I).

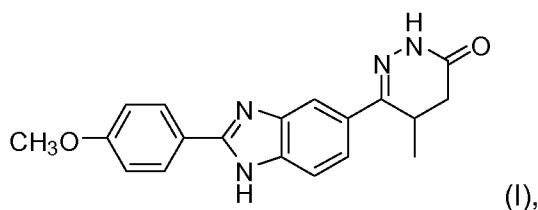
20 Such a process for the manufacture of compounds of formula (I), based on the intermediate compound of formula (II), is described as follows. It is to be noted that compounds of formula (VIII) and (IX) are intermediates only, which are neither isolated nor fully characterized. Said compounds are included in the below reaction scheme only for illustrative purposes and are
25 not to be understood to limit the present invention to a particular pathway for the reaction from compound of formula (II) to compound of formula (I).

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In embodiments A-1 to A-3, the present invention comprises a process for the manufacture of a non-solvated crystalline compound of formula (I), comprising the steps of:

- 5 (a) providing a solvated compound of formula (I)



- (b) optionally removing residual water by azeotropic distillation;

- (c) treating said compound to obtain a non-solvated crystalline compound of formula (I) by re-crystallisation from suspension, preferably at reflux temperatures, more preferably at

10 80°C, preferably for 0.5 to 10 hours, more preferably from 3 to 5 hours;

wherein the solvent is selected from the group consisting of linear or branched C_{1-4} alcohols, such as methanol, ethanol, 1-propanol, 2-propanol, and n-butanol; or C_{1-4} alkylesters, such as butylacetate or ethylacetate; and mixtures thereof; preferably the solvent is selected from the group consisting of ethanol, n-butanol, and ethylacetate, most preferably the solvent is ethylacetate;

15

(d) isolating the non-solvated crystalline compound of formula (I),
with the proviso that if the solvated compound of formula (I) is a hydrated compound of
formula (I), the residual water has to be removed by azeotropic distillation in step (b).

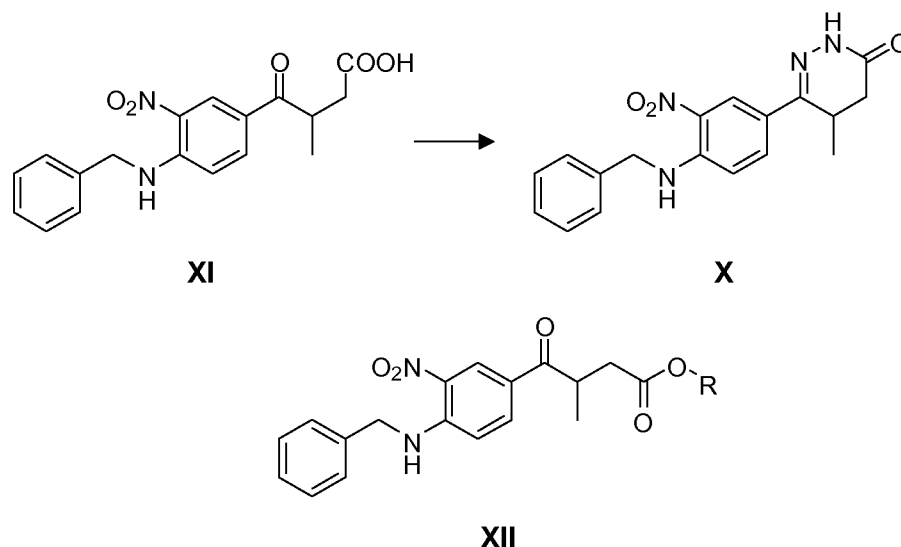
- 5 In embodiments A-4 to A-6, the present invention comprises a process for the manufacture
of a non-solvated crystalline compound of formula (I), comprising the steps of:
- (a) providing a solvated compound of formula (I),
 - (b) dissolving the solvated compound of formula (I) in a polar aprotic solvent, in particular
DMF, preferably at temperatures of from 70 to 153°C, in particular of from 90 to 100°C;
 - 10 (c) optionally removing residual water by azeotropic distillation;
 - (d) treating the solution with an anti-solvent, preferably at temperatures from 0 to 5 °C,
preferably under agitation, optionally with seeding; wherein the anti-solvent is selected
from the group consisting of C₁₋₄ alkylesters, preferably butylacetate or ethylacetate,
and mixtures thereof, most preferably ethylacetate;
 - 15 (e) isolating and drying the non-solvated crystalline compound of formula (I),
with the proviso that if the solvated compound of formula (I) is a hydrated compound of
formula (I), the residual water has to be removed by azeotropic distillation in step (c).

According to a highly preferred embodiment of the present invention, a crystalline non-
20 solvated compound of formula (I) is obtained in high yields and high purities from a solvated
compound of formula (I), in particular a hydrated compound of formula (I), when residual
water is removed, prior to treatment of the solvated compound, by azeotropic distillation,
preferably utilizing n-butanol, ethyl acetate, ethanol or toluene as solvent.

25 To provide the compound of formula (I) in pharmaceutical purity (i.e. purity of 99% or higher)
a process for the synthesis of highly pure compounds of formula (II) and/or stable salts
thereof, as well as a reliable process for the transformation of compound (II) into the
compound of formula (I) had to be provided.

30 Surprisingly it has been found that, starting from a compound of formula (XI), or a compound
of formula (XII), wherein R is C₁₋₄ alkyl;

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a compound of formula **(X)** can be obtained in yields of up to 60%, preferably more than 70%, in purities of more than 99.4%, preferably more than 99.7% with no need for further purification. The reaction time preferably is from 10 to 12 hours.

- 10 Further, it has been found that, said conversion can be accelerated significantly by addition of sub-stoichiometric amounts, preferably up to 0.5 molar equivalents, more preferably up to 1.0 equivalents, most preferably from 0.5 to 1.0 equivalents, of a proton donor, preferably an organic acid, more preferably acetic acid, as a catalyst. Said addition reduces the total reaction time at comparably low temperatures, which leads to a significantly improved
- 15 impurity profile and to yields of more than 70 %, preferably more than 80 %, with purities of more than 99.4 %, preferably more than 99.7 %. The reaction time then preferably is from 3 to 7 hours, more preferably either one of 3 to 4 hours, 4 to 5 hours, 5 to 6 hours, or 6 to 7 hours. The reaction is preferably carried out at reflux temperatures until the conversion is completed.

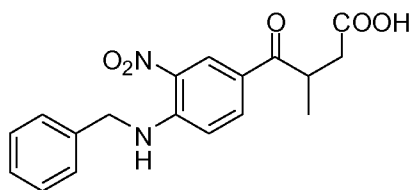
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The compound **(X)** is then hydrogenated to form intermediate compound **(II)**, preferably by catalytic hydrogenation with a palladium catalyst.

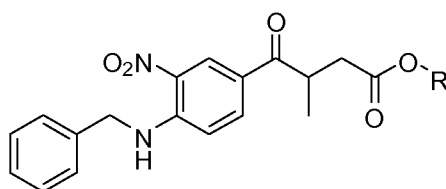
- In embodiments A-7 to A-10, the present invention comprises a process for the manufacture
- 25 of a solvated compound of formula **(I)**, comprising the steps of:

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(a) reacting a compound of formula **(XI)**

**XI**

or a compound of formula **(XII)**, wherein R corresponds to C₁₋₄ alkyl, preferably methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec.-butyl or tert.-butyl, more preferably ethyl;

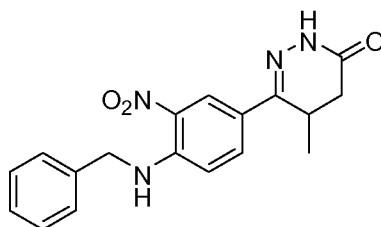
**XII**

with hydrazine, preferably hydrazine hydrate, in a solvent to yield a compound of formula **(X)**, wherein the solvent preferably is a water-miscible solvent selected from linear or branched C₁₋₄ alcohols, such as methanol, ethanol, 1-propanol, 2-propanol, and n-butanol, most preferably ethanol;

wherein hydrazine, respectively hydrazine hydrate, is used in amounts of 1 to 2 molar equivalents, preferably in amounts of 1.0 to 1.5 molar equivalents, and more preferably in amounts of 1.0 to 1.2 molar equivalents relative to the compounds of formula **(XI)** and **(XII)**, respectively;

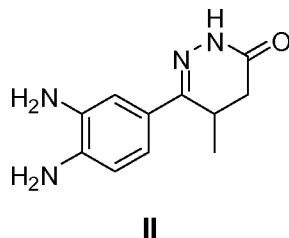
wherein the reaction mixture preferably is heated to temperatures below 100°C, more preferably to 80°C, in particular to reflux temperature, preferably for 3 to 16 hours, more preferably for 6 to 7 hours; and

(b) subsequently hydrogenating the compound of formula **(X)**

**X**

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to a compound of formula (II);



wherein the hydrogenation preferably is carried out in a solvent, preferably selected from the group consisting of linear or branched C₁₋₄ alcohols, such as methanol, ethanol, 1-propanol, 2-propanol, and n-butanol, more preferably methanol, optionally in the presence of water;

wherein the hydrogenation preferably is carried out in the presence of a catalyst, wherein the catalyst is preferably a palladium-catalyst, more preferably a palladium-catalyst on charcoal, preferably loaded with 5 to 10 % palladium, in particular 10 %, wherein the catalyst is present in an amount of 1 to 10 % (m/m), more preferably 1 to 5 % (m/m), and in particular in an amount of 2 % (m/m) relative to the compound of formula (X);

wherein the hydrogenation preferably is carried out at 1 to 12 bar, preferably at 1 to 5 bar, and even more preferably at 4 to 5 bar; and wherein the hydrogenation is carried out at elevated temperatures, preferably at temperatures of from 30 to 60 °C; optionally the hydrogenation is carried out under agitation;

(c) mixing the compound of formula (II) with an oxidant; and a solvent, wherein the solvent is a polar aprotic solvent, preferably DMF, and wherein the oxidant preferably is sodium metabisulfite;

(d) heating the mixture to 50 to 150°C, preferably 90 to 130°C and more preferably to 110 to 115°C;

(e) adding 4-Methoxybenzaldehyde, optionally under agitation, in amounts of from 0.75 to 1.5 molar equivalents, preferably in stoichiometric amounts, preferably over 0.25 to 2 hours, even more preferably within 0.5 hours;

optionally filtering the mixture, preferably at 0 to 90 °C, more preferably at 60 to 70 °C; rinsing the filter residue with the solvent, and combining the filtrates;

(f) adding a proton acceptor, wherein the proton acceptor preferably is aqueous ammonia;

(g) adjusting the pH to an alkaline value; preferably in the pH range of 8 to 9, preferably at

temperatures of 40 to 60 °C; wherein the pH preferably is adjusted by adding aqueous sodium hydroxide, in particular 2 N aqueous sodium hydroxide;

(h) treating the reaction mixture with water, optionally under agitation, preferably at room temperature;

5 (i) optionally seeding the mixture;

(j) allowing the hydrate of the compound of formula **(I)** to precipitate, optionally under agitation; and separating the crystalline hydrate of the compound of formula **(I)**, optionally drying the solid;

10 (k) optionally converting the hydrate of the compound of formula **(I)** to a solvate other than the hydrate of the compound of formula **(I)**.

Step (a) preferably is carried out in the presence of a proton donor, preferably an organic acid, more preferably acetic acid, in sub-stoichiometric amounts, more preferably in amounts of 0.5 molar equivalents relative to the compounds of formula **(XI)** and **(XII)**, respectively.

15 Most preferably step (a) is carried out in the presence of acetic acid in catalytic amounts. The resulting compound of formula **(X)** preferably is a crystalline compound with a purity of at least 99 %, and more preferably the resulting compound **(X)** is substantially free of residual hydrazine.

20 In an alternative process for the manufacture of a compound of formula **(I)**, the process comprises, the following steps, in addition to steps (a) and (b) above:

(c) mixing the compound of formula **(II)** with an oxidant, 4-methoxybenzaldehyde and a solvent, wherein the solvent is a polar aprotic solvent, preferably DMF, and wherein the oxidant preferably is sodium metabisulfite;

25 (d) heating the mixture to a temperature of from 120 to 125 °C

(e) optionally stirring the mixture, preferably for 1 hour;

(f) cooling the reaction mixture to room temperature;

(g) adding water, preferably at a temperature of from 0 to 4 °C;

(h) optionally seeding the mixture;

30 (i) allowing the hydrate of the compound of formula **(I)** to precipitate, preferably to crystallize, optionally under agitation;

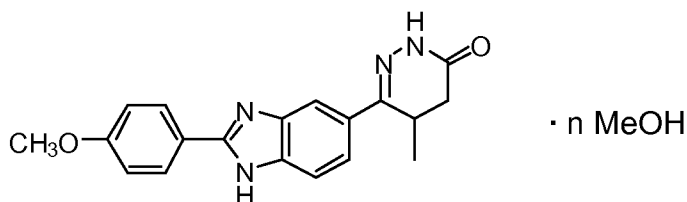
wherein steps (j) and (k) are the same as above.

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In yet another alternative process for the manufacture of a compound of formula (I), the process comprises, the following steps, in addition to steps (a) and (b) above:

- (c) mixing the compound of formula (II) with a solvent, wherein the solvent is a polar aprotic solvent, preferably DMF;
 - (d) heating the mixture to a temperature from 50 to 150°C, preferably from 70 to 130°C and in particular to 80°C;
 - (e) adding 4-Methoxybenzaldehyde, optionally under agitation, in amounts of from 0.75 to 1.5 molar equivalents, preferably in stoichiometric amounts, preferably over 0.25 to 2 hours, even more preferably within 0.5 hours; and preferably allowing the formation of an intermediate compound of formula (VIII) as represented in the scheme above;
 - (f) adding said reaction mixture to a mixture of an oxidant in a solvent, wherein the solvent preferably is a polar aprotic solvent, more preferably DMF, and wherein the oxidant preferably is sodium metabisulfite;
 - (g) adjusting the temperature from 100 to 120°C, preferably at about 110°C; and optionally stirring the mixture; preferably for at least 1 hour, more preferably for 2 hours;
 - (h) allowing the reaction mixture to cool to room temperature and adding the reaction mixture to water, optionally under agitation, preferably at a temperature from 0 to 4 °C;
 - (i) optionally seeding the mixture;
- wherein steps (j) and (k) are the same as above.

In a preferred process according to embodiment A-9, in step (k) of any of the processes described above, the hydrate of the compound of formula (I) is converted to a compound of the formula (I) • n MeOH



(I)

wherein n is from 1 to 2 molar equivalents, preferably n is from 0.125 to 1.25 molar equivalents.

In some embodiments of the present invention, the compound of formula (I) is obtained as crystalline hydrate. Crystalline hydrates of a compound of formula (I) preferably comprise water in an amount of 1 to 10 % by weight, more preferably 3 to 8 % by weight and even more preferably 4 to 6 % by weight.

5

In other embodiments of the present invention, the compound of formula (I) preferably is obtained as crystalline solvate other than the hydrate of the compound of formula (I).

Preferred solvates of the compound of formula (I) are methanol solvates, comprising the solvent in an amount of 1 to 5 % by weight, preferably 1 to 3 % by weight and even more preferably 1 to 2 % by weight.

Methanol solvates of the compound of formula (I) can be obtained by converting the hydrate of the compound of formula (I) to a methanol solvate of the compound of formula (I).

15 In a preferred conversion process of embodiment A-12, the hydrate of the compound of formula (I) is dissolved in a polar aprotic solvent, preferably DMF, heated to a temperature of from 50 to 150°C, preferably from 70 to 130°C and in particular to 80°C; then the solution is optionally filtered and cooled to 50°C; methanol is added, optionally with stirring. The mixture is cooled slowly to a temperature of from 0 to 5 °C and preferably stirred for a further 2 to 3
20 hours. The resulting solid is separated, preferably washed with methanol and optionally dried, to yield a methanol solvate of the compound of formula (I).

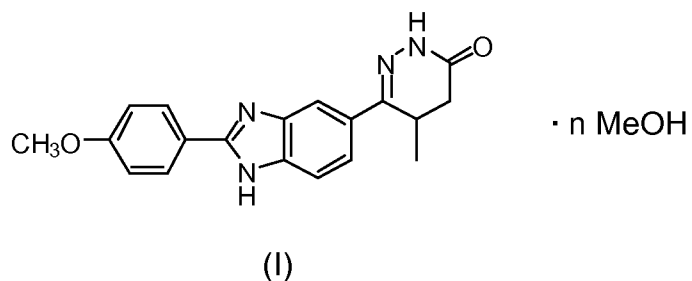
More preferably a crystalline compound of formula (I) • n MeOH (*n* is from 1 - 2 molar equivalents, preferably *n* is from 0.125 to 1.25 molar equivalents) is obtained in high yields
25 and high purities from a compound of formula (I).

In another embodiment of the invention, residual water is removed, prior to conversion, by azeotropic distillation, preferably utilizing n-butanol, ethyl acetate, ethanol or toluene as solvent.

30

In yet another embodiment A-13, the present invention relates to a compound of formula (I) in the form of a crystalline methanol solvate (I) • n MeOH (wherein *n* is 1 to 2 molar equivalents, preferably *n* is from 0.125 to 1.25 molar equivalents).

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In yet another embodiment A-14, the present invention relates to a compound of formula (I)
5 obtained by any of the processes described above.

Finally, in yet another embodiment A-15, the present invention relates to the use of the
above described compounds of formula (I) for the manufacture of a pharmaceutical
composition comprising the compound of formula (I) together with at least one
10 pharmaceutically acceptable carrier, diluent, or excipient.

Examples

Residual solvent content was determined using Gas Chromatography (GC). **Residual water** content was determined using Karl Fischer titration on a Titrando 835 (Metrohm) with double Pt-electrode. **HPLC** is High Performance Liquid Chromatography and was conducted using a commercially available HPLC-system consisting of a gradient pump, an auto sampler, column thermostat and UV-detector (Agilent or Dionex). **MP** is the melting point and is determined according to known methods on a B545 (Büchi), in particular thermomicroscopically, preferably verified by DSC. **DSC** is Differential Scanning Calorimetry and was conducted on a commercially available DSC822 (Mettler) with inert gas: nitrogen, temperature program from 30°C to 400 °C and heating rate: 10 °C/min. **NMR** is Nuclear Magnetic Resonance Spectroscopy and was conducted on a commercially available Bruker AVANCE 300 spectrometer at 301K. **IR** is Infrared Spectrometry and was conducted using a commercially available FTIR-spectrometer Spectrum one (Perkin-Elmer). **LCMS** is Liquid Chromatography Mass Spectrometry and was conducted using a commercially available HPLC-system consisting of a gradient pump, an auto sampler, column thermostat, UV-detector and MS-detector (Agilent or Dionex). **XRPD**. powder diffractometer D5000 (Fa. Siemens) using Cu-anode, Ni-filter, variable (θ -dependent) divergence and antidiffusion screen.

Example 1

1.A) Preparation of 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoic acid (XI)

The starting material 4-(4-chloro-3-nitrophenyl)-3-methyl-4-oxobutanoic acid is readily accessible by nitration of 4-(4-chlorophenyl)-3-methyl-4-oxobutanoic acid according to *Eur. J. Med. Chem.* **1993**, 28, 129.

A round bottom flask was charged with 4-(4-chloro-3-nitrophenyl)-3-methyl-4-oxobutanoic acid (77.9 g; 286.8 mmol) and absolute ethanol (390 mL). The mixture was heated to 40 - 50 °C and benzylamine (153.1 g, 1.43 mol, 5 eq.) was added over about 20 minutes with stirring. The mixture was then heated to reflux temperature and stirring was continued for 7 h. The mixture was concentrated under reduced pressure and toluene (624 mL) and water (235 mL) were added to the warm residue with stirring. Aq. hydrochloric acid (37 %, 82.1 g) was added to adjust the pH to a value of 2.0 - 1.5. After stirring for 20 minutes the organic

phase was separated. The aqueous mixture was extracted with toluene (1 x 78 mL). The combined organic phases were washed with water (2 x 155 mL). The organic phase was treated with water (625 mL) and aq. sodium hydroxide (50 %, 21.5 g) to adjust the pH to a value of 12 - 13. Stirring was continued for 20 minutes and the phases were separated. The aqueous phase was washed with toluene (3 x 78 mL) and treated with tert-Butylmethylether (MTBE) (390 mL). Aq. hydrochloric acid (37 %, 28 g) was added with stirring to adjust the pH to a value of 2. The phases were separated and the aqueous phase was extracted with MTBE (78 mL). The organic phases were combined and the solvent was distilled off at 40 - 50 °C under reduced pressure. The crude product was dried under reduced pressure (100 mbar, 50 °C, 90 minutes) to give the title compound. **Yield:** 89.35 g (260.99 mmol, 90.9 %). **HPLC:** 98.8 %. The product can be obtained in crystalline form by crystallisation from warm ethanol (approx. 1: 4 m/v). **HPLC:** 99.65 %. **Mp:** 102 - 109 °C, **DSC:** 101.5 / 107.93 °C (onset / peak). **¹H-NMR** (300 MHz, CDCl₃, ppm): δ 8.86 (s, 1 H, arom.), 8.80 - 8.79 (s, br., 1 H, NH), 8.04 - 8.00 (dd, ³J = 6.0 Hz, ⁴J = 3.0 Hz, 1 H, arom.), 7.39 - 7.33 (m, 5 H, arom.), 6.92 - 6.89 (d, ³J = 9 Hz, 1 H, arom), 4.63 - 4.61 (d, J = 6.0 Hz, 2 H, PhCH₂), 3.87 - 3.80 (m, 1 H, CH), **3.03 - 2.94** (m, 1 H, CH₂), 2.52 - 2.45 (m, 1 H, CH₂), 1.24 - 1.22 (d, ³J = 6 Hz, 3 H, CH₃). **¹³C-NMR** (75 MHz, CDCl₃, ppm): δ 199.26 (keto-C=O), 177.15 (carboxy-C=O), 147.76 (C, arom.), 136.31 (C, arom.), 135.55 (CH, arom.), 131.54 (C, arom), 129.12 (2x CH, arom.) 128.56 (C, arom.), 128.07 (CH, arom.), 127.02 (2 x CH, arom.), 123.63 (CH, arom.), 114.39 (CH, arom.), 47.30 (PhCH₂), 36.96, 36.39, 18.14 (CH₃). **IR** (KBr, cm⁻¹): 3374, 2975, 1709 (ν_{C=O}), 1675 (ν_{C=O}), 1617, 1564, 1530, 1454, 1431, 1355, 1275, 1226, 1194, 1054, 1022, 997, 896, 819, 741, 700, 527. **LCMS** (ESI⁺, m/z): = 342.6 [MH]⁺.

1.B) Preparation of ethyl 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxo-butanoate (XII)

4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoic acid (**XI**, 103.77 g, 0.303 mol), prepared according to example 1 was dissolved in absolute ethanol (500 mL) and treated with a solution of hydrogen chloride in ethanol (9 M, 2 mL). The mixture was heated to reflux and water was removed by continuous azeotropic distillation until the complete conversion was obtained. The solvent was evaporated at 50-80 °C under reduced pressure to obtain methyl 4-(3,4-diaminophenyl)-3-methyl-4-oxobutanoate in practically quantitative yield, which was used without further purification. **HPLC:** 95.7 %. **¹H-NMR** (300 MHz, CDCl₃, ppm): δ 8.88

(s, 1 H, arom.), 8.06 - 8.02 (d, 1 H, arom.), 7.41 - 7.26 (m, 5 H, arom.), 6.91 - 6.88 (d, 1 H, arom.), 4.62 - 4.61 (d, 2 H, CH₂), 4.12 - 4.05 (q, 2 H, CH₂), 3.90 - 3.83 (m, 1 H, CH), 2.99 - 2.90 (dd, 1H, CH₂), 2.48 - 2.41 (dd, 1 H, CH₂), 1.22 - 1.18 (t, 6 H, 2 x CH₃). **¹³C-NMR** (75 MHz, CDCl₃, ppm): δ 199.58 (keto-C=O), 172.19 (carboxy-C=O), 147.66 (C, arom.), 136.35 (C, arom.), 135.52 (CH, arom.), 131.53 (C, arom), 129.07 (2x CH, arom.) 128.47 (C, arom.), 128.01 (CH, arom.), 127.03 (2 x CH, arom.), 123.97 (CH, arom.), 114.32 (CH, arom.), 60.56 (CH₂), 47.25 (PhCH₂), 37.63, 36.44, 18.04 (CH₃), 18.14 (CH₃). **IR** (KBr, cm⁻¹): 3375, 3032, 2979, 2936, 1733 (ν_{C=O}), 1675 (ν_{C=O}), 1616, 1564, 1530, 1496, 1454, 1432, 1354, 1275, 1184, 1095, 1053, 1028, 997, 902, 822, 740, 698, 622, 529. **LCMS** (ESI⁺, m/z): 371.1 [MH]⁺.

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Example 2

Preparation of 6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (X)

15 2.A) Employing excess hydrazine hydrate, and acetic acid as solvent (according to prior art method disclosed in DE 3129447)

A round bottom flask was charged with 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoic acid (**XI**, 88.5 g, 258 mmol), prepared according to example 1 and acetic acid (225 mL). The mixture was heated to 40 - 50 °C with stirring and added to a solution of hydrazine hydrate (163 mL, 2.67 mol, 10.3 eq.) in acetic acid (500 mL). After the addition was completed the mixture was heated at 80 - 85 °C for about 3 - 4 h with stirring. The mixture was allowed to reach room temperature and poured into water (1800 mL). Stirring was continued for a further 30 min after which the precipitate was separated and washed with water (4 x 100 mL). The solid was dried at 50 - 60 °C to yield 71.74 g (212 mmol, 82.2 % of the title compound. **HPLC**: 98.8 %. For further purification the product (70.00 g, 206 mmol) was re-crystallized from refluxing n-butanol (1100 mL) to yield after separation of the crystalline solid at 0 °C, washing with n-butanol (2 x 41 mL) and drying at 50 - 60 °C the title compound in yields of 97 % (68.12 g, 201 mmol, overall yield: 78 %). **HPLC**: 99.97 %. **Mp**: 208-211 °C; Lit. 187 - 191 °C (DE 3129447), 207 - 209 °C (Eur. J. Med. Chem. 1993, 28, 129), **DSC**: 209.59 / 210.64 °C (onset / peak), **¹H-NMR** (300 MHz, CDCl₃, ppm): δ 8.67 (s, 2H, 2 x NH), 8.48 - 8.47 (d, ⁴J = 3.0 Hz, 1 H, arom.), 7.98 - 7.94 (dd, ⁴J = 3.0 Hz, ³J = 9.0 Hz, 1 H, arom.), 7.39 - 7.26 (m, 5 H, arom), 6.91 - 6.88 (d, ³J = 9.0 Hz, 1 H, arom), 4.62 - 4.60 (d, J = 6.0 Hz, 2 H, PhCH₂), 3.36 - 3.31 (m, 1 H, CH), 2.74 - 2.66 (dd, ³J = 9.0 Hz, ²J = 18.0 Hz, 1

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H,CH₂), 2.51 - 2.45 (dd, ³J = 3.0 Hz, ²J = 18.0 Hz, 1 H, CH₂), 1.25-1.23 (d, ³J = 6 Hz, 3 H, CH₃). ¹³C-NMR (75 MHz, CDCl₃, ppm): 166.42 (keto-C=O), 152.06 (C, arom.), 145.91 (C, arom.), 136.75 (C, arom.), 133.58 (CH, arom.), 131.66 (C, arom.), 129.04 (2 x CH, arom.), 127.92 (CH, arom.), 127.02 (2 x CH, arom.), 124.22 (CH, arom.), 122.45 (CH, arom.), 114.96 (CH, arom.), 47.21 (PhCH₂), 33.79, 27.65, 16.28 (CH₃). IR (KBr, cm⁻¹): 3368 (ν_{N-H}), 3219, 1689 (ν_{C=O}), 1630, 1563, 1522 (ν_{C=C, arom.}), 1455, 1402, 1345, 1269, 1245, 1195, 1153, 1053, 1038, 956, 821, 761, 726, 696, 556. LCMS (ESI⁺, m/z): 339.0 [MH]⁺.

10 **2.B) Employing ethanol as solvent, 0.5 equivalents of acetic acid, and 1.2 equivalents of hydrazine hydrate**

A round bottom flask was charged with 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoic acid (**XI**, 132.38 g, 0.387 mol), prepared according to example 1, hydrazine hydrate (29.16 g, 0.464 mol), acetic acid (11.65 g, 0.194 mol) and ethanol (560 g) and the mixture was heated at reflux for 6 - 7 h with stirring. The mixture was allowed to reach room temperature and the precipitated product was filtered off, washed with ethanol (2 x 20 mL) and dried at 60 °C to yield pure **X** (107.9 g, 82 %) without the need for further purification. HPLC: 99.7 %.

20 **2.C) Employing ethanol as solvent, 0.5 equivalents of acetic acid, and 1.5 equivalents of hydrazine hydrate.**

6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**) was obtained in a similar manner as described in example 2 item B. Reaction time: 6 - 7 h. Yield: 0.75 g (2.22 mmol, 71 %). HPLC: 99.8 %.

25 **2.D) Employing ethanol as solvent, 0.5 equivalents of acetic acid, and 2.0 equivalents of hydrazine hydrate**

6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**) was obtained in a similar manner as described in example 2 item B. Reaction time: 3 - 4 h. Yield: 0.77 g (2.28 mmol, 72 %). HPLC: 99.8 %.

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2.E) Employing ethanol as solvent, 1.0 equivalents of acetic acid, and 2.0 equivalents of hydrazine hydrate

6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**) was obtained in a similar manner as described in example 2 item B. Reaction time: 3 - 4 h. Yield: 0.77 g (2.28 mmol, 72 %). **HPLC**: 99.4 %.

5 **2.F) Employing ethanol as solvent and 1.5 equivalents of hydrazine hydrate**

6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**) was obtained in a similar manner as described in example 2 item B. Reaction time: 6 - 7 h. Yield: 0.76 g (2.25 mmol, 71 %). **HPLC**: 99.8 %.

10 **2.G) Employing ethanol as solvent and 1.2 equivalents of hydrazine hydrate**

6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**) was obtained in a similar manner as described in example 2 item B. Reaction time 10 - 12 h. Yield: 0.63 g (1.86 mmol, 59 %). **HPLC**: 99.7 %.

15 **2.H) Employing Ethyl 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxobutanoate (XII) as starting material**

Ethyl 4-(4-(benzylamino)-3-nitrophenyl)-3-methyl-4-oxo-butanoate (**XII**, 1.15 g, 3.11 mmol), prepared according to example 3 was dissolved in ethanol (21 mL). Hydrazine hydrate (51%, 0.191 mL, 3.16 mmol) and acetic acid (0.089 mL, 0.5 eq.) were added and the mixture was
20 heated at reflux for about 16 h with stirring. The resulting suspension was allowed to reach room temperature. The precipitate was separated, washed with ethanol (2 x 1 mL), and dried at 50 °C to yield 0.56 g (1.66 mmol, 53.5 %) of 6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydro-pyridazin-3-one. **HPLC**: 98.9 %.

25 **Example 3**

Preparation of 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (II)

A round bottom flask was charged with 6-(4-benzylamino-3-nitrophenyl)-5-methyl-2,3,4,5-tetrahydropyridazin-3-one (**X**, 31.0 g, 0.0916 mol), prepared according to example 2 item B, methanol (170 mL) and aq. hydrochloric acid (1 N, 91.6 mL) with stirring. After addition of
30 Pd/C (10 %, 0.62 g) hydrogen was applied (4 - 5 bar) and stirring was continued for 2 h at 30 °C. The catalyst was separated and the methanol was distilled off under reduced pressure. The clear filtrate was treated with aq. sodium hydroxide (2 N, 35 mL) with stirring. The resulting suspension was allowed to reach 18 °C after which the precipitated product was

separated, washed with water and dried at 50 - 60 °C to yield the title compound (16.68 g, 83.4 %). **HPLC**: 99.3 %. **Mp**: 185 - 190 °C; Lit. 183 - 185 °C (*Eur. J. Med. Chem.* 1993, 28, 129), **DSC**: 190.28 / 191.34 °C (onset / peak). **¹H-NMR** (300 MHz, DMSO, ppm): δ 10.61 (s, 1 H, NH), 7.04 (s, 1 H, arom.), 6.85 - 6.82 (dd, ⁴J = 3.0 Hz ³J = 9.0 Hz, 1 H, arom.), 6.52 - 6.49 (d, ³J = 9.0 Hz, 1 H, arom.), 4.69 (s, br., 4 H, 2 x NH₂), 3.24 - 3.19 (m, 1 H, CH), 2.61 - 2.53 (dd, ³J = 6.0 Hz, ²J = 18.0 Hz, 1 H, CH₂), 2.18 - 2.13 (d, ²J = 18.0 Hz, 1 H, CH₂), 1.04 - 1.02 (d, ³J = 6 Hz, 3 H, CH₃). **¹³C-NMR** (75 MHz, DMSO, ppm): δ 166.00 (*keto*-C=O), 153.41 (C, olef.), 137.05 (C, arom.), 134.42 (C, arom.), 123.28 (CH, arom.), 115.98 (CH, arom.), 113.31 (CH, arom.), 111.39 (CH, arom.), 33.60 (CH₂), 26.86 (CH), 16.08 (CH₃). **IR** (KBr, cm⁻¹): 3397 (ν_{N-H}), 3262, 2961, 1672 (ν_{C=O}), 1522 (ν_{C=C, aromatic}), 1445, 1366, 1342, 1293, 1213, 1188, 1138, 1081, 1038, 1022, 956, 909, 870, 806, 744, 592. **LCMS** (ESI⁺, m/z): 219 [MH]⁺.

Example 4

Preparation of crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydro-pyridazin-3(2H)-one monohydrate (I • H₂O)

4.A) Method 1

A reactor was charged with 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**II**, 1.0 eq.), prepared according to example 3, and sodium metabisulfite (1.1 eq.) in DMF (3.5 L/kg; V:m_(II)). The mixture was heated to 110 - 115 °C and 4-Methoxybenzaldehyde (1.0 eq.) was added over 30 min with stirring. After the addition was complete stirring was continued for a further 60 min. The suspension was cooled to 60 - 70 °C, filtered and the filter cake was washed with DMF (1.24 L/kg; V:m_(II)). The clear filtrate was treated with aq. ammonia at 45 - 55 °C to adjust the pH to a value of 8 - 9. The mixture was then cooled to 25 - 30 °C and water (6.87 L/kg; V:m_(II)) was added slowly with stirring. Stirring was continued for a further 1 - 2 h at room temperature and the precipitated product was separated by filtration. The solid was washed with water (4 x 1.24 L/kg; V:m_(II)) and acetone (4 x 2.47 L/kg; V:m_(II)) and dried under reduced pressure at 40 - 60 °C to obtain 93.8 % of crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydro-pyridazin-3(2H)-one monohydrate. **Residual solvents**: H₂O, 4.97 % (KF). **HPLC**: 99.04 %. **Mp**: 162-164 °C. **¹H-NMR** (DMSO, 300 MHz): δ = 12.82 (s, br. 1 H, NH), 10.89 (s, 1 H, NH), 8.14 - 8.11 (d, 2 H, 2 x CH, arom), 7.93 (s, 1 H, arom), 7.71-7.68 (1 H, d, arom.), 7.59 - 7.56 (1d, H, arom.), 7.13 - 7.10 (d, 2 H, arom.), 3.83 (s, 3 H, CH₃O), 3.53 - 3.44 (m, 1 H, CH), 3.56 (s, br), 2.87-2.68 (dd, 1 H, CH₂), 2.28 - 2.22

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(dd, 1 H, CH₂), 1.13 - 1.11 (d, 3 H, CH₃). ¹³C-NMR (DMSO, 75 MHz): δ = 166.23, 160.76, 153.31, 152.58, 128.78, 128.09, 122.37, 119.98, 114.37, 55.30, 33.65, 27.45, 16.02. IR (KBr, cm⁻¹): 3273, 1620, 1493, 1459, 1422, 1393, 1380, 1342, 1297, 1252, 1179, 1079, 1034, 960, 924, 893, 833, 813, 773, 744, 687, 639, 608, 519.

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XRPD

Angle 2-Theta °	d value Angstrom	Intensity %
5.944	14.85700	1.4
11.152	7.92770	28.8
11.640	7.59646	2.4
12.779	6.92155	55.7
13.208	6.69809	20.7
14.274	6.20001	1.3
15.073	5.87314	4.8
15.773	5.61396	21.6
16.113	5.49615	5.8
17.231	5.14202	1.5
17.585	5.03940	1.7
17.879	4.95710	1.7
18.442	4.80707	8.8
19.058	4.65297	8.7
19.388	4.57471	3.4
20.752	4.27698	100.0
21.240	4.17972	11.0
22.382	3.96905	8.9
23.869	3.72501	29.7
24.556	3.62235	3.6
25.967	3.42863	7.0
26.669	3.33987	16.0
28.404	3.13975	26.9
28.969	3.07978	18.9
29.426	3.03295	16.6
30.706	2.90937	4.8
31.755	2.81557	9.4
33.421	2.67894	4.0
34.300	2.61233	3.9
35.280	2.54194	3.3
35.879	2.50090	3.1
37.149	2.41822	2.3
39.253	2.29331	1.9

4.B) Method 2

A round bottom flask was charged with 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**II**, 163.7 g, 0.75 mol), prepared according to example 3, and DMF (526 mL). The mixture was heated to 80 °C and 4-methoxybenzaldehyde (102.2 g, 0.75 mol) was added over 30 min with stirring. After the addition was completed stirring was continued for approx. 90 min. Subsequently the mixture was cooled to about 40 °C. A second round bottom flask was charged with sodium metabisulfite (156.8 g, 0.825 mol) and DMF (500 mL) and the mixture was heated to 110 °C. At 110 °C the solution of the Schiff base in DMF was added under stirring over about 60 minutes and the stirring was continued for a further 100 minutes. The reaction mixture was cooled to room temperature and the organic phase was separated by decantation. The organic phase was added to ice-water (2250 g) over about 30 minutes and stirring was continued for a further 60 minutes. The precipitated product was separated by filtration and washed with water (2 x 50 mL). The moist product was suspended in acetone (500 mL) and refluxed for 15 minutes with stirring. The solid was separated by filtration and washed with acetone (2 x 50 mL). The procedure was repeated once. After drying at 60 °C (8 h) 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one monohydrate (70 %) was obtained. **HPLC**: 98.4 %. **Residual solvents**: H₂O, 4.80 % (KF). **Mp.** 160-165 °C.

4.C) Method 3

A round bottom flask was charged with 6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (36.0 g, 0.165 mol), prepared according to example 3, sodium metabisulfite (34.5 g, 0.179 mol), 4-methoxybenzaldehyde (22.46 g, 0.165 mol) and DMF (115 mL). The mixture was heated to 120 - 125 °C and stirred for a further 50 minutes at 120 - 125 °C. The reaction mixture was cooled to room temperature and added under stirring to ice-water (595 g). The precipitated product was separated by filtration and washed with water (2 x 10 mL). The moist product was suspended in acetone (200 mL), refluxed under stirring for about 10 minutes and the solid was separated by filtration and washed with acetone (10 mL). The product was refluxed again with acetone (135 mL) and washed with acetone (3 x 15 mL) after filtration. This procedure was repeated with ethyl acetate (135 mL). The product was

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dried over night at room temperature and subsequently at 60 °C (2 h). **Yield:** 50.91 g (0.144 mol, 92.3 %), **HPLC:** 99.2 %, **Residual solvents:** H₂O, 5.2 % (KF). **Mp.** 163-167 °C

Example 5

Preparation of crystalline methanol solvates of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • n MeOH (n = 0.125 to 1.25 molar equivalents)

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6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydro-pyridazin-3(2H)-one • H₂O (**I** • H₂O, 100 g, 283.8 mmol), prepared according to example 4 item A, was dissolved in DMF (200 mL) with heating. The solution was filtered, cooled to 50 °C and hot methanol (1000 mL) was added with stirring. The mixture was cooled slowly to 0 - 5 °C and stirred for a further 2 - 3 h. The resulting solid was separated, washed with methanol (3 x 100 mL) and dried at 70 °C to yield 80 g (239.25 mmol, 80 %) of crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one • n methanol. **HPLC**: 99.93 %. **Residual solvents**: H₂O, 0.5 % (KF); MeOH, 30000 ppm (approx. 0.32 molar equivalents, GC).

15

XRPD

Angle 2-Theta °	d value Angstrom	Intensity %
5.945	14.85419	1.0
11.151	7.92845	29.1
11.696	7.56029	2.7
12.803	6.90863	41.1
13.209	6.69759	21.4
14.387	6.15134	1.6
14.755	5.99876	3.0
15.050	5.88195	3.9
15.774	5.61378	23.9
16.117	5.49495	8.1
16.558	5.34940	2.9
17.248	5.13705	2.0
17.680	5.01250	1.9
18.452	4.80438	8.8
19.049	4.65530	8.8
19.429	4.56514	3.7
20.742	4.27891	100.0
21.240	4.17972	10.8
21.747	4.08345	2.6
22.388	3.96794	6.6
23.866	3.72540	29.5

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Angle 2-Theta °	d value Angstrom	Intensity %
24.542	3.62439	4.8
25.962	3.42924	9.4
26.660	3.34104	12.1
27.493	3.24164	2.3
28.427	3.13718	22.1
28.977	3.07891	16.4
29.407	3.03491	15.0
30.622	2.91715	4.9
31.744	2.81660	6.6
32.639	2.74138	2.6
33.367	2.68314	3.8
34.361	2.60777	4.8
35.220	2.54611	3.7
35.879	2.50085	3.0
37.218	2.41389	4.5
39.041	2.30528	3.2

Example 6

Preparation of pure non-solvated crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) by conversion of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • n methanol

A round bottom flask was charged with 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • n methanol (53.4 g, 159.7 mmol), prepared according to example 5, and ethyl acetate (265 mL). The mixture was heated at reflux about 5 h with stirring. The solid was isolated, washed with ethyl acetate (2 x 10 mL) and dried at 60 °C to give 52.26 g (156.3 mmol, 97.9 %) of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one. **HPLC**: 99.94 %. **Assay**: 100.1 % (titration). **Mp**: 240 - 243 °C (boetius), **DSC**: 240.10 / 241.87 °C (onset / peak). **¹H-NMR** (300 MHz, DMSO, ppm): δ 12.85 (s, 1 H, NH), 10.89 (s, 1 H, NH), 8.14 - 8.11 (d, ³J = 9.0 Hz, 2 H, 2 x CH arom), 7.72 - 7.59 (m, 3 H, 3 x CH), 7.14 - 7.11 (d, ³J = 9.0 Hz, 2 H, 2 x CH, arom), 3.85 (s, 3 H, CH₃O), 3.52 - 3.47 (m, 1 H, CH), 2.76 - 2.69 (dd, ³J = 6.0 Hz, ²J = 15.0 Hz, 1 H, CH₂), 2.29 - 2.23 (d, ²J = 18.0 Hz, 1 H, CH₂), 1.15 - 1.12 (d, ³J = 9 Hz, 3 H, CH₃). **¹³C-NMR** (75 MHz, DMSO, ppm): δ 166.12, 160.66, 153.19, 127.99, 122.28, 114.28, 55.22, 33.56, 27.35, 15.94. **UV/Vis**: ε₍₁₎ = 27593.02 L·mol⁻¹·cm⁻¹ at λ_{max (1)} = 266.21 nm, ε₍₂₎ = 42009.00 L·mol⁻¹·cm⁻¹

at $\lambda_{\max}(2) = 328.52 \text{ nm}$. IR (KBr, cm^{-1}): 3234 ($\nu_{\text{N-H}}$), 2972, 2904, 1671 ($\nu_{\text{C=O}}$), 1627, 1611, 1578, 1492, 1445, 1420, 1372, 1339, 1297, 1253, 1181, 1125, 1074, 1026, 961, 922, 903, 837, 812, 792, 743, 694, 585, 526.

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XRPD

Angle 2-Theta °	d value Angstrom	Intensity %
7.979	11.07152	1.1
11.053	7.99860	3.5
12.275	7.20451	1.4
12.641	6.99698	5.4
15.234	5.81147	8.7
16.049	5.51789	9.1
16.820	5.26680	0.9
18.698	4.74173	100.0
19.206	4.61755	43.2
19.690	4.50518	30.9
21.687	4.09458	27.9
23.724	3.74748	12.2
25.103	3.54460	2.0
26.864	3.31608	1.7
27.936	3.19128	9.0
28.706	3.10734	7.8
29.213	3.05460	10.5
30.318	2.94573	20.8
31.144	2.86945	2.9
32.778	2.73002	4.8
33.385	2.68174	5.1
34.000	2.63466	2.9
37.512	2.39566	4.8

Example 7

Preparation of pure non-solvated crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) by re-crystallization of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • n methanol

10

6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • 0.32 methanol (15 g, 43.5 mmol), prepared according to example 5, was dissolved in DMF (30 mL) at 90 - 100 °C. The clear solution was allowed to reach 70 °C and ethyl acetate

(200 mL) was added with stirring. The mixture was cooled to 0 - 5 °C and stirring was continued for 6h. The solid was separated and washed with ethyl acetate to give Pimobendan (4.0 g). From the mother liquor a second crop of Pimobendan (5.5 g) was obtained by dilution with further ethyl acetate (400 mL) and cooling to 0 °C for about 12 h.

5 **Total yield:** 9.5 g (28.4 mmol, 63 %). **HPLC:** 99.34 %. **DSC:** 241.93 / 244.22 °C (onset / peak).

Example 8

10 **Preparation of pure non-solvated crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) by conversion of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • H₂O by employing n-butanol as the solvent**

6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • H₂O (5 g, 14.19 mmol), prepared according to example 4 item A, was suspended in n-butanol (50 mL). About 30 mL of the solvent were distilled off at 116 - 118 °C (normal pressure). This procedure was repeated once. The solution was cooled to room temperature and the solid was isolated by filtration. **Yield:** 3.55 g (10.6 mmol, 76 %). **HPLC:** 99.78 %. **DSC:** 239.77 / 244.35 °C (onset / peak).

20 Example 9

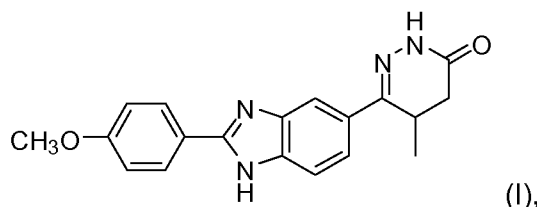
Preparation of pure non-solvated crystalline 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) by conversion of 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • H₂O by employing ethyl acetate as the solvent

25 6-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-5-yl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (I) • H₂O (5 g, 14.19 mmol), prepared according to example 4 item A, was suspended in ethyl acetate (50 mL). About 30 mL of the solvent were distilled off at normal pressure. This procedure was repeated 6 times. The solution was cooled to room temperature and the solid was isolated by filtration. **Yield:** 4.22 g (12.6 mmol, 92.5 %). **HPLC:** 99.56 %. **DSC:** 241.99 / 30 243.85 °C (onset / peak).

Claims

1. A process for the manufacture of a non-solvated crystalline compound of formula (I), comprising the steps of:

5 (a) providing a solvated compound of formula (I)



(b) optionally removing residual water by azeotropic distillation;

(c) treating said compound to obtain a non-solvated crystalline compound of formula (I) by re-crystallisation from suspension, wherein the solvent is selected from the group consisting of linear or branched C₁₋₄ alcohols, such as methanol, ethanol, 1-propanol, 2-propanol, and n-butanol; or C₁₋₄ alkylesters, such as butylacetate or ethylacetate; and mixtures thereof;

(d) isolating the non-solvated crystalline compound of formula (I);

with the proviso that if the solvated compound of formula (I) is a hydrated compound of formula (I), the residual water has to be removed by azeotropic distillation in step (b).

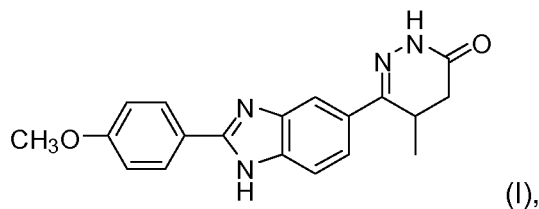
2. A process according to claim 1, wherein the re-crystallisation from suspension in step (c) is carried out at reflux temperatures for 0.5 to 10 hours.

3. A process according to claim 1 or 2, wherein residual water is removed, prior to treatment of the solvated compound, by azeotropic distillation utilizing n-butanol, ethyl acetate, ethanol or toluene as solvent.

4. A process for the manufacture of a non-solvated crystalline compound of formula (I), comprising the steps of:

(a) providing a solvated compound of formula (I)

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(b) dissolving the solvated compound of formula (I) in a polar aprotic solvent;

5 (c) optionally removing residual water by azeotropic distillation;

(d) treating the solution with an anti-solvent, wherein the anti-solvent is selected from C₁₋₄ alkylesters, such as butylacetate or ethylacetate; and mixtures thereof; and

10 (e) isolating and drying the non-solvated crystalline compound of formula (I);

with the proviso that if the solvated compound of formula (I) is a hydrated compound of formula (I), the residual water has to be removed by azeotropic distillation in step (c).

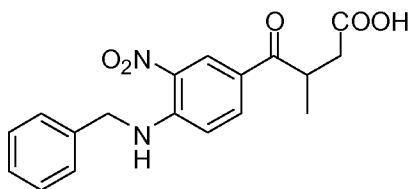
15

5. A process according to claim 4, wherein step (d) is carried out at temperatures from 0 to 5°C.

6. A process according to claim 4 or 5, wherein residual water is removed, prior to
20 treatment of the solvated compound, by azeotropic distillation utilizing n-butanol, ethyl acetate, ethanol or toluene as solvent.

7. A process for the manufacture of a solvated compound of formula (I), comprising the
25 steps of:

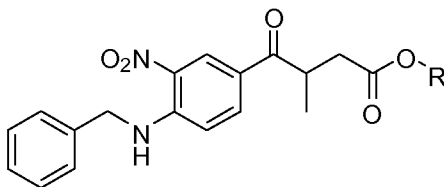
(a) reacting a compound of formula (XI)



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XI

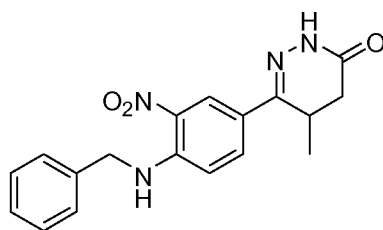
or a compound of formula **(XII)**, wherein R corresponds to C₁₋₄ alkyl;

**XII**

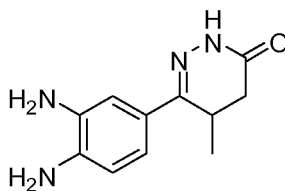
5

with hydrazine in a solvent to yield a compound of formula **(X)**,
wherein hydrazine is used in amounts of 1 to 2 molar equivalents relative to the
compounds of formula **(XI)** and **(XII)**, respectively; and

10 (b) subsequently hydrogenating the compound of formula **(X)**

**X**

to a compound of formula **(II)**;

**II**

15

- (c) mixing the compound of formula **(II)** with an oxidant; and a solvent, wherein the solvent is a polar aprotic solvent;
- (d) heating the mixture to 50 to 150 °C;
- (e) adding 4-Methoxybenzaldehyde, in amounts of from 0.75 to 1.5 molar equivalents;
- 20 (f) adding a proton acceptor;
- (g) adjusting the pH to an alkaline value;
- (h) treating the reaction mixture with water;
- (i) optionally seeding the mixture;

- (j) allowing the hydrate of the compound of formula **(I)** to precipitate; and separating the crystalline hydrate of the compound of formula **(I)**;
- (k) optionally converting the hydrate of the compound of formula **(I)** to a solvate other than the hydrate of the compound of formula **(I)**.

5

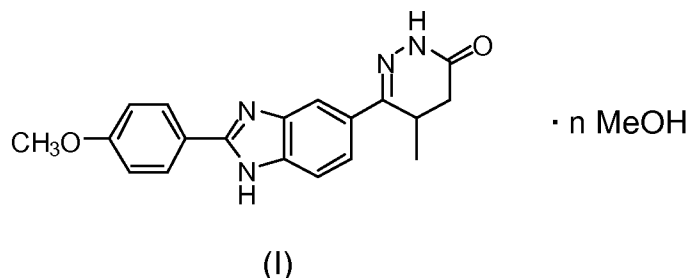
8. A process according to claim 7, wherein step (a) is carried out in the presence of a proton donor in sub-stoichiometric amounts relative to the compounds of formula **(XI)** and **(XII)**, respectively.

- 10 9. A process according to claim 7 or 8, wherein after steps (a) and (b), the process is as follows:
- (c) mixing the compound of formula **(II)** with an oxidant, 4-methoxybenzaldehyde and a solvent, wherein the solvent is a polar aprotic solvent;
 - (d) heating the mixture to a temperature of from 120 to 125 °C;
 - 15 (e) optionally stirring the mixture;
 - (f) cooling the reaction mixture to room temperature;
 - (g) adding water;
 - (h) optionally seeding the mixture;
 - (i) allowing the hydrate of the compound of formula **(I)** to precipitate;
 - 20 wherein steps (j) and (k) are the same as in claim 7 or 8.

10. A process according to claim 7 or 8, wherein after steps (a) and (b), the process is as follows:
- (c) mixing the compound of formula **(II)** with a solvent, wherein the solvent is a polar
 - 25 aprotic solvent;
 - (d) heating the mixture to a temperature from 50 to 150 °C;
 - (e) adding 4-Methoxybenzaldehyde, in amounts of from 0.75 to 1.5 molar equivalents;
 - (f) adding said reaction mixture to a mixture of an oxidant in a solvent;
 - (g) adjusting the temperature from 100 to 120 °C for at least 1 hour;
 - 30 (h) allowing the reaction mixture to cool to room temperature and adding the reaction mixture to water;
 - (i) optionally seeding the mixture;
 - wherein steps (j) and (k) are the same as in claim 7 or 8.

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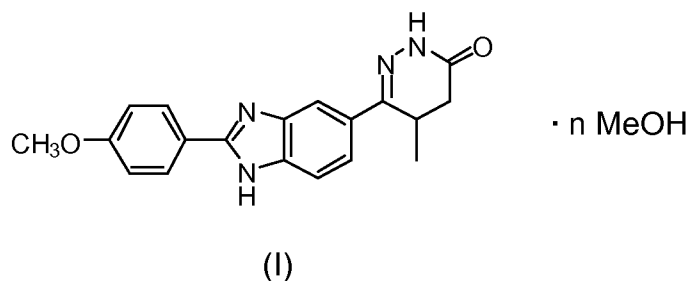
11. A process according to any one of claims 7 to 10, wherein in step (k) the hydrate of the compound of formula (I) is converted to a compound of the formula (I) • n MeOH



5 wherein n is from 1 to 2 molar equivalents.

12. A process according to claim 11, wherein the process of converting comprises dissolving the hydrate of the compound of formula (I) in a polar aprotic solvent, heating to a temperature from 50 to 150°C; adding methanol; slowly cooling the mixture to a temperature of from 0 to 5 °C; separating the resulting solid and optionally drying the resulting solid.

13. A compound of formula (I), wherein the compound is in the form (I) • n MeOH



wherein n is from 1 to 2 molar equivalents.

14. A compound of formula (I), wherein the compound is obtained by the process according to any one of claims 1 to 12.

15. Use of a compound according to claim 13 or 14 for the manufacture of a pharmaceutical composition comprising the compound of formula (I) together with at least one pharmaceutically acceptable carrier, diluent, or excipient.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/055415

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/04 A61K31/501 A61P9/00
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 A61K A61P

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2006 219452 A (TOA EIYO LTD) 24 August 2006 (2006-08-24) paragraph [0032]; examples 3,4 -----	1-6



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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 May 2011

Date of mailing of the international search report

20/07/2011

Name and mailing address of the ISA/

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Authorized officer

Johnson, Claire

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/055415

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-6

Processes for the preparation of non-solvated crystalline (I)

2. claims: 7-12

Processes for the preparation of solvated (I)

3. claims: 13-15

The compound of formula (I).nMeOH and its use

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/055415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2006219452 A	24-08-2006	NONE	
