The present invention relates to a process for the preparation of flupirtine maleate, Flupirtine.
PROCESS FOR THE PREPARATION OF FLUPIRTINE MALEATE

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5 Background

Flupirtine, i.e., ethyl {2-amino-6-[4-(fluorobenzyl)amino]pyridin-3-yl} carbamate of the following formula, is a centrally acting, non-opioid, nonsteroidal anti-inflammatory analgesic.

![Flupirtine molecule](image)

Flupirtine, especially in the form of its maleic acid salt (mainly sold under the trade names Katadolon® and Trancolong®), has been used for many years in the therapy of pain, such as neuralgias, pain associated with degenerative joint diseases, headaches and postoperative pain. Furthermore, there are reports of the usefulness of flupirtine in the treatment of diseases not related to pain, such as batten disease, tinnitus, diseases which are associated with damage to the hematopoietic cell system, dysfunction of the lower urinary tract, and dystonia.

It is known that flupirtine maleate shows polymorphism, i.e., it exists in different polymorphic forms (cf., e.g., DE 31 33 519 C2, WO 2008/007117, WO 2008/110357, and K.-F. Landgraf et al., Eur. J. Pharm. Biopharm. 1998, 46(3):329-337), such as polymorph A or polymorph B (as described and characterized in DE 31 33 519 C2), or polymorph V, polymorph W, polymorph X, polymorph Y, or polymorph Z (as described and characterized in WO 2008/007117).

The preparation of flupirtine and physiologically usable salts thereof is described in DE 17 95 858 C2, DE 31 33 519 C2, DE 34 16 609 Al, and EP 0 977 736. For example, the preparation of flupirtine maleate as disclosed in DE 31 33 519 C2 can be summarized as shown in Figure 1.

According to DE 31 33 519 C2, 2-amino-6-chloro-3-nitropyridine (ACNP) is reacted with 4-fluorobenzylamine in isopropanol yielding the intermediate 2-amino-3-nitro-6-(p-fluorobenzylamino) pyridine (ANFP) which is isolated, mixed with dioxane and catalytically reduced (Raney-Ni / hydrogen). After filtration, the resulting product 2,3-diamino-6-(p-fluorobenzylamino) pyridine (DAFP) is mixed with ethyl chloroformate and triethylamine. After completion of the acylation reaction, the reaction mixture is filtered and the filtrate is mixed with isopropanol and maleic acid. The precipitating crude flupirtine maleate is isolated and washed with isopropanol. However, according to
DE 31 33 519 C2, the thus obtained crude flupirtine maleate contains colored impurities and has to be further purified in order to remove these impurities. To this end, DE 31 33 519 C2 teaches a sequence of purification steps including converting the crude flupirtine maleate to the free flupirtine base using concentrated NH₃; isolating the free flupirtine base; treating with and/or recrystallization in the presence of charcoal to yield purified flupirtine; and adding maleic acid to yield purified flupirtine maleate.

In order to simplify the preparation of purified flupirtine maleate, EP 0 977 736 suggests a process, wherein the steps of hydrogenation of ANFP to DAFP in the presence of Raney-Ni, acylation with ethyl chloroformate and precipitation of flupirtine with maleic acid are carried out in water-soluble alcohols, in particular isopropanol. According to EP 0 977 736, pure polymorph A of flupirtine maleate can be obtained by stirring mixtures of polymorphs A and B in isopropanol (the ratio of flupirtine maleate to isopropanol being 1:1 to 1:0.8) at a temperature in the range of -10°C to 60°C for about 2 h to 5 h. However, we were unable to obtain pure polymorph A by the above procedure described in EP 0 977 736.

We have developed a process for the preparation of flupirtine maleate which is much easier than that disclosed in DE 31 33 519 C2, produces flupirtine maleate in good yield and purity with fewer steps, avoids the use of dioxane as solvent for the reduction of ANFP to DAFP as taught in DE 31 33 519 C2, and does not need the presence of water-soluble alcohols, in particular isopropanol, in all reaction steps as taught in EP 0 977 736. In particular, we have surprisingly found that the above reduction can be performed in an ester solvent and/or an aprotic amide solvent thereby avoiding dioxane which is known to have toxicity problems and safety problems due to the possible formation of explosive peroxides, a hazard which all ethers face.

**Summary of the invention**

The present invention provides a process for the preparation of flupirtine maleate comprising the steps of (i) reacting 2-amino-3-nitro-6-(4-fluorobenzylamino) pyridine (ANFP) with one or more reducing agents to yield 2,3-diamino-6-(4-fluorobenzylamino) pyridine (DAFP); (ii) reacting DAFP with X-C(0)OCH₂CH₃, wherein X is a leaving group, to yield ethyl [2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl]carbamate (flupirtine); and (iii) reacting flupirtine with maleic acid to yield flupirtine maleate, wherein at least one of steps (i) and (ii) is carried out in an ester solvent and/or an aprotic amide solvent.
In one embodiment of the process of the present invention, the ester solvent is selected from the group consisting of acetate esters and carbonate esters. More preferably, the ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, ethyl acetoacetate, triacetin, and propylene carbonate. Most preferably, the ester solvent is ethyl acetate.

In any of the above embodiments of the process of the present invention, step (i) may be performed in a solvent selected from the group consisting of an ester solvent, an aprotic amide solvent, and a water-soluble solvent (such water-soluble alcohol (e.g., ethanol) or a water-soluble nitrogen-containing solvent (such as acetonitrile)). The amount of solvent used in step (i) may be 2 to 20 parts by volume (such as 3 to 7 parts by volume, 4 to 6 parts by volume, 4.5 to 5 parts by volume, 7 to 15 parts by volume, 8 to 12 parts by volume, 9 to 10 parts by volume) relative to 1 part by weight of ANFP. The solvent used in step (i) may be (substantially) anhydrous or may contain water (the amount of water present in step (i) may be 2 to 40% by volume, preferably 2 to 20% by volume, more preferably 5 to 15%, by volume, more preferably 8 to 10% by volume, based on the total volume of the ester solvent, aprotic amide solvent and water-soluble solvent used in step (i)).

In any of the above embodiments of the process of the present invention, step (i) may be performed by using a redox catalyst. Preferably, the redox catalyst comprises a metal selected from the group consisting of the transition metals of the 8th to 10th groups of the periodic table of the elements. More preferably, the redox catalyst comprises a metal selected from the group consisting of Pt, Pd, Ni, Ir, Rh, and Ru. Even more preferably, the redox catalyst is selected from the group consisting of Pd/C, Pearlman's catalyst, Adam's catalyst, Pt/C, and Raney-Ni. Most preferably, the redox catalyst is Pd/C.

In any of the above embodiments of the process of the present invention, the redox catalyst may be used in an amount of 0.1 to 20% by weight, preferably 0.5 to 15% by weight, more preferably, 1.0 to 10% by weight, more preferably 1.5 to 7% by weight, more preferably 2.0 to 6% by weight, more preferably 2.5 to 5% by weight, more preferably 3.0 to 4.5% by weight, based on the amount of ANFP.

Alternatively, step (i) may be performed in absence of one (two, three, four) or more of the redox catalysts specified above. For example, step (i) is performed in absence of one (two, three, four) or more of the redox catalysts selected from group consisting Raney-Ni, Pd/C, Pearlman's catalyst, Adam's catalyst, and Pt/C, such as in the absence of Raney-Ni and/or Pd/C. In one embodiment, step (i) is performed in absence of any redox catalyst.

In any of the above embodiments of the process of the present invention, the one or more reducing agents may be selected from the group consisting of hydrogen; metals, preferably base metals (such as
Fe, Zn, Sn, or Sm); metal hydrides (such as lithium aluminum hydride (LiAlH$_4$) or diisobutylaluminum); reducing metal compounds (such as SnC$_3$ or FeC$_3$); reducing boron compounds (such as diborane, decaborane, 9-borabicyclononane or sodium borohydride (NaBH$_4$)); reducing carbon compounds (such as formic acids and salts thereof); reducing silicon compounds (such as polymethylhydrosiloxane or triethylsilane); reducing sulfur compounds (such as dithionite); and reducing nitrogen compounds (such as hydrazine). Preferably, the one or more reducing agents comprise hydrogen or dithionite. In one preferred embodiment, the one or more reducing agents comprise hydrogen, in particular if step (i) is performed by using a redox catalyst. In this embodiment, the solvent used in step (i) is preferably an ester solvent or an aprotic amide solvent. In another preferred embodiment, the one or more reducing agents comprise dithionite, in particular if step (i) is performed in absence of one or more of the redox catalysts specified above or in absence of any redox catalyst. In this embodiment, the solvent used in step (i) is preferably a water-soluble solvent, such as a water-soluble alcohol (e.g., ethanol) or a water-soluble nitrogen-containing solvent (e.g., acetonitrile).

In any of the above embodiments of the process of the present invention, step (i) may be performed by using a phase transfer catalyst.

In any of the above embodiments of the process of the present invention, step (i) may be performed at a temperature of from 20°C to 80°C. The lower limit of the temperature range for performing step (i) may be 21°C, 22°C, 23°C, 24°C, 25°C, 26°C, 27°C, 28°C, 29°C, 30°C, 31°C, 32°C, 33°C, 34°C, 35°C, 36°C, 37°C, 38°C, or 39°C. The upper limit of the temperature range for performing step (i) may be 70°C, preferably 60°C, more preferably 50°C, even more preferably 45°C, 44°C, 43°C, 42°C, 41°C, or 40°C. A preferred temperature range for performing step (i) is 20°C to 30°C, in particular if in step (i) a redox catalyst is present. Another preferred temperature range is 30°C to 50°C, in particular if step (i) is performed in absence of one or more of the redox catalysts specified above or in absence of any redox catalyst.

In any of the above embodiments of the process of the present invention, step (i) may be performed for a period of time in the range of 0.5 to 36 h, preferably 1 to 24 h, more preferably 1.5 to 12 h, more preferably 2 to 6 h, more preferably 3 to 5 h. Alternatively, step (i) may be performed until the reaction is substantially complete, i.e., until substantially the entire initial amount of ANFP is consumed.

In step (i) of the process of the present invention, the temperature can be raised continuously to the desired value or it can be raised gradually (i.e., in two or more steps). For example, the reaction mixture of step (i) may be continuously heated to any one of the above temperatures or temperature
ranges (e.g., 30°C to 40°C, such as 34°C to 37°C (preferably 34°C to 36°C or 36°C to 37°C) or 40°C to 50°C, such as 44°C to 47°C) over a period of time (e.g., 30 min to 2 h, such as 50 min to 70 min, preferably 55 min to 60 min) and then the temperature or temperature range may be maintained for a period of time (e.g., 5 min to 1 h, such as 10 min to 45 min, preferably 15 min to 30 min).

Alternatively, the reaction mixture of step (i) may be incubated at any one of the above temperatures or temperature ranges (e.g., 30°C to 40°C, such as 34°C to 37°C, preferably 34°C to 36°C or 36°C to 37°C) for a period of time (e.g., 30 min to 2 h, such as 50 min to 70 min, preferably 55 min to 60 min), and then the reaction mixture of step (i) is heated to a higher temperature or temperature range (e.g., 40°C to 50°C, such as 44°C to 48°C) over a period of time (e.g., 10 min to 1 h, such as 20 min to 45 min, preferably 30 min to 35 min). Optionally, the reaction mixture is maintained at the higher temperature or temperature range for a period of time (for example, 5 min to 2 h, such as 10 min to 1.5 h, preferably 30 min to 1 h, more preferably 40 min to 50 min). This procedure (i.e., heating at a particular temperature or temperature range for a period of time and then raising the temperature or temperature range to a higher temperature or temperature range over a period of time, optionally maintaining the higher temperature or temperature range) can be continued until the highest temperature or temperature range is reached. Finally, the reaction mixture of step (i) may be cooled to any temperature lower than the highest temperature or temperature range, preferably to the temperature or temperature range at which the next step (e.g., step (a) (see below) or step (ii)) is to be performed.

In any of the above embodiments, after step (i) and before step (ii) the process of the present invention may further comprise the step of (a) performing a solvent exchange. The performance of a solvent exchange before step (ii) is particularly preferable for the embodiment of the process of the present invention wherein the solvent used in step (ii) differs from the solvent used in step (i).

The solvent exchange may comprise the steps of (a1) removing the volatile components (such as the solvent used in step (i) (e.g., ester solvent, aprotic amide solvent, water-soluble solvent), volatile chemical base (e.g., ammonia), etc.) from the reaction mixture of step (i) and (a2) adding to the remaining residue one or more solvents other than the solvent(s) used in step (i). If water is present in the reaction mixture of step (i), the volatile components to be removed in step (a1) may comprise water which may be removed as water or as azeotrope with one or more of the solvents used in step (i). In a preferred embodiment of step (a1), the volatile components comprise only compounds and/or azeotropes having a boiling point (at standard atmospheric pressure) lower than the boiling point of water (at standard atmospheric pressure). The volatile components may be removed by any means known to the skilled person, for example, by distillation, preferably under reduced pressure (such as below standard atmospheric pressure, e.g., below about 100 kPa, preferably below 10 kPa, more preferably below 100 Pa, more preferably below 1 Pa), optionally at elevated temperature (i.e., above
20°C, such as 25°C to 80°C, 30°C to 70°C, 35°C to 65°C, 40°C to 50°C or 60°C to 62°C. Preferably, the one or more solvents to be added in step (a2) comprise one or more of the solvents in which step (ii) is to be carried out. More preferably, the one or more solvents to be added in step (a2) are the solvent or mixture of solvents in which step (ii) is to be carried out. The amount of the one or more solvents to be added in step (a2) is not limited and may be adjusted in such a way that the mixture of the one or more solvents to be added in step (a2) and the DAFP obtained in step (i) form one phase. Preferably, the amount of the one or more solvents to be added in step (a2) is equal to the amount of solvent used in step (ii). For example, if step (i) is performed in a water-soluble solvent (such as a water-soluble alcohol (e.g., ethanol) or a water-soluble nitrogen-containing solvent (e.g., acetonitrile)), optionally in the presence of water and/or a chemical base (preferably a volatile chemical base, such as aqueous ammonia), the solvent exchange may comprise the steps of removing the volatile components (such as the water-soluble solvent and, if present, the volatile chemical base) from the reaction mixture and adding to the remaining residue an ester solvent and/or aprotic amide solvent. Step (a2) may be performed at any suitable conditions, e.g., at standard conditions or at elevated temperature (e.g., 25°C to the reflux temperature of the remaining residue) or reduced temperature (e.g., below 20°C, such as 5°C to 19°C). After completion of step (a2), the temperature of the resulting mixture is preferably adjusted to the temperature at which step (ii) is to be performed.

Optionally, in addition to the one or more solvents other than the solvent(s) used in step (i), water can be added to the remaining residue obtained from step (a1), in particular if the step of removing the volatile components is performed under stirring. The water can be added before, after or simultaneously with step (a2). The amount of water may be 3 to 7 parts by volume, preferably 4 to 6 parts by volume, more preferably 4.5 to 5 parts by volume, relative to 1 part by weight of ANFP. If the one or more solvents added in step (a2) (e.g., an ester solvent and/or an aprotic amide solvent, preferably and ester solvent) are not completely miscible with water, the process of the invention preferably comprises, after step (a2) and before step (ii), the step of (b) separating the water layer from the layer formed by the one or more solvents added in step (a2). Thus, in a preferred embodiment, step (ii) is performed with the layer formed by the one or more solvents added in step (a2) after the water layer has been removed. Preferably, step (b) is performed after the temperature of the mixture obtained from step (a2) has been adjusted to the temperature at which step (ii) is to be performed.

In any of the above embodiments of the process of the present invention, the leaving group X may be selected from the group consisting of -Cl, -Br, -I, and a sulfonyl moiety. Preferably, the sulfonyl moiety is selected from the group consisting of 4-toluenesulfonyl, 4-bromobenzenesulfonyl, 4-nitrobenzenesulfonyl, 2-nitrobenzenesulfonyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, methylsulfonyl, and fluorosulfonyl.
In any of the above embodiments of the process of the present invention, in step (ii) the molar ratio between DAFP and X-C(0)OCH₂CH₃ may be 1:1 to 1:2.1, such as 1:1 to 1:2, preferably 1:1 to 1:1.8, more preferably, 1:1.1 to 1:1.5, more preferably 1:1.2 to 1:1.4.

In any of the above embodiments of the process of the present invention, step (ii) may be performed in a solvent selected from the group consisting of an ester solvent, an aprotic amide solvent, and a water-soluble alcohol. The solvent in which step (ii) is to be performed may also be a mixture of any two or more of these solvents (e.g., a mixture of an ester solvent (such as ethyl acetate) and a water-soluble alcohol (such as isopropanol)). The amount of solvent used in step (ii) may be 5 to 20 parts by volume, such as 7 to 15 parts per volume, preferably 8 to 12 parts by volume, more preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 1 part by weight of DAFP or ANFP. The solvent used in step (ii) may be (substantially) anhydrous or may contain water (the amount of water present in step (ii) may be 2 to 20% by volume, preferably 5 to 15% by volume, more preferably 8 to 10%, by volume, based on the total volume of the ester solvent, aprotic amide solvent and water-soluble alcohol used in step (ii)).

In any of the above embodiments of the process of the present invention, a chemical base may be added in step (ii). The reactants present in step (ii) may be mixed in any possible sequence. For example, DAFP, X-C(0)OCH₂CH₃, and a chemical base are mixed simultaneously. In a preferred embodiment, a reaction mixture is prepared containing DAFP and X-C(0)OCH₂CH₃ and after incubation for 5 min to 1 h, preferably 10 to 50 min, more preferably 15 to 45 min, more preferably 30 to 40 min, a chemical base is added to the reaction mixture and then the reaction mixture is preferably incubated for 5 min to 1 h, preferably 10 to 50 min, more preferably 15 to 45 min, more preferably 30 to 40 min. The amount of chemical base added may be 1:1 to 1:2.5 molar equivalents, such as 1:1 to 1:2.4 or 1:2.1 molar equivalents, preferably 1:1 to 1:2 molar equivalents, more preferably 1:1.1 to 1:1.5 molar equivalents, more preferably 1:1.2 to 1:1.4 molar equivalents, relative to DAFP.

In any of the above embodiments of the process of the present invention, step (ii) may be performed at a temperature of 20°C to 80°C. The lower limit of the temperature range for performing step (ii) may be 25°C, 26°C, 27°C, 28°C, 29°C, 30°C, 31°C, 32°C, 33°C, 34°C, 35°C, 36°C, 37°C, 38°C, or 39°C. The upper limit of the temperature range for performing step (i) may be 70°C, preferably 60°C, more preferably 50°C, even more preferably 45°C, 44°C, 43°C, 42°C, 41°C, or 40°C. A preferred temperature range for performing step (ii) is 20°C to 55°C.

In any of the above embodiments of the process of the present invention, step (ii) may be performed for a period of time in the range of 5 min to 2 h, preferably 10 min to 1.5 h, more preferably 15 min to 1 h, more preferably 30 to 45 min.
In one embodiment, the temperature at which step (ii) is performed is maintained over the above mentioned period of time and can be selected from any one of the above temperatures or temperature ranges (e.g., 35°C to 55°C). In another embodiment, the temperature at which step (ii) is performed can be varied. This is in particular preferable if in step (ii) first DAFP and X-C(0)OCH₂CH₃ are incubated and then a chemical base is added. For example, DAFP and X-C(0)OCH₂CH₃ may be first incubated at a first temperature (which may be any one of the above temperatures or temperature ranges, e.g., 20°C to 50°C, such as 45°C to 50°C) for a period of time (e.g., 5 min to 1 h, preferably 10 to 50 min, more preferably 15 to 45 min, more preferably 30 to 40 min), then a chemical base is added and the resulting reaction mixture is incubated at a second temperature, i.e., a temperature or temperature range which is either higher (e.g., 50°C to 55°C) or lower (e.g., 38°C to 45°C) than the first temperature, for a period of time (e.g., 5 min to 1 h, preferably 10 min to 50 min, more preferably 15 min to 45 min, more preferably 30 min to 40 min).

In any of the above embodiments of the process of the present invention, the molar ratio between flupirtine and maleic acid in step (iii) may be 1:1 to 1:2, preferably 1:1.1 to 1:1.9, more preferably 1:1.2 to 1.8, even more preferably 1:1.5 to 1:1.7.

In any of the above embodiments of the process of the present invention, in step (iii) maleic acid may be added as solution in water or a water-soluble alcohol. The amount of water or water-soluble alcohol for preparing the maleic acid solution may be 4 to 15 parts by volume (such as 5 to 15 parts by volume, preferably 5.5 to 11.5 parts by volume) relative to 1 part by weight of maleic acid.

In any of the above embodiments of the process of the present invention, step (iii) may be performed at a temperature of -10°C to 80°C, preferably -5°C to 70°C, more preferably 0°C to 60°C, more preferably 10°C to 50°C, more preferably 20°C to 40°C, more preferably 25°C to 30°C. A preferred temperature range for performing step (iii) is 35°C to 45°C.

In any of the above embodiments of the process of the present invention, step (iii) may be performed for a period of time in the range of 5 to 50 min, preferably 10 to 30 min, more preferably 15 to 20 min.

In one embodiment, the temperature at which step (iii) is performed is maintained over the above mentioned period of time and can be selected from any one of the above temperatures or temperature ranges (e.g., 15°C to 55°C, such as 50°C to 55°C or 35°C to 45°C). In another embodiment, the temperature at which step (iii) is performed can be varied. For example, flupirtine and maleic acid may be first incubated at a first temperature (which may be any one of the above temperatures or temperature ranges, e.g., 15°C to 55°C, such as 50°C to 55°C or 35°C to 45°C) for a period of time.
(e.g., 5 min to 1.5 h, preferably 10 min to 70 min, more preferably 15 min to 65 min, more preferably 30 min to 60 min) and then the reaction mixture is cooled (e.g., to a temperature of 15°C to 30°C, such as 15°C to 20°C or 30°C to 40°C) over a period of time (e.g., 10 min to 1.5 h, such as 20 min to 70 min, preferably 30 min to 60 min, more preferably 40 min to 50 min).

In any of the above embodiments, the process of the present invention may further comprise the step of adding an oxygen scavenger agent in step (ii) and/or step (iii). The amount of oxygen scavenger agent added in step (ii) may be 0.01 to 2.5% by weight, such as 0.01 to 2.1% by weight, preferably 0.01 to 2% by weight, more preferably 0.05 to 1.5% by weight, more preferably 0.1 to 1% by weight, based on the amount of DAFP used in step (ii). The amount of oxygen scavenger agent added in step (iii) may be 0.01 to 2.5% by weight, such as 0.01 to 2.1% by weight, preferably 0.01 to 2% by weight, more preferably 0.05 to 1.5% by weight, more preferably 0.1 to 1% by weight, based on the amount of flupirtine used in step (iii).

In any of the above embodiments, the process of the present invention may further comprise the step of filtering the reaction mixture after step (i) and before step (ii) and/or after step (ii) and before step (iii). Preferably, the filtration step is performed at the same temperature at which the following step is performed. For example, if a filtration step is performed after step (i) and before step (ii) said filtration step is preferably performed at the temperature at which step (ii) is performed. Likewise, if a filtration step is performed after step (ii) and before step (iii) said filtration step is preferably performed at the temperature at which step (iii) is performed. If a redox catalyst is used in step (i), it is preferred to perform a filtration step after step (i) and before step (ii) and/or after step (ii) and before step (iii).

In any of the above embodiments of the process of the present invention, in at least step (ii), preferably in at least steps (i) and (ii), more preferably in each of steps (i) to (iii), only degassed solvents may be used. Preferably, every solvent used in the process of the present invention is a degassed solvent.

In any of the above embodiments of the process of the present invention, at least steps (i) and (ii) may be performed under an atmosphere of an inert gas. Preferably, each of steps (i) to (iii), more preferably the whole process of the present invention is performed under an inert gas. Preferably, the inert gas is oxygen-free.

In any of the above embodiments, the process of the present invention may further comprise the step of isolating the flupirtine maleate. Preferably, in step (iii) a solvent is used in which flupirtine maleate precipitates under standard conditions. In a preferred embodiment, the solvent used in step (iii) is selected from the group consisting of an ester solvent, an aprotic amide solvent, and a water-soluble alcohol. The solvent used in step (iii) may also be a mixture of two or more solvents selected from the
group consisting of ester solvents, aprotic amide solvents, and water-soluble alcohols. The solvent used in step (iii) may be (substantially) anhydrous or may contain water. Preferably, the solvent used in step (iii) is a (substantially) anhydrous mixture of an ester solvent (such as ethyl acetate) and a water-soluble alcohol (such as isopropanol), or a mixture of an ester solvent and water, or a mixture of an ester solvent, a water-soluble alcohol, and water. The precipitated flupirtine maleate may be isolated from the reaction mixture by any conventional means, such as filtration, decantation, and/or centrifugation.

In any of the above embodiments of the process of the present invention, two or more steps may be performed without isolating and/or purifying the intermediates. For example, the reaction mixture which is obtained from step (i) of the process of the present invention and which preferably comprises (1) the intermediate DAFP, (2) an ester solvent and/or an aprotic amide solvent, and (3) optionally, a redox catalyst may be used directly, i.e., without further isolation and/or purification of the intermediate DAFP, in step (ii). Thus, in this preferred embodiment, the reaction mixture obtained from step (i) is mixed with X-C(0)OCH₂CH₃ and optionally, a chemical base. In another preferred embodiment, the reaction mixture which is obtained from step (ii) and which preferably comprises (1) the intermediate flupirtine, (2) an ester solvent and/or an aprotic amide solvent, and (3) optionally, a water-soluble alcohol and/or water is used directly, i.e., without further isolation and/or purification of the intermediate flupirtine, in step (iii).

In one preferred mode of any of the above embodiments, the process of the present invention comprises the steps of (i) suspending ANFP and a redox catalyst in an ester solvent (the amount of ester solvent may be 8 to 12 parts by volume, preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 1 part by weight of ANFP) and reacting ANFP with hydrogen; (ii) adding X-C(0)OCH₂CH₃ and incubating the resulting reaction mixture, preferably at a temperature as defined above, preferably for a period of time in the range of 5 min to 2 h (more preferably 20 to 40 min); optionally, adding a chemical base to the reaction mixture and incubating the reaction mixture, preferably at a temperature as defined above, preferably for a period of time in the range of 5 min to 2 h (more preferably 20 to 40 min); optionally, adding an oxygen scavenger agent; optionally, adding a water-soluble alcohol (the amount of water-soluble alcohol may be 8 to 12 parts by volume, preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 10 parts by volume of ester solvent added in step (i)); filtering the reaction mixture, preferably at a temperature at which the following step (iii) is performed; optionally, washing the redox catalyst with a water-soluble alcohol; filtering the reaction mixture comprising the redox catalyst and the water-soluble alcohol, preferably at a temperature at which the following step (iii) is performed; optionally, repeating the washing / filtrating steps one or more times; (iii) mixing the filtrate (optionally, combined with the filtrate(s) of
the optional washing / filtrating step(s)) obtained from step (ii) with maleic acid in a water-soluble alcohol which may contain an oxygen scavenger agent; and optionally, isolating the flupirtine maleate.

In another preferred mode of any of the above embodiments, the process of the present invention comprises the steps of (i) reacting ANFP, a reducing agent (such as a dithionite salt), and a chemical base (such as aqueous ammonia) in an ester solvent (the amount of ester solvent may be any of the above-mentioned amounts, such as 8 to 12 parts by volume, preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 1 part by weight of ANFP), optionally, in the presence of water (the total amount of water present in step (i) may be any of the above-mentioned amounts, such as 2 to 20% by volume, preferably 5 to 15% by volume, more preferably 8 to 10% by volume, based on the volume of the ester solvent) and/or a phase transfer catalyst; optionally, heating the reaction mixture, preferably to a temperature of up to 80°C (such as 40°C to 50°C); (ii) adding X-C(0)OCH₂CH₃; incubating the resulting reaction mixture, preferably at a temperature of 20°C to 80°C (such as 40°C to 50°C), preferably for a period of time in the range of 5 min to 2 h (such as 30 min to 1.5 h); optionally, adding a chemical base to the reaction mixture and incubating the reaction mixture, preferably at a temperature of 20°C to 80°C (such as 40°C to 50°C), preferably for a period of time in the range of 5 min to 2 h (such as 30 min to 1.5 h); optionally, adding a water-soluble alcohol (the amount of water-soluble alcohol may be 8 to 12 parts by volume, preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 10 parts by volume of ester solvent added in step (i)); (iii) mixing the reaction mixture obtained from step (ii) with maleic acid in water, a water-soluble alcohol, or a mixture of water and a water-soluble alcohol each of which may contain an oxygen scavenger agent; and optionally, isolating the flupirtine maleate.

In another preferred mode of any of the above embodiments, the process of the present invention comprises the steps of (i) reacting ANFP, a reducing agent (such as a dithionite salt), and a chemical base (preferably a volatile chemical base, such as aqueous ammonia) in a water-soluble solvent (such as a water-soluble alcohol or a water-soluble nitrogen-containing solvent) (the amount of water-soluble alcohol may be 8 to 12 parts by volume, preferably 9 to 11 parts by volume, more preferably 10 parts by volume, relative to 1 part by weight of ANFP), optionally, in the presence of water (the total amount of water present in step (i) may be 2 to 40% by volume, preferably 2 to 20% by volume, more preferably 5 to 15% by volume, more preferably 8 to 10% by volume, based on the volume of the water-soluble alcohol) and/or a phase transfer catalyst; optionally, heating the reaction mixture, preferably to a temperature of up to 80°C (such as 40°C to 50°C); performing a solvent exchange (e.g., by (1) removing the volatile components (such as the water-soluble solvent and volatile chemical base (e.g., ammonia)) from the reaction mixture (e.g., by distillation); adding water (the amount of water may be 3 to 7 parts by volume, preferably 4 to 6 parts by volume, more preferably 4.5 to 5 parts by volume, relative to 1 part by weight of ANFP) to maintain stirring; and (2) extracting the resulting
aqueous reaction mixture one or more times with an ester solvent (the total volume of the ester solvent
may be 3 to 5 times the volume of water added); (ii) adding X-C(0)OCH₂CH₃ to the combined ester
solvent extracts; incubating the resulting reaction mixture, preferably at a temperature of 20°C to 80°C
(such as 40°C to 50°C), preferably for a period of time in the range of 5 min to 2 h (such as 30 min to
1.5 h); optionally, adding a chemical base to the reaction mixture and incubating the reaction mixture,
preferably at a temperature of 20°C to 80°C (such as 45°C to 55°C), preferably for a period of time in
the range of 5 min to 2 h (such as 30 min to 1.5 h); optionally, adding an oxygen scavenger agent;
optionally, adding additional ester solvent (the amount of the additional ester solvent may be 20% to
30%, preferably 25%, of the volume of the reaction mixture, or 2 to 5.5 parts by volume, preferably 3
to 4.5 parts by volume, more preferably 3.5 to 3.8 parts by volume relative to 1 part by weight of
ANFP); (iii) mixing the reaction mixture obtained from step (ii) with maleic acid (the maleic acid may
be provided as a solution in a water, a water-soluble alcohol, or a mixture of water and a water-soluble
alcohol each of which may contain an oxygen scavenger agent); and optionally, isolating the flupirtine
maleate.

In any of the above modes and embodiments, the process of the present invention may further
comprise the step of washing flupirtine maleate one or more times with water, a water-soluble ketone
(such as acetone), and/or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in
a water-soluble alcohol (preferably isopropanol)), preferably at a temperature of -10°C to 20°C, more
preferably 0°C to 10°C.

In any of the above modes and embodiments, the process of the present invention may further
comprise the step of drying the flupirtine maleate, e.g., at a temperature in the range of 20°C to 60°C,
preferably, 25°C to 50°C, more preferably, 30°C to 40°C. The drying may be performed under
reduced pressure, such as below atmospheric pressure (about 100 kPa), preferably below 10 kPa, more
preferably below 100 Pa, more preferably below 1 Pa.

In any of the above modes and embodiments, the process of the present invention may further
comprise the step of converting the flupirtine maleate, either partially or (substantially) completely,
into a particular polymorphic form (such as polymorph A, polymorph B, etc.). This conversion step
may be performed prior to and/or after the isolation of the flupirtine maleate. By this conversion step,
it is possible to obtain a flupirtine maleate preparation which is either (substantially) pure or enriched
with respect to one particular polymorphic form.

If the conversion step is performed prior to the isolation of the flupirtine maleate, a flupirtine maleate
preparation which is either (substantially) pure or enriched with respect to polymorph B, may be
obtained by the following steps (after step (iii) of the process of the present invention): heating the
reaction mixture obtained from step (iii) to a temperature of 55°C to 75°C, preferably 60°C to 70°C, most preferably 61°C to 65°C, to dissolve the flupirtine maleate; cooling the reaction mixture to a temperature of -10°C to 20°C, more preferably -5°C to 15°C, most preferably 0°C to 5°C (e.g., over a period of time of 5 min to 30 min, preferably 10 min to 15 min); filtering off the crystals; optionally, washing the crystals one or more times with a water-soluble ketone (such as acetone) or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in a water-soluble alcohol (preferably isopropanol)), wherein the water-soluble ketone or the aqueous solution of a water-soluble alcohol preferably has a temperature of -10°C to 10°C, more preferably -5°C to 5°C, most preferably 0°C to 5°C; and drying the crystals as specified above. If the conversion step is performed after the isolation of the flupirtine maleate, a flupirtine maleate preparation which is either (substantially) pure or enriched with respect to polymorph B, may be obtained by the following steps: mixing flupirtine maleate with a water-soluble alcohol (such as isopropanol) and water (the ratio of water-soluble alcohol to water may be 50:50 to 90:10, preferably 60:40 to 80:20, more preferably 65:35 to 75:25, more preferably 70:30 (vol/vol or wt/wt); the total amount of water-soluble alcohol and water may be 10 to 20 parts per weight, preferably 12 to 18 parts per weight, more preferably 15 parts per weight, based on 1 part by weight of flupirtine maleate); heating the reaction mixture to a temperature of 55°C to 75°C, preferably 60°C to 70°C, most preferably 61°C to 65°C, to dissolve the flupirtine maleate; cooling the reaction mixture to a temperature of -10°C to 20°C, more preferably -5°C to 15°C, most preferably 0°C to 5°C (e.g., over a period of time of 5 to 20 min, preferably 10 to 15 min); filtering off the crystals; optionally, washing the crystals with a water-soluble ketone (such as acetone) or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in a water-soluble alcohol (preferably isopropanol)), wherein the water-soluble ketone or the aqueous solution of a water-soluble alcohol preferably has a temperature of -10°C to 10°C, more preferably -5°C to 5°C, most preferably 0°C to 5°C; and drying the crystals as specified above. Alternatively, for obtaining a flupirtine maleate preparation which is either (substantially) pure or enriched with respect to polymorph B, flupirtine maleate may be heated without solvent to a temperature of 40°C to 180°C, preferably 80°C to 150°C, more preferably 80°C to 130°C. Preferably, the heating step is repeated one or more times.

In any of the above modes and embodiments of the process of the present invention, step (i), step (ii), and/or step (iii) may be performed under stirring.

In any of the above modes and embodiments of the process of the present invention, ANFP may be prepared by reacting 2-amino-6-chloro-3-nitropyridine (ACNP) with 4-fluorobenzylamine. The reaction of ACNP with 4-fluorobenzylamine may be carried out in an ester solvent, an aprotic amide solvent, a water soluble-alcohol, or a mixture of two or more of these liquids. Preferably, a chemical base (such as an organic amine) may be added.
Other features and advantages of the present invention will be apparent from the following detailed description and claims.

**Detailed description of the invention**

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated member, integer or step or group of members, integers or steps but not the exclusion of any other member, integer or step or group of members, integers or steps although in some embodiments such other member, integer or step or group of members, integers or steps may be excluded, i.e., the subject-matter consists in the inclusion of a stated member, integer or step or group of members, integers or steps. The terms "a" and "an" and "the" and similar reference used in the context of describing the invention (especially in the context of the claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), provided herein is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

Unless otherwise indicated, the term "flupirtine maleate" as used herein refers to any polymorphic form of said compound (such as polymorph A or polymorph B, as described and characterized in DE 31 33 519 C2, or polymorph V, polymorph W, polymorph X, polymorph Y, or polymorph Z, as described and characterized in WO 2008/007117) and any polymorphic form of its tautomers and isomers (i.e., the fumarate). In one embodiment, flupirtine maleate may be prepared as (substantially) pure polymorphic form (such as (substantially) pure polymorph A, B, V, W, X, Y, or Z), preferably as (substantially) pure polymorph B. In another embodiment, flupirtine maleate may be prepared as any mixture of two or more (such as 3, 4, 5, 6, 7, 8, 9, or 10 or more) of the above polymorphic forms (such as a mixture of polymorph B with one or more polymorphs other than polymorph B), wherein the proportion of any of the two or more polymorphic forms present in said mixture relative to the total amount of flupirtine maleate present in said mixture may have any value as long as the sum of all proportions of said two or more polymorphic forms present in said mixture is 100%. For example, in a
mixture of two polymorphic forms of flupirtine maleate (such as a mixture of polymorphs A and B) the proportion $x_1$ for each of the two polymorphic forms may be between 0.001 to 99.999% (e.g., 0.01 to 99.99%, such as 0.1 to 99.9%, 1 to 99%, 5 to 95%, 10 to 90%, 15 to 85%, 20 to 80%, 25 to 75%, 30 to 70%, 35 to 65%, 40 to 60%, 45 to 55%, or 50%) as long as the sum of the proportions $x_A$ and $x_B$ is 100%. In one embodiment, the process of the present invention may comprise the step of converting the flupirtine maleate, either partially or (substantially) completely, into a particular polymorphic form (such as polymorph A, polymorph B, etc.), wherein said conversion step may be performed prior to and/or after the isolation of flupirtine maleate. For example, in the process of the present invention a particular polymorphic form of flupirtine maleate (e.g., a polymorphic form which can be easily separated from the reaction mixture obtained in step (iii) and/or which can be obtained in higher yield and/or purity from the reaction mixture obtained in step (iii) (such as polymorph B) compared to other polymorphic forms of flupirtine maleate) is first prepared and then converted to the desired polymorphic form in order to obtain a flupirtine maleate preparation which is either (substantially) pure or enriched with respect to the desired polymorphic form.

According to EP 0 977 736 and DE 31 33 519 C2, stirring mixtures of polymorphs A and B (the amount of polymorph A being at most 40%) in an organic solvent (such as isopropanol) at a temperature in the range of -10°C to 70°C for about 20 min to 5 h is sufficient to obtain flupirtine maleate preparations containing polymorph A in an amount of 60% to 90% (cf. DE 31 33 519 C2) or even 100% (pure polymorph A; cf. EP 0 977 736). However, we were not able to convert flupirtine maleate polymorph B into polymorph A by simply stirring polymorph B (or a mixture of polymorphs A and B) in an organic solvent (such as isopropanol) under the conditions disclosed in EP 0 977 736 and DE 31 33 519 C2. In fact, we found that stirring in isopropanol as taught in EP 0 977 736 and DE 31 33 519 C2 does not significantly alter the ratio of polymorph B to polymorph A in a flupirtine maleate preparation containing polymorph B or a mixture of polymorphs A and B.

According to DE 31 33 519 C2, polymorph A may also be obtained by reacting flupirtine with maleic acid in presence of crystals of pure flupirtine maleate polymorph A. However, we found that if a solution of flupirtine maleate is obtained as taught in EP 0 977 736 and DE 31 33 519 C2 (i.e., by hydrogenating ANFP in the presence of a redox catalyst to yield DAFP; reacting DAFP with ethyl chloroformate to yield flupirtine; and reacting flupirtine with maleic acid in presence of crystals of pure flupirtine maleate polymorph A), the resulting flupirtine maleate crystals mainly consist of polymorph A but also contain an impurity (ethyl (2,6-diaminopyridin-3-yl) carbamate maleate) which may be present in significant amounts (up to 28%, depending on the particular reaction conditions used to prepare flupirtine) and which cannot be removed from the flupirtine maleate crystals by washing or stirring a slurry of the flupirtine maleate crystals in an appropriate solvent without dissolving the flupirtine maleate crystals completely. In contrast, we surprisingly found that a flupirtine maleate
preparation which is (substantially) pure with respect to polymorph A, i.e., whose total amount of impurities (in particular, ethyl (2,6-diaminopyridin-3-yl) carbamate maleate and/or polymorphic forms other than polymorphic form B) is less than 1%, may be prepared by crystallizing flupirtine maleate as polymorph B; converting polymorph B into polymorph A; and optionally, washing polymorph A.

Thus, a flupirtine maleate preparation which is either (substantially) pure or enriched with respect to polymorph A, may be obtained by the following steps: providing flupirtine maleate as polymorph B (such as specified above); mixing the flupirtine maleate with a water-soluble alcohol (such as isopropanol) and water (the ratio of water-soluble alcohol to water may be 50:50 to 90:10, preferably 60:40 to 80:20, more preferably 65:35 to 75:25, more preferably 70:30 (vol/vol or wt/wt); the total amount of water-soluble alcohol and water may be 10 to 20 parts per weight, preferably 12 to 18 parts per weight, more preferably 15 parts per weight, based on 1 part by weight of flupirtine maleate); heating the reaction mixture to a temperature of 55°C to 75°C, preferably 60°C to 70°C, most preferably 61°C to 65°C, to dissolve the flupirtine maleate; cooling the reaction mixture to a temperature of -10°C to 20°C, more preferably -5°C to 15°C, most preferably 0°C to 5°C (e.g., over a period of time of 0.5 to 8 h, preferably 1 to 4 h, more preferably 2 to 3.5 h, more preferably 2.5 to 3 h); adding crystals of pure flupirtine maleate polymorph A (preferably in an amount of 0.5% to 2.5%, more preferably 1% to 2%, based on the total amount of flupirtine maleate in the aqueous solution) during the cooling step, preferably once the aqueous solution has reached a temperature of 45°C to 50°C, preferably 46°C to 49°C, more preferably 47°C to 48°C; filtering off the crystals; optionally, washing the crystals with a water-soluble ketone (preferably acetone) or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in a water-soluble alcohol (preferably isopropanol)), wherein the water-soluble ketone or the aqueous solution of a water-soluble alcohol preferably has a temperature of -10°C to 10°C, more preferably -5°C to 5°C, most preferably 0°C to 5°C; and drying the crystals as specified above. In one embodiment, the above steps starting from the step of mixing flupirtine maleate with a water-soluble alcohol and water to the step of drying the crystals are repeated one or more times. The flupirtine maleate to be provided may be prepared by any of the modes and embodiments described above for the process of the present invention. One embodiment of the process of the present invention is illustrated in Figure 2.

"Polymorphism" as referred to herein means that a solid material (such as a compound) is able to exist in more than one form or crystalline structure, i.e., "polymorphic modifications" or "polymorphic forms". The terms "polymorphic modifications", "polymorphic forms", and "polymorphs" are used interchangeable in the present invention. According to the present invention, these "polymorphic modifications" include crystalline forms, amorphous forms, solvates, and hydrates. Mainly, the reason for the existence of different polymorphic forms lies in the use of different conditions during the crystallization process, such as the following:
• solvent effects (the Packing of crystal may be different in polar and nonpolar solvents);
• certain impurities inhibiting growth pattern and favor the growth of a metastable polymorphs;
• the level of supersaturation from which material is crystallized (in which generally the higher the concentration above the solubility, the more likelihood of metastable formation);
• temperature at which crystallization is carried out;
• geometry of covalent bonds (differences leading to conformational polymorphism);
• change in stirring conditions.

Polymorphic forms may have different chemical, physical, and/or pharmacological properties, including but not limited to, melting point, X-ray crystal and diffraction pattern, chemical reactivity, solubility, dissolution rate, vapor pressure, density, hygroscopicity, flowability, stability, compactability, and bioavailability. Polymorphic forms may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. According to Ostwald's rule, in general it is not the most stable but the least stable polymorph that crystallizes first. Thus, quality, efficacy, safety, processability and/or manufacture of a chemical compound, such as flupirtine maleate, can be affected by polymorphism. Often, the most stable polymorph of a compound (such as flupirtine maleate) is chosen due to the minimal potential for conversion to another polymorph. However, a polymorphic form which is not the most stable polymorphic form may be chosen due to reasons other than stability, e.g. solubility, dissolution rate, and/or bioavailability.

The term "crystalline form" of a material as used herein means that the smallest components (i.e., atoms, molecule or ions) of said material form crystal structures. A "crystal structure" as referred to herein means a unique three-dimensional arrangement of atoms or molecules in a crystalline liquid or solid and is characterized by a pattern, a set of atoms arranged in a particular manner, and a lattice exhibiting long-range order and symmetry. A lattice is an array of points repeating periodically in three dimensions and patterns are located upon the points of a lattice. The subunit of the lattice is the unit cell. The lattice parameters are the lengths of the edges of a unit cell and the angles between them. The symmetry properties of the crystal are embodied in its space group. In order to describe a crystal structure the following parameters are required: chemical formula, lattice parameters, space group, the coordinates of the atoms and occupation number of the point positions.

The term "amorphous form" of a material as used herein means that the smallest components (i.e., atoms, molecule or ions) of said material are not arranged in a lattice but are arranged randomly. Thus, unlike crystals in which a short-range order (constant distances to the next neighbor atoms) and a long-range order (periodical repetition of a basic lattice) exist, only a short-range order exists in an amorphous form.
The term "solvate" as used herein refers to an addition complex of a dissolved material in a solvent (such as an ester solvent, an aprotic amide solvent, a water-soluble alcohol, water or a mixture of two or more of these liquids), wherein the addition complex exists in the form of a crystal or mixed crystal. The amount of solvent contained in the addition complex may be stoichiometric or non-stoichiometric.

A "hydrate" is a solvate wherein the solvent is water.

Methods for the characterization of polymorphs of a material (such as a drug) are known to the skilled person (cf., e.g., DE 31 33 519 C2, WO 2008/007117, and K.-F. Landgraf et al., Eur. J. Pharm. Biopharm. 1998, 46(3):329-37) and include, but are not limited to, X-ray diffraction, in particular single crystal X-ray diffraction, powder X-ray diffraction, thermal analysis (such as differential scanning calorimetry (DSC), hot-stage microscopy, and thermal gravimetric analysis), and several spectrometry methods (such as solid state nuclear magnetic resonance (ssNMR), infrared and near red, and Raman).

The term "ester solvent" as used herein refers to any solvent containing at least one ester group. Preferably, the term "ester solvent" does not include ester solvents which are miscible with water in any ratio at a temperature of about 20°C. In one embodiment, the ester solvent is one which is miscible with water in a ratio of 1 to 32 parts by weight of ester solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the ester solvent is one which is miscible with water in a ratio of 2 to 24 parts by weight of ester solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the ester solvent is one which is miscible with water in a ratio of 3 to 12 parts by weight of ester solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the ester solvent is one which is miscible with water in a ratio of 4 to 9 parts by weight of ester solvent relative to 100 parts by weight of water at a temperature of about 20°C.

In one embodiment, the ester solvent is an ester which can be considered as derived from the reaction of an aliphatic carboxylic acid with an aliphatic alcohol (although the actual preparation of said ester solvent may require compounds which are not an aliphatic carboxylic acid and/or an aliphatic alcohol). For example, the aliphatic carboxylic acid is a linear, branched or cyclic carboxylic acid. In one embodiment, the aliphatic carboxylic acid has a total of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and has at least one carboxylic acid group, preferably at least 2 carboxylic acid groups, wherein the maximum number of carboxylic acid groups may be the half of the total number of carbon atoms in the aliphatic carboxylic acid, rounded down to the next integer if the half is not an integer (for example, 4 carbon atoms \(\rightarrow\) 2 carboxylic acid groups; 5 or 6 carbon atoms \(\rightarrow\) 3 carboxylic acid groups; 7 or 8 carbon atoms \(\rightarrow\) 4 carboxylic acid groups; etc). The aliphatic carboxylic acid may contain one or more additional functional groups (such as CN, keto, amide groups) in addition to the
one or more carboxylic acid groups as long as said one or more additional functional groups are (substantially) inert with respect to the reactants used in the process of the present invention (i.e., said one or more additional functional groups do not chemically react / do not form covalent bonds with the reactants used in the process of the present invention). Preferably, the aliphatic carboxylic acid does not contain carbon-carbon double or triple bonds. Preferably, with the exception of the carboxylic acid groups, the aliphatic carboxylic acid contains only hydrogen and carbon atoms. Preferred aliphatic carboxylic acids are those having 1, 2, 3, 4, 5, or 6 carbons atoms and 1, 2, or 3 carboxylic acid groups, such as formic acid, acetic acid, acetoacetic acid, propionic acid (or its 2-isomer), butanoic acid (or its 2-isomer), oxalic acid, malonic acid, cyanoacetic acid, succinic acid, succinamic acid, and propane-1,2,3-tricarboxylic acid. A particularly preferred aliphatic carboxylic acid is acetic acid. Thus, a preferred group of ester solvents are acetic ester solvents. In one embodiment, the aliphatic alcohol is a linear, branched or cyclic alcohol, which may have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and which has at least one OH group, preferably at least 2 OH groups, wherein the maximum number of OH groups may be the half of the total number of carbon atoms in the aliphatic alcohol, rounded down to the next integer if the half is not an integer (for example, 4 carbon atoms \(\rightarrow\) 2 OH groups; 5 or 6 carbon atoms \(\rightarrow\) 3 OH groups; 7 or 8 carbon atoms \(\rightarrow\) 4 OH groups; etc). The aliphatic alcohol may contain one or more additional functional groups (such as CN, keto, amide groups) in addition to the one or more alcohol groups as long as said one or more additional functional groups are (substantially) inert with respect to the reactants used in the process of the present invention (i.e., said one or more additional functional groups do not chemically react / do not form covalent bonds with the reactants used in the process of the present invention). Preferably, the aliphatic alcohol does not contain carbon-carbon double or triple bounds. Preferably, with the exception of the OH groups, the aliphatic alcohol contains only hydrogen and carbon atoms. Preferred aliphatic alcohols are those having 1, 2, 3, 4, 5, or 6 carbons atoms and 1, 2, or 3 OH groups, such as methanol, ethanol, n-propanol, isopropanol, 1-butanol, 2-butanol, tert-butanol, glycol, 1,2-propanediol, 1,3-propanediol, and glycerol.

In one embodiment, the ester solvent is a carbonate ester. The term "carbonate ester" as used herein can be considered as derived from the reaction of carbonic acid with an aliphatic alcohol (although the actual preparation of said carbonate ester solvent may require compounds which are not carbonic acid and/or an aliphatic alcohol). In one embodiment, the aliphatic alcohol is as defined above. Preferred aliphatic alcohols are those having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and at least 2 OH groups. Specific examples include glycol, 1,2-propanediol, 1,3-propanediol, and glycerol.

Preferred ester solvents include acetate esters and carbonate esters. Exemplary ester solvents include methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, ethyl acetoacetate, triacetin, and propylene carbonate.
Instead of or in addition to an ester solvent, an aprotic amide solvent may be used in the process of the present invention. The term "amide solvent" as used herein refers to any solvent containing at least one amide group. Preferably, the term "amide solvent" does not include amide solvents which are miscible with water in any ratio at a temperature of about 20°C. In one embodiment, the amide solvent is one which is miscible with water in a ratio of 1 to 32 parts by weight of amide solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the amide solvent is one which is miscible with water in a ratio of 2 to 24 parts by weight of amide solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the amide solvent is one which is miscible with water in a ratio of 3 to 12 parts by weight of amide solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the amide solvent is one which is miscible with water in a ratio of 4 to 9 parts by weight of amide solvent relative to 100 parts by weight of water at a temperature of about 20°C.

In one embodiment, the aprotic amide solvent is an amide which can be considered as derived from the reaction of an aliphatic carboxylic acid with an aliphatic amine (although the actual preparation of said amide solvent may require compounds which are not an aliphatic carboxylic acid and/or an aliphatic amine). For example, the aliphatic carboxylic acid may be as defined above for the ester solvent. In one embodiment, the aliphatic amine is a linear, branched or cyclic amine which may have 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 carbon atoms and which has at least one primary or secondary amine group, preferably at least 2 primary or secondary amine groups, wherein the maximum number of primary or secondary amine groups may be the half of the total number of carbon atoms in the aliphatic amine, rounded down to the next integer if the half is not an integer (for example, 4 carbon atoms → 2 primary or secondary amine groups; 5 or 6 carbon atoms → 3 primary or secondary amine groups; 7 or 8 carbon atoms → 4 primary or secondary amine groups; etc). The aliphatic amine may contain one or more additional functional groups (such as CN, keto, ester, tertiary amine groups) in addition to the one or more primary or secondary amine groups as long as said one or more additional functional groups are (substantially) inert with respect to the reactants used in the process of the present invention (i.e., said one or more additional functional groups do not chemically react / do not form covalent bonds with the reactants used in the process of the present invention). Preferably, the aliphatic amine does not contain carbon-carbon double or triple bounds. Preferably, with the exception of the nitrogen atoms of the primary or secondary amine groups, the aliphatic amine contains only hydrogen and carbon atoms. Preferred aliphatic amines are those having 1, 2, 3, 4, 5, or 6 carbons atoms and 1, 2, or 3 primary or secondary groups, such as methylamine, ethylamine, n-propylamine, 2-propylamine, 1-butylamine, 2-butylamine, tert-butylamine, 1,2-diaminopropane, 1,3-diaminopropane, and 1,2,3-triaminopropane. In one embodiment, the aprotic amide solvent is selected from the group consisting of dimethylformamide, dimethylacetamide, and N-methyl-2-pyrrolidone.
The term "water-soluble solvent" as used herein refers to any solvent which is a liquid under standard conditions and is miscible with water at a temperature of about 20°C. Preferably, the term "water-soluble solvent" does not include solvents which are only slightly miscible with water at a temperature of about 20°C, i.e., which are miscible with water in a ratio of not more 32 parts by weight of solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble solvent is one which is miscible with water in a ratio of at least about 50 parts by weight of water-soluble solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble solvent is one which is miscible with water in a ratio of at least about 75 parts by weight of water-soluble solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble solvent is one which is miscible with water in any ratio at a temperature of about 20°C. Preferred water-soluble solvents include water-soluble alcohols and water-soluble nitrogen-containing solvents.

The term "water-soluble alcohol" as used herein refers to any alcohol which has at least one OH group, is a liquid under standard conditions and is miscible with water at a temperature of about 20°C. Preferably, the term "water-soluble alcohol" does not include alcohols which are only slightly miscible with water at a temperature of about 20°C, i.e., which are miscible with water in a ratio of not more 32 parts by weight of alcohol relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble alcohol is one which is miscible with water in a ratio of at least about 50 parts by weight of water-soluble alcohol relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble alcohol is one which is miscible with water in a ratio of at least about 75 parts by weight of water-soluble alcohol relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble alcohol is one which is miscible with water in any ratio at a temperature of about 20°C. Particularly preferred water-soluble alcohols include methanol, ethanol, propanol, isopropanol, butanol, tert-butanol, glycol, 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, and glycerol.

The term "water-soluble nitrogen-containing solvent" as used herein refers to any solvent which contains at least one nitrogen atom, is a liquid under standard conditions and is miscible with water at a temperature of about 20°C. Preferably, the term "water-soluble nitrogen-containing solvent" does not include nitrogen-containing solvents which are only slightly miscible with water at a temperature
of about 20°C, i.e., which are miscible with water in a ratio of not more 32 parts by weight of
nitrogen-containing solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one
embodiment, the water-soluble nitrogen-containing solvent is one which is miscible with water in a ratio of at least about 50 parts by weight of water-soluble nitrogen-containing solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble nitrogen-containing solvent is one which is miscible with water in a ratio of at least about 75 parts by weight of water-soluble nitrogen-containing solvent relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble nitrogen-containing solvent is one which is miscible with water in any ratio at a temperature of about 20°C. Particularly preferred water-soluble nitrogen-containing solvent include acetonitrile, dimethylformamide, dimethylacetamide, pyridine, piperidine, and N-methyl-2-pyrrolidone.

The term "water-soluble ketone" as used herein refers to any compound which contains a keto group, is a liquid under standard conditions and is miscible with water at a temperature of about 20°C. Preferably, the term "water-soluble ketone" does not include liquid ketones which are only slightly miscible with water at a temperature of about 20°C, i.e., which are miscible with water in a ratio of not more 32 parts by weight of liquid ketone relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble ketone is one which is miscible with water in a ratio of at least about 50 parts by weight of water-soluble ketone relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble ketone is one which is miscible with water in a ratio of at least about 75 parts by weight of water-soluble ketone relative to 100 parts by weight of water at a temperature of about 20°C. In one embodiment, the water-soluble ketone is one which is miscible with water in any ratio at a temperature of about 20°C. A particularly preferred water-soluble ketone is acetone.

The term "reagent" as used herein refers to a substance or compound that is added to a system in order to bring about a chemical reaction (i.e., a "reactant") or is added to see if a reaction occurs. Preferably, a "reactant" is a substance that is consumed in the course of a chemical reaction. In contrast, solvents and catalysts, although they are involved in the reaction, are not referred to as reactants in the present invention.
The term "leaving group" as used herein refers to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage. The ability of a leaving group to depart is generally correlated with the pKa of the conjugate acid, with lower pKa being associated with better leaving group ability. Since leaving group ability is a kinetic phenomenon, relating to a reaction's rate, whereas pKa is a thermodynamic phenomenon, describing the position of an equilibrium, the correlation is not perfect. However, it is a general rule that more highly stabilized anions act as better leaving groups. Preferred leaving groups are halogens (i.e., -Cl, -Br, or -I) and sulfonyl moieties. Preferred sulfonyl moieties have the formula -OS(0)2R, wherein R is F, Cl, alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms, perfluorinated alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms (such as CF3 or nonafluorobutyl), or aryl, optionally substituted with 1 to 3 substituents selected from the group consisting of halogens (F, Cl, Br, I), alkyl having 1, 2, 3, 4, 5, or 6 carbon atoms, and nitro. Exemplary leaving groups include -Cl, -Br, -I, 4-toluenesulfonyl, 4-bromobenzesulfonyl, 4-nitrobenzenesulfonyl, 2-nitrobenzenesulfonyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, methylsulfonyl, and fluorosulfonyl.

A "catalyst" as used herein refers to a substance which catalyzes a chemical reaction, e.g., increases the rate of a chemical reaction by lowering the activation energy, but which, unlike other reactants that participate in the chemical reaction, is not consumed by the reaction itself. A catalyst may participate in multiple chemical reactions, such as a redox reaction. In one embodiment, the catalyst does not comprise a carrier material, e.g., each component of the catalyst is catalytically active (such as bare metal). In another embodiment, the catalyst comprises one or more catalytically active components and a carrier material. A "carrier material" as used in the context of catalysts refers to neutral material used to support a catalyst. Exemplary carrier materials include carbon, activated carbon, charcoal, aluminum oxides (such as alumina and activated alumina), pumice, magnesia, zirconia, kieselguhr or diatomaceous earth, fuller's earth, silicon carbide, or a mixture of two or more of carrier materials.

The content of catalytically active component(s) in the catalyst may be 0.1 to 20% by weight, preferably 0.5 to 15% by weight, more preferably, 1.0 to 10% by weight, more preferably 1.5 to 7% by weight, more preferably 2.0 to 6% by weight, more preferably 2.5 to 5% by weight, more preferably 3.0 to 4.5% by weight. In one embodiment, the catalyst may comprise an enzyme. The enzyme may be a variant of a naturally occurring enzyme, wherein said variant has been prepared by recombinant means and has one or more improved properties compared to the naturally occurring enzyme, such as higher stability in an organic solvent (e.g., ester solvent, aprotic amide solvent, or water-soluble alcohol), higher catalytic activity in said organic solvent, and/or higher substrate specificity. The amount of catalyst in a chemical reaction may depend from various parameters, such as the type of the chemical reaction, the reactants participating in said chemical reaction, the type of catalysis (homogeneous vs. heterogeneous), and the catalyst used (without or with carrier material). Generally, if the catalyst comprises a carrier material, the amount of catalyst used in a chemical reaction (such as a redox reaction) may be 0.1 to 20% by weight, preferably 0.5 to 15% by weight, more preferably, 1.0
to 10% by weight, more preferably 1.5 to 7% by weight, more preferably 2.0 to 6% by weight, more preferably 2.5 to 5% by weight, more preferably 3.0 to 4.5% by weight, relative to the amount by weight of the starting material used (e.g., the amount of a compound to be reduced, such as ANFP). If the catalyst does not comprise a carrier material, the amount of catalyst used in a chemical reaction (such as a redox reaction) may be the same as defined above or lower, e.g., only 1/10, 1/20, 1/50, or 1/100 of the above ranges (e.g., 0.1 to 1% by weight or 0.01 to 0.1% by weight). In one embodiment, if the catalyst does not comprise a carrier material, the amount of catalyst used in a chemical reaction may be 0.01 to 10 mol-%, preferably 0.1 to 5 mol-%, more preferably, 0.5 to 4 mol-%, more preferably 1 to 3 mol-%, more preferably 1.5 to 2 mol-%, relative to the molecular amount of the starting material used (e.g., the amount of a compound to be reduced, such as ANFP).

A "redox reaction" or "reduction-oxidation reaction" as used herein means a reaction in which electrons are transferred between species or in which atoms change oxidation number. The species or atom which donates one or more electrons is the "reducing agent" or "reductant"; and the species or atom which accepts the one or more electrons is the "oxidizing agent" or "oxidant". Reducing and oxidizing agents function as conjugate reductant-oxidant pairs or redox pairs; thus, the reductant undergoes the reaction: reductant → conjugate oxidant + n e⁻; and the oxidant undergoes the reaction: oxidant + n e⁻ → conjugate reductant. Exemplary reducing agents for the process of the present invention include the following:

(i) hydrogen, such as nascent hydrogen or hydrogen gas (if hydrogen gas is used as reducing agent, the reaction conditions may be selected from the following: H₂ pressure: 100 to 4000 kPa, preferably, 200 to 3000 kPa, more preferably 400 to 2000 kPa, more preferably, 500 to 1000 kPa; reaction temperature and time: as defined for step (i));

(ii) metals, preferably base metals, more preferably Fe, Zn, Sn, or Sm, or alloys of these metals (such as Zn-Hg amalgam); the metal or alloy is preferably used in combination with an acid (such as mineral acids, e.g., HCl, HBr, HNO₃, H₃PO₄, H₂SO₄, NH₄Cl), optionally, in the presence of water;

(iii) metal hydrides, such as lithium aluminum hydride (LiAlH₄) and diisobutylaluminum hydride (DIBAH);

(iv) reducing metal compounds, i.e., compounds comprising a metal ion which has the ability to donate one or more electrons; exemplary reducing metal compounds are Sn(II) salts (such as SnCl₂) and Fe(II) salts (such as FeCl₂);

(v) reducing boron compounds, such as diborane (B₂H₆), decaborane (B₁₀H₁₄), 9-borabicyclononane (9-NN) and sodium borohydride (NaBH₄);

(vi) reducing carbon compounds, such as formic acids and salts thereof (in particular triethylenimmonium formate), ascorbic acid and salts thereof, and oxalic acid and salts thereof;

(vii) reducing silicon compounds, such as polymethylhydrosiloxane (PMHS) and triethylsilane;
(vii) reducing sulfur compounds, such as sulfites and dithionites, and
(viii) reducing nitrogen compounds, such as hydrazine.

Generally, the amount of reducing agent used in step (i) of the process of the present invention may be 1.5 to 3, preferably 2.0 to 2.5 times of the theoretical amount required for reducing ANFP to DAFP.

Preferred reducing agents include hydrogen, Fe (particularly in combination with HCl), Zn (particularly in combination with NH_2Cl), Sm, decaborane, formic acid and its salts, PMHS, triethylsilane, and dithionites (such as sodium dithionite).


The term "base metals" as used herein refers to metals whose conjugate oxidation-reduction pairs have more negative standard potentials than the standard hydrogen electrode. Preferably, base metals include the following metals: Li, Be, Na, Mg, Al, K, Ca, Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Zn, Ga, Ge, Rb, Sr, Y, Zr, Nb, Mo, Cd, In, Sn, Sb, Cs, Ba, Hf, Ta, W, Ti, Pb, Bi, La, Ce, Nd, Sm, and Yb.

A "redox catalyst" as used herein refers to a catalyst as defined herein which catalyzes a redox reaction. The redox catalyst may comprise a metal selected from the group consisting of the transition metals of the 8th to 10th groups of the periodic table of the elements. More preferably, the redox catalyst comprises a metal selected from the group consisting of Pt, Pd, Ni, Ir, Rh, and Ru. Even more preferably, the redox catalyst is selected from the group consisting of Pd/C, Pd(OH)_2/C (Pearlman's catalyst), platinum dioxide (such as platinum(IV) oxide hydrate, PtO_2·H_2O (Adam's catalyst)), Pt/C, and Raney-Ni. Most preferably, the redox catalyst is Pd/C or Pt/C. Preferred contents of the
catalytically active components (such as Pd in Pd/C) in the redox catalysts as well as preferred
amounts of redox catalysts used in a redox reaction are as defined above for "catalyst".

The term "phase transfer catalyst" as used herein refers to a catalyst that facilitates the migration of a
reactant from one phase into another phase where reaction occurs. Preferably, phase transfer catalysts
are selected from the group consisting of quaternary ammonium compounds (such as $N(R^1)O^+X^-$,
wherein $R^1$ is alkyl, $R^2$ is Cg.ig alkyl or benzyl, and X is Cl, Br, or I; e.g.,
benzyltrimethylammonium chloride), quaternary phosphonium compounds (such as $[P(R^1)C(R^2)]^+X^-$,
wherein $R^1$ is alkyl, $R^2$ is Cg.ig alkyl or benzyl, and X is Cl, Br, or I; e.g.,
hexadecyltributylphosphonium bromide), crown ethers (such as 12-crown-4 (facilitating the dissolving
of lithium salts in organic solvents such as ester solvents, aprotic amide solvents, water-soluble
alcohols, and/or water-soluble ketones), 15-crown-5 (facilitating the dissolving of sodium salts in
organic solvents such as ester solvents, aprotic amide solvents, water-soluble alcohols, and/or water-
soluble ketones), 18-crown-6, dibenzo-18-crown-6, and diaza-18-crown-6 (each facilitating the
dissolving of potassium salts in organic solvents such as ester solvents, aprotic amide solvents, water-
soluble alcohols, and/or water-soluble ketones)), and cryptands (such as 1,10-diaza-4,7,13, 16,21,24-
hexaoxabicyclo[8.8.8]hexacosane). Preferred amounts of phase transfer catalysts used in the process
of the present invention are as defined above for "catalyst".

An "oxygen scavenger agent" as used herein refers to a chemical substance added to a mixture in
order to remove or inactivate oxygen in said mixture. Preferably, the oxygen scavenger agent is a
sulfite salt, more preferably sodium sulfite.

A "chemical base" as used herein is any compound which is capable of receiving one or more protons
(Bronsted-Lowry acid-base theory). Preferably, the chemical base is non-nucleophilic. The chemical
base may be NH$_3$, a carbonate salt (such as K$_2$CO$_3$ or Cs$_2$CO$_3$), an organic amine (such as a cyclic
amine (e.g., 1,8-diazabicycloundec-7-ene (DBU)) or an aliphatic amine as defined above), an alkoxide
(such sodium tert-butoxide or potassium tert-butoxide), an amine salt (such as lithium
diisopropylamide (LDA) or lithium tetramethylpiperidide (LiTMP)), or a silicon-based amide (such as
sodium bis(trimethylsilyl)amide (NaHMDS) or potassium bis(trimethylsilyl)amide (KHMD)).
Preferred organic amines include trialkylamines, wherein the alkyl groups have independently 1, 2, 3,
4, 5, or 6 carbon atoms, such as triethylamine (TEA), N,N-diisopropylethylamine (DIPEA), or
trimethylamine.

A "degassed solvent" as used herein refers to a solvent (including ester solvents as defined herein,
aprotic amide solvents as defined herein, water-soluble alcohols as defined herein, water-soluble
ketones as defined herein, and water, as well as mixtures of any two or more of these liquids) from
which dissolved gases have been removed. The removal of the dissolved gases (in particular dissolved oxygen) from a solvent may be performed by one or more of the following procedures: (i) subjecting the solvent to be degassed to reduced pressure (often referred to as vacuum degasification), optionally, with sonication and/or stirring; (ii) heating the solvent to be degassed just below the boiling temperature of said solvent, optionally, with sonication (preferably ultrasonication) and/or stirring; (iii) flowing the solvent to be degassed inside a gas-liquid separation membrane and evacuating outside (membrane degasification); (iv) bubbling the solvent to be degassed with an inert gas, optionally, with sonication, stirring and/or heating; (v) adding an oxygen scavenger agent to the solvent to be degassed; (vi) placing the solvent to be degassed into a flask, flash-freezing the solvent, preferably with liquid nitrogen, applying reduced pressure, sealing the flask, thawing the solvent, preferably by using a water bath, and optionally, repeating the freeze-reduced pressure-thaw cycle, typically three times. Preferably, the removal of dissolved gases (in particular dissolved oxygen) from a solvent is performed by boiling the solvent to be degassed under an inert gas (such as nitrogen), optionally, with stirring, at atmospheric pressure for one hour. The inert gas may be selected from the group consisting of nitrogen and noble gases. More preferably, the inert gas is nitrogen.

The term "inert gas" as used herein refers to a non-reactive gas. Inert gases include nitrogen, carbon dioxide, sulfur hexafluoride, and noble gases. Preferred inert gases are nitrogen, sulfur hexafluoride, helium, argon, and neon.

The term "noble gas" as used herein refers to any of the group consisting of helium, neon, argon, krypton, and xenon.

The starting materials, ACNP and 4-fluorobenzylamine, are commercially available and methods for their preparation as well as for structurally similar compounds are described in the literature; cf, e.g., DE 31 33 519 C2, US 2006/080790, and GB 1,184,848.

Methods which may be used for monitoring the progress of one or more reaction steps of the process of the present invention include the methods for characterization of polymorphs of a material as described above as well as HPLC, liquid chromatography (LC), thin layer chromatography (TLC), gas chromatography (GC), mass spectrometry (MS), GC-MS, nuclear magnetic resonance (NMR) spectroscopy (preferably for $^{13}$C, $^{18}$O, $^{18}$B, $^{15}$N, $^{19}$N, $^{17}$O, $^{18}$F, $^{23}$Na, $^{29}$Si, $^{31}$P, $^{35}$Cl), infrared (IR) spectroscopy, Raman spectroscopy, and elemental analysis.

The term "substantially pure" as used herein means that a compound or preparation has a purity of at least 99%, preferably at least 99.99%, more preferably at least 99.999%, more preferably at least 99.9999%. Preferably, in a substantially pure compound or preparation the amount of impurities are
below the detection limit of the analysis method used. The analysis method may be chosen from those methods which are used for monitoring the progress of one or more reaction steps of the process of the present invention. For example, a "flupirtine maleate preparation which is substantially pure with respect to polymorphic form B" means that at least 99% of the flupirtine maleate preparation is polymorphic form B, preferably that the total amount of impurities (in particular, ethyl (2,6-diaminopyridin-3-yl) carbamate maleate and/or polymorphic forms other than polymorphic form B) in said flupirtine maleate preparation is below the detection limit of the analysis method used.

The term "substantially complete" as used herein means that in a reaction substantially the entire initial amount of the starting material is consumed. The term "substantially the entire initial amount" as used herein means at least 95%, preferably at least 98%, more preferably at least 99%, more preferably at least 99.9%, more preferably at least 99.99%, more preferably at least 99.999%, of the initial amount. Preferably, when a reaction is substantially complete, the amount of starting material is below the detection limit of the analysis method used. The analysis method may be chosen from those methods which are used for monitoring the progress of one or more reaction steps of the process of the present invention.

The term "substantially completely converted" as used herein means that after conversion, the amount of converted compound in the preparation is at least 95%, preferably at least 98%, more preferably at least 99%, more preferably at least 99.9%, more preferably at least 99.99%, more preferably at least 99.999%, while the amount of unconverted compound is less than 5%, preferably, less than 2%, more preferably less than 1%, more preferably less than 0.1%, more preferably less than 0.01%, more preferably less than 0.001%. Preferably, in a preparation of a substantially completely converted compound the amount of unconverted compound is below the detection limit of the analysis method used. The analysis method may be chosen from those methods which are used for monitoring the progress of one or more reaction steps of the process of the present invention. For example, "converting flupirtine maleate substantially completely into polymorphic form B" means that after conversion, at least 95% of the flupirtine maleate in the preparation are polymorphic form B, preferably that the total amount of polymorphic forms other than polymorphic form B is below the detection limit of the analysis method used.

The term "substantially anhydrous" as used herein in conjunction with a solvent or mixture means that the solvent or mixture contains water in an amount of not more than 5% by weight, preferably, not more than 1% by weight, more preferably not more than 0.1%, by weight, more preferably not more than 0.01%, by weight, based on the total weight of the solvent or mixture.
The term "partially converted" as used herein in conjunction with a compound means that the compound has not been completely converted. Preferably, "partially converted" means that 1 to 95%, preferably less than 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or less than 5% have been converted.

The term "enriched" as used herein in conjunction with a preparation of a polymorphic form means that the preparation includes a higher ratio of designated polymorphic form to non-designated polymorphic form as compared to the original preparation from which it was obtained.

The term "standard conditions" as used herein refers to a temperature of 20°C and an absolute pressure of 101.325 kPa.

The term "one or more times" as used herein means at least once, preferably once, twice, 3, 4, 5, or 6 times.

A "solvent" as used herein refers to any chemical compound which is a liquid under standard conditions, which dissolves a solid, liquid, or gaseous solute, resulting in a solution that is soluble in a certain volume (e.g., 100 mL) of solvent at a specified temperature (preferably about 20°C), and which is inert with respect to said solute, preferably with respect to the reactants used in the process of the present invention. I.e., the solvent does not chemically react / does not form covalent bonds with the reactants used in the process of the present invention.

The expression "solvent exchange" as used herein means that one or more solvents contained in a mixture are removed from the mixture and to the remaining residue one or more solvents are added, wherein the one or more solvents which are added to the remaining residue differ from the one or more solvents initially present in the mixture. For example, if a mixture comprising solvents A and B is subjected to a solvent exchange both solvents A and B may be removed from the mixture and to the remaining residue either solvent A or solvent B or one or more solvents other than A and B is/are added. Alternatively, if only solvent A is removed from the mixture, either solvent B or one or more solvents other than A and B may be added to the remaining residue. The solvent exchange may be performed by any means known to the skilled person and includes thermal solvent exchange (such as by vaporization using, for example, a rotary evaporator) and non-thermal solvent exchange (such as by molecular separation processes, e.g., nanofiltration, pervaporation, membrane technology, or a combination thereof; cf. the products sold by Sulzer and Evonik Industries. The remaining residue may be in the form of a liquid (such as a solution, emulsion, or dispersion/suspension) or a solid.
The expression "reflux temperature" used herein in conjunction with a remaining residue refers to the boiling point of the liquid contained in the remaining residue which has the lowest boiling point of all liquids contained in the remaining residue.

The expressions "is carried out in a solvent" and "is preformed in a solvent" as used herein in conjunction with a reaction mean that the major component of the liquid part of the reaction mixture concerned is composed of said solvent. Similarly, the expressions "is carried out in one or more solvents", "is preformed in one or more solvents", "is carried out in a mixture of solvents", and "is preformed in a mixture of solvents" as used herein in conjunction with a reaction mean that the major component of the liquid part of the reaction mixture concerned is composed of said one or more solvents or mixture of solvents, respectively. For example, if a reaction is to be carried out in solvent A (or a mixture of solvents A and B, respectively), it is preferred that at least 30% (such as at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or 100%) by weight or by volume of the liquid part of the reaction mixture is composed of said solvent A (or said mixture of solvents A and B, respectively), the balance being liquid(s) other than solvent A (or the mixture of solvents A and B, respectively), with the proviso that none of said liquids is present in the liquid part of the reaction mixture in an amount (by weight or volume) higher than that of solvent A (or the mixture of solvents A and B, respectively). Preferably, the total amount of liquid(s) other than solvent A (or the mixture of solvents A and B, respectively) in the liquid part of the reaction mixture may be at most 50% (such as at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 9%, at most 8%, at most 7%, at most 6%, at most 5%, at most 4%, at most 3%, at most 2%, at most 1%) by weight or volume.

The expression "solvent which is not completely miscible with water" as used herein means that a mixture of the solvent with water does not form a single phase but forms two liquid phases (e.g., at standard conditions of temperature and pressure; and/or particular amounts used for the solvent and water).

The term "volatile" as used herein in conjunction of a component of a mixture refers to a compound which can be separated from the mixture by vaporization, e.g., by gradually increasing the temperature (starting from, e.g., about 20°C) and/or reducing the pressure (starting from, e.g., standard atmospheric pressure). In one embodiment, the volatile components also include azeotropes. Preferably, volatile components comprise all compounds and/or azeotropes having a boiling point (at standard atmospheric pressure) lower than the boiling point of water (at standard atmospheric pressure).
The expression "1 part by volume of A relative to 1 part by weight of B" as used herein in conjunction with a mixture of A and B means that for each unit amount of B (measured in gram) one unit amount of A (measured in milliliter [mL]) is present in the mixture. For example, a mixture comprising 3 parts by volume of A relative to 1 part by weight of B means that the mixture comprises 3 mL of A for each g of B, or 3 L of A for each kg of B.

As mentioned in DE 31 33 519 C2, the crude flupirtine maleate preparation obtained by the process described in said patent is colored (blue) due to the presence of impurities. Even after recrystallization the resulting flupirtine maleate preparation is still colored (green) and thus, a complicated and time-consuming purification sequence using charcoal has to be performed in DE 31 33 519 C2 in order to remove the colored impurities. We have surprisingly found that the generation of colored impurities can be reduced and/or said colored impurities can be easily removed from flupirtine maleate preparations by one or more of the following steps:

- using an ester solvent and/or aprotic amide solvent in at least one of steps (i) and (ii);
- using solvents which have been degassed by boiling under inert gas;
- reducing the amount of redox catalyst or even omitting the redox catalyst;
- lowering the reaction temperature in the catalytic hydration of ANFP to below 40°C;
- adding an oxygen scavenger agent;
- first crystallizing flupirtine maleate from step (iii) as polymorph B, isolating polymorph B and converting polymorph B into polymorph A;
- washing flupirtine maleate with a water-soluble ketone (preferably acetone) or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in a water-soluble alcohol (preferably isopropanol)).

The process of the present invention prevents the generation of precursors of the colored impurities (e.g., ethyl (2,6-diaminopyridin-3-yl) carbamate maleate), thereby allowing the preparation of substantially pure flupirtine maleate which is not colored.

Unless otherwise indicated, all percentages set forth herein are percentages by weight.

The term "optionally" as used herein means that the subsequently described event, circumstance or condition may or may not occur, and that the description includes instances where said event, circumstance, or condition occurs and instances in which it does not occur.
Figures

Figure 1:
Schematic overview of the preparation of flupirtine maleate as described in DE 3 1 33 519 C2

Figure 2:
Schematic overview of one embodiment of the process of the present invention

Figure 3:
HPLC chromatogram of flupirtine maleate obtained by the process of the present invention (STAGE 3: flupirtine maleate)

Figures 4 and 5:
DSC scans of polymorph A (Figure 4) and polymorph B (Figure 5) of flupirtine maleate obtained by the process of the present invention

Figure 6:
GC chromatogram of flupirtine maleate obtained by the process of the present invention

Figure 7:
Powder X-ray diffraction (XRD) results for pure polymorphs A and B of flupirtine maleate obtained by the process of the present invention

Examples

The Examples are designed in order to further illustrate the present invention. They are not to be construed as limiting the scope of the invention in any way.

Analytical methods

Infrared spectrometry
A KBr disc of a sample of flupirtine maleate was prepared according to standard procedures in the art and the infrared spectrum is recorded over the range of from 4000 to 600 cm⁻¹ on a Perkin Elmer Spectrum One Instrument. The following peaks obtained for flupirtine maleate were identified:
The IR spectrum showed characteristic peaks for flupirtine maleate and compared to that published in the literature; cf., e.g., US 4,481,205. According to US 4,481,205, polymorphs A and B of flupirtine maleate can be distinguished by an absorption in the region 1160 to 1170 cm\(^{-1}\), since pure polymorph B is characterized by a band at 1160 cm\(^{-1}\) and pure polymorph A by a band at 1170 cm\(^{-1}\). Although this distinction can be seen in our IR spectra this would only give an indication as to the polymorph. Thus, X-ray diffraction (XRD) is still considered the only technique which can give definite confirmation of the polymorphic form of flupirtine maleate.

<table>
<thead>
<tr>
<th>Diagnostic Peak (cm(^{-1}))</th>
<th>Functional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>3429</td>
<td>NH(_2)</td>
</tr>
<tr>
<td>3219</td>
<td>-OH (maleic acid)</td>
</tr>
<tr>
<td>1704</td>
<td>C=O (maleic acid)</td>
</tr>
<tr>
<td>1680</td>
<td>C=O (carbamate)</td>
</tr>
<tr>
<td>1642-1526</td>
<td>aromatic ring vibrations / carbamate</td>
</tr>
<tr>
<td>1387-1298</td>
<td>C-N / C-O</td>
</tr>
<tr>
<td>1278</td>
<td>C-O (maleic acid)</td>
</tr>
</tbody>
</table>

Mass spectrometry (MS)
A high resolution mass spectrum for flupirtine maleate was obtained (Broker FTMS-Apex II; ionization source: positive electrospray).

m/z 305.1416180 representing [MH] for the flupirtine free base (in solution the flupirtine maleate molecule dissociates to give the flupirtine free base); expected for \(\text{C}_{5}\text{H}_{13}\text{FNO}_{2}\) is 305.1408305 (error \(= 2.581 \text{ ppm})\).

Nuclear magnetic resonance (NMR) spectroscopy
The \(^1\text{H NMR}\) (300 MHz; dg-dimethylsulphoxide) was assigned as follows:
The $^{13}$C NMR (300 MHz; de-dimethylsulphoxide) was assigned as follows:

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Splitting observed</th>
<th>No. of protons</th>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>triplet</td>
<td>3</td>
<td>CH$_3$ coupled to CH$_2$</td>
</tr>
<tr>
<td>4.0</td>
<td>quartet</td>
<td>2</td>
<td>CH$_2$ coupled to CH$_3$</td>
</tr>
<tr>
<td>4.4</td>
<td>singlet</td>
<td>2</td>
<td>CH$_3$N</td>
</tr>
<tr>
<td>5.8</td>
<td>doublet</td>
<td>1</td>
<td>Pyridine ring H$_2$</td>
</tr>
<tr>
<td>6.2</td>
<td>singlet</td>
<td>2</td>
<td>Maleic acid CH</td>
</tr>
<tr>
<td>7.1</td>
<td>multiplet</td>
<td>2</td>
<td>Aromatic ring H$_A$</td>
</tr>
<tr>
<td>7.2</td>
<td>doublet</td>
<td>1</td>
<td>Pyridine ring H$_1$</td>
</tr>
<tr>
<td>7.4</td>
<td>multiplet</td>
<td>2</td>
<td>Aromatic ring H$_B$</td>
</tr>
<tr>
<td>8.3</td>
<td>broad singlet</td>
<td>1</td>
<td>NIH</td>
</tr>
</tbody>
</table>

The $^{13}$C NMR (300 MHz; de-dimethylsulphoxide) was assigned as follows:

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>Splitting observed</th>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.0</td>
<td></td>
<td>C1 CH$_3$</td>
</tr>
<tr>
<td>44.6</td>
<td></td>
<td>C9 CH$_2$N</td>
</tr>
<tr>
<td>60.7</td>
<td></td>
<td>C2 CH$_3$O</td>
</tr>
<tr>
<td>94.7</td>
<td></td>
<td>C6</td>
</tr>
<tr>
<td>107.4</td>
<td></td>
<td>C4</td>
</tr>
<tr>
<td>115.4</td>
<td>Coupled to F J 21.3</td>
<td>C12 and C14 are equivalent</td>
</tr>
<tr>
<td>115.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>129.6</td>
<td>Coupled to F J 8.1</td>
<td>C11 and C15 are equivalent</td>
</tr>
<tr>
<td>129.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>133.4</td>
<td></td>
<td>Maleic acid CH are equivalent</td>
</tr>
<tr>
<td>135.9</td>
<td></td>
<td>C5</td>
</tr>
<tr>
<td>139.7</td>
<td></td>
<td>C10</td>
</tr>
<tr>
<td>151.5</td>
<td></td>
<td>C7</td>
</tr>
<tr>
<td>153.0</td>
<td></td>
<td>C8</td>
</tr>
<tr>
<td>155.5</td>
<td></td>
<td>C3 C=O</td>
</tr>
<tr>
<td>160.1</td>
<td>Coupled to F J 240</td>
<td>C13</td>
</tr>
<tr>
<td>163.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>167.4</td>
<td></td>
<td>Maleic acid C=O are equivalent</td>
</tr>
</tbody>
</table>
HPLC was used to determine the purity of flupirtine maleate preparations and the maleic acid content.

*Mobile phase A:*

900 ml of water (HPLC grade), 100 ml of MeOH, and 1 ml of trifluoroacetic acid (TFA)

*Mobile phase B:*

200 ml of water (HPLC grade), 800 ml of MeOH, and 1 ml of TFA

*Diluent:*

0.1% TFA in water

*Flupirtine maleate standard (prepared in duplicate):*

Approximately 40 mg (± 1 mg) of flupirtine maleate reference standard were weighed, dissolved in 2 mL MeCN, and diluted with diluent.

*Maleic acid standard (prepared in duplicate):*

Approximately 64 mg (± 1 mg) of maleic acid reference material were weighed, dissolved in and diluted with diluent; then 20 mL were diluted with 80 mL of diluent.

*Sample solution (prepared in duplicate):*

Approximately 40 mg of sample were weighed, dissolved in 2 mL MeCN, and diluted with diluent.

*Chromatographic conditions:*

Column: Zorbax eclipse XDB C18 50 mm x 4.6 mm 1.8 µm

Injection volume: 10 µL

Flow rate: 1 mL/min

Detector: 246 nm

Column temperature: 30°C

Gradient:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>17</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>17.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Chromatographic run time: 20 min
Peak identification:

<table>
<thead>
<tr>
<th>Compound</th>
<th>RT</th>
<th>RRT</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>maleic acid</td>
<td>0.7</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>ethyl (2,6-diaminopyridin-3-y1l) carbamate maleate</td>
<td>2.7</td>
<td>0.26</td>
<td>0.915</td>
</tr>
<tr>
<td>flupirtine maleate</td>
<td>10.4</td>
<td>1.00</td>
<td>1.000</td>
</tr>
</tbody>
</table>

(RT: retention time; RRT: relative RT; RF: response factor)

Under the above conditions two blanks were injected followed by the flupirtine maleate standards and the maleic acid standards. The normalized % purity was determined by single injections of the sample solutions. A representative chromatogram of flupirtine maleate obtained by the process of the present invention is shown in Figure 3.

Differential scanning calorimetry (DSC)

Samples were analysed in duplicate using 4.00 to 6.00 mg weighed into a crucible with a sealed lid. Prior to analysis a blank (i.e., an empty sealed crucible) was run. A temperature of from 40°C to 200°C was scanned at 20°C/minute.

Polymorph A of flupirtine maleate shows peaks between 160 to 170°C, and 180 to 190°C, while polymorph B shows a peak at 185°C only. Representative scans of polymorphs A and B obtained by the process of the present invention are shown in Figures 4 and 5.

The DSC results for the samples show the expected profile for polymorph A with two peaks, one at approximately 169°C and the other at approximately 185°C. This can be explained as follows.

Although polymorph A is more stable at ambient temperature, flupirtine maleate is an enantiotropic system showing a transition temperature above which polymorph B is more stable. In the DSC measurement, the lower temperature endotherm shows the melting of polymorph A, but a second, higher temperature endotherm corresponding to the melting of polymorph B is also seen since polymorph B is formed during the heating process. The presence of both endotherms in the DSC is normal even when the original sample contained only polymorph A. A sample of pure polymorph B gives a single endotherm at approximately 185°C. DSC cannot therefore be used to conclusively show the absence of polymorph B in a sample, although the absence of the lower temperature endotherm could be used to indicate a sample of pure polymorph B.

Gas chromatography (GC)

GC headspace was used to determine residual solvents in flupirtine maleate preparations.

Strong standard preparation (prepared in duplicate):

2.0 mL ethyl acetate, 2.0 mL acetone and 2.0 mL isopropanol (IPA) were transferred by pipette into a 100 mL volumetric flask containing 50 mL dimethylformamide (DMF) and diluted with DMF.
Calibration standards preparation:
Calibration Standard 1:
1.0 mL strong standard 1 to 100 mL with DMF. 10.0 mL were transferred by pipette into a headspace vial. (0.32% w/w)

Calibration standard 2:
2.0 mL strong standard 1 to 100 mL with DMF. 10.0 mL were transferred by pipette into a headspace vial. (0.63% w/w)

Calibration standard 3:
4.0 mL strong standard 1 to 100 mL with DMF. 10.0 mL were transferred by pipette into a headspace vial. (1.3% w/w)

Check standard:
4.0 mL strong standard 2 to 100 mL with DMF. 10.0 mL were transferred by pipette into a headspace vial.

Sample solution (prepared in duplicate):
Approximately 0.5 g of sample was weighed into a headspace vial. 10.0 mL of DMF were added.

Chromatographic conditions:
Column: ZB 624 60m x 0.32 mm 1.8 µm film

Inlet temperature: 200°C
Detector temperature: 250°C
Oven temperature: 40°C (hold for 8 min) then 20°C/min to 210°C (hold for 5 min)
Chromatographic run time: 21.5 min
Pressure: 138 kPa (20 psi) constant pressure

Split flow: 10.3 mL/min
Split ratio: 3.5:1
Column flow: 2.9 mL/min

Headspace Parameters:

Oven temperature: 70°C
Syringe conditioning: 90°C
Incubation time: 15 min
Shake: shake on 1 min, off 0 min
Analysis Time: 28 min
Prep Time: 2.0 min
Sample Injection: 1.0 mL
Carrier gas: nitrogen

**Calibration Table:**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Std 1</th>
<th>Std 2</th>
<th>Std 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Acetate</td>
<td>0.001804</td>
<td>0.003608</td>
<td>0.007216</td>
</tr>
<tr>
<td>Weight/vial (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetone</td>
<td>0.001582</td>
<td>0.003164</td>
<td>0.006328</td>
</tr>
<tr>
<td>Weight/vial (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropanol</td>
<td>0.00157</td>
<td>0.00314</td>
<td>0.00628</td>
</tr>
<tr>
<td>Weight/vial (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Under the above conditions two blanks were injected followed by the calibration standards 1 to 3 and the check standard. The IPA, ethyl acetate and acetone content were determined by injecting duplicate preparations of the sample solution.

The retention times of the components were as follows:

<table>
<thead>
<tr>
<th>Component</th>
<th>RT</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>5.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Acetone</td>
<td>6.7</td>
<td>0.41</td>
</tr>
<tr>
<td>IPA</td>
<td>7.2</td>
<td>0.44</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>10.9</td>
<td>0.67</td>
</tr>
<tr>
<td>DMF</td>
<td>16.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

A representative chromatogram of the flupirtine maleate obtained by the process of the present invention is shown in Figure 6.

**Powder X-ray diffraction (XRD)**

The diffractograms were recorded with a powder diffractometer D5000 (Siemens, Germany). The analysis conditions were as follows: PSD fast-scan; start: 4.008°; end: 30.024°; step: 0.014°; step time: 3 s.

The XRD results for flupirtine maleate obtained by the process of the present invention are shown in Figure 7 and confirm conclusively that the material is pure polymorph A by comparison with the literature (K-F. Landgraf et al, Eur. J. Pharm. Biopharm., 46 (1998) 329-337). The reflection at $2\Theta = 5.2^\circ$ is particularly diagnostic, since this is the strongest reflection in samples of polymorph B, but is
absent in samples of polymorph A. All peak positions for the material closely match those given in the literature.

It is suggested in the literature that grinding the material can cause a change in polymorph. This has been attempted by grinding material confirmed as polymorph A; re-analysis of the ground material confirmed it was still polymorph A.

**Example 1: Preparation of 2-amino-3-nitro-6-(4-fluorobenzylamino) pyridine (ANFP)**

2-Amino-6-chloro-3-nitropyridine (ACNP, 10.0 kg) was suspended in isopropanol (49 L) under stirring and a nitrogen blanket. 4-Fluorobenzylamine (7.7 kg) and triethylamine (8.4 kg) were added and the mixture was heated to reflux. Stirring at reflux was maintained for 14 h. The reaction mixture was cooled to 50°C and samples were taken for checking completion of the reaction by HPLC (amount of residual ACNP: 0.02%). Water (163 kg) was added and the mixture was stirred for 5 min, then cooled to 5°C and stirred for 30 minutes. The precipitate was filtered off, washed with water (41 L) and dried under reduced pressure at 50°C. Yield: 14.6 kg (96.8% of theory).

**Example 2: Preparation of crude flupirtine maleate**

ANFP (7.0 kg), Pd/C (5% Pd on carbon; 1.0 kg) and degassed ethyl acetate (70 L) were charged into a pressure hydrogenator and the reaction mixture was maintained at 25°C. The pressure hydrogenator was purged three times with nitrogen and then three times with hydrogen (200 kPa per purge). The reaction mixture was stirred for 34 h at a temperature of 25°C and a hydrogen pressure of 200 kPa. The pressure was released, the pressure hydrogenator was purged three times with nitrogen (200 kPa per purge) and the reaction was monitored for completion by LC (amount of residual ANFP: 0.7%). Ethyl chloroformate (3.15 kg together with 0.5 L degassed ethyl acetate), triethylamine (3.15 kg together with 0.5 L degassed ethyl acetate), and sodium sulfite (70 g together with 250 mL degassed ethyl acetate) were added to the pressure hydrogenator (in intervals of 30 min), wherein the reaction mixture was stirred and the temperature was maintained at 40°C. Degassed isopropanol (51 kg) was added, the reaction mixture was filtered at 40°C to remove the redox catalyst, and the catalyst was washed with isopropanol (28 kg). The filtrates were passed directly into a solution of maleic acid (5.0 kg) and sodium sulfite (70 g) in degassed isopropanol (39 kg) at 40°C under stirring. The slurry was heated to 65°C, then cooled to 3°C and stirred at 3°C for 15 min. The crude flupirtine maleate was filtered off at 5°C, washed twice with degassed isopropanol (25 kg and 18 kg, respectively) at 5°C and dried at about 50°C under reduced pressure. Yield of crude flupirtine maleate: 9.85 kg (88% of theory).

XRD-analysis of the crude flupirtine maleate revealed that the crude flupirtine maleate obtained is polymorph B.
Example 3: Preparation of pure flupirtine maleate
Crude flupirtine maleate (14.0 kg) was mixed with isopropanol (146.8 L) and deionized water (63.2 L) and the reaction mixture was stirred and heated to 65°C to dissolve the crude flupirtine maleate. The solution was cooled to 0°C over 5.25 h and maintained at 0°C for 1 h. The crystals were filtered off, washed with an aqueous isopropanol solution (25.2 L isopropanol and 2.8 L water) or acetone (20 L), and dried at about 30°C under reduced pressure. Purity of flupirtine maleate: 99.9% (mixture of polymorphs A and B).

Example 4: Preparation of pure flupirtine maleate polymorph A
Flupirtine maleate (12.0 kg) was mixed with isopropanol (127.4 L) and deionized water (54.6 L) and the reaction mixture was stirred and heated to 65°C to dissolve the flupirtine maleate. The solution was cooled to 47°C to 48°C, a slurry of pure polymorph A of flupirtine maleate (240 g in 1 L 50/50 isopropanol/water) was added, and the reaction mixture was cooled to 0°C over 1 h. The crystals were filtered off, washed with an aqueous isopropanol solution (21.6 L isopropanol and 2.4 L water), and dried at about 32°C under reduced pressure. Purity of flupirtine maleate polymorph A: 99.9% (polymorph B: 0.05%).

Example 5: Preparation of flupirtine maleate without redox catalyst
A jacketed glass vessel (2 L) was fitted with an overhead stirrer, a reflux condenser and a nitrogen supply tube. Ethyl alcohol (96%, 500 mL) was charged, followed by ANFP (50.0 g), sodium dithionite (145 g) and aqueous ammonia (600 mL; ammonia content by titration: 28.7%). The reaction mixture was heated with stirring to 44-47°C over 55 min and maintained at that temperature for further 15 min. Ethyl alcohol and ammonia were removed by distillation at reduced pressure (70-80 kPa), while gradually increasing the temperature in the vessel to 60-62°C over 4 h. Water (250 mL) was added as necessary to maintain the stirring. Ethyl acetate (750 mL) was added and the mixture was extracted, then the layers were separated. The ethyl acetate layer was treated with ethyl chloroformate (32 mL) at 47°C and 5 min later with triethylamine (55 mL) at 53°C. After 30 min additional ethyl acetate (200 mL) was added to allow for easier stirring, then maleic acid aqueous solution (35 g maleic acid in 200 mL water) was added over 5 min. The light blue crystallization slurry was cooled to 17°C over 50 min and crude flupirtine maleate was collected by filtration on a Buchner funnel, washed on filter with purified water (500 mL) and cold (5°C) ethyl acetate (2 x 40 mL). Crude flupirtine maleate was isolated (weight 187.6 g) and, after drying at reduced pressure (~80 kPa, 45°C), 76.6 g of dry product was obtained (96.1% purity by HPLC, 175 mmol, 91.8% yield).

A glass vessel (2 L) was fitted with air cooled condenser, overhead stirrer and thermometer. The crude flupirtine maleate was charged (73.6 g) and suspended in isopropanol/water (10:4 mixture, total of
1.03 L). The mixture was heated to 61°C over 30 min to dissolve the solids. Then the solution was gradually cooled with stirring to 0-5°C over 3 h and 20 min. Purified flupirtine maleate was collected by filtration on a Buchner funnel and washed with cold isopropanol/water 9:1 mixture (75 mL), dried at reduced pressure (-80 kPa, 35°C). Yield: 61.86 g (86.3% of theory); purity: 98.7%.

A glass vessel (2 L) was fitted with an air cooled condenser, an overhead stirrer and a thermometer. Purified flupirtine maleate (123.65 g) was charged and suspended in isopropanol/water (10:4 (vol/vol), total of 1.30 L). The mixture was heated to 65°C over 30 min to dissolve the solids. Then the solution was gradually cooled with stirring. At 48°C 10 mg of flupirtine maleate polymorph A seed crystals were added. Cooling was continued to 0-5°C over 4 h. The final product flupirtine maleate was collected by filtration on a Buchner funnel and washed with cold isopropanol/water 9:1 mixture (60 mL), dried at reduced pressure (-80 kPa, 45°C). Yield: 78.99 g (84.5% of theory); purity of polymorph A: 99.8%; sum of impurities: 0.14%.

**Example 6: Prior art processes**

We wanted to assess whether or not it is sufficient to simply stir flupirtine maleate preparations (containing polymorph A in an amount of at most 40%) in an organic solvent (such as isopropanol) at a temperature in the range of -10°C to 70°C for about 20 min to 5 h in order to obtain flupirtine maleate preparations containing polymorph A in an amount of 60% to 100%, as taught in EP 0 977 736 and DE 31 33 519 C2. To this end, we stirred the flupirtine maleate obtained from Examples 2 and 3, above, in isopropanol at ambient temperature and determined the ratio of polymorph B to polymorph A by XRD. Surprisingly, we found that the ratio of polymorph B to polymorph A was not significantly altered by stirring in isopropanol contrary to the teachings in EP 0 977 736 and DE 31 33 519 C2.

Furthermore, we wanted to assess whether or not it is possible to obtain pure flupirtine maleate polymorph A by seeding a solution of flupirtine maleate with crystals of flupirtine maleate polymorph A, as taught in DE 31 33 519 C2. To this end, we hydrogenated ANFP in the presence of a redox catalyst to yield DAFP, reacted DAFP with ethyl chloroformate to yield flupirtine, reacted flupirtine with maleic acid resulting in a slurry, heated the slurry until the precipitate dissolved, added crystals of pure flupirtine maleate polymorph A, isolated the resulting precipitated crystals, and analyzed said precipitated crystals by HPLC and XRD. These analyses revealed that the precipitated crystals mainly consisted of polymorph A but also contained the impurity ethyl (2,6-diaminopyridin-3-yl) carbamate maleate. This impurity was present in significant amounts (up to 28% if the hydrogenation of ANFP was performed over night) and could not be removed from the precipitated crystals by washing or stirring a slurry of the precipitated crystals in an appropriate solvent without dissolving the flupirtine maleate crystals completely.
In contrast, we surprisingly found that by using a "two-step crystallization", i.e., crystallizing flupirtine maleate as polymorph B; isolating polymorph B; and converting polymorph B into polymorph A with seeding, a flupirtine maleate preparation can be obtained which is (substantially) pure with respect to polymorph A, i.e., whose total amount of impurities (in particular, ethyl (2,6-diaminopyridin-3-yl) carbamate maleate and/or polymorphic forms other than polymorphic form B) is less than 1%.

**Example 7: Varying reaction conditions**

The processes described in Examples 2 to 4 were repeated under slightly different reaction conditions (such as varying the redox catalyst (e.g., Pt/C), the reducing system (e.g., a formate salt with redox catalyst or a dithionite salt without redox catalyst; cf. also Example 5), the ester solvent, the reaction temperatures and times, the amounts of reactants, and washing/purification reagents) and flupirtine maleate was obtained with yield and purity values similar to those presented above in Examples 2 to 4.

For example, the following procedure has been used to prepare flupirtine maleate. A round bottom flask (1 L) was charged with acetonitrile (200 mL), followed by ANFP (20.0 g, 76 mmol), sodium dithionite (55.0 g, 315 mmol) and 29% aqueous ammonia (250 mL). The reaction mixture was stirred and gently heated at 36 to 37°C for 60 min. The mixture was heated up to 44°C over 35 min and then gradually cooled. The colour turned from yellow (starting material) to white. Acetonitrile, ammonia and water were removed by distillation at reduced pressure on a rotary evaporator. After distillation the mixture was diluted with water (100 mL) and ethyl acetate (310 mL) under a nitrogen stream. The water layer was separated and discarded. The air sensitive ethyl acetate layer was treated with ethyl chloroformate (14.5 mL, 151 mmol), while stirring and slowly flushing with nitrogen for 30 min. Triethylamine (25 mL, 179 mmol) was added and stirred for 30 min. An aqueous solution of maleic acid prepared from maleic acid (14.0 g, 120 mmol) and water (160 mL) was added to the reaction mixture. The mixture was maintained at 40°C for 1 h, then cooled to 20°C. The precipitate was collected by filtration, the vessel and the precipitate were washed with an additional portion of ethyl acetate (55 mL). The obtained wet product was dried in a vacuum drying oven at 50°C, until the loss on drying was less than 1.0%. Yield: 29.5 g (94.3%, assay, 66.2 mmol; 87.1% of theory); purity: 99.84%.

In some instances, where solvents in the process of the present invention are used which have not been thoroughly degassed, the purity of the flupirtine maleate obtained is not satisfactory. It was found that the best way to remove dissolved gases (in particular dissolved oxygen) from a solvent is by boiling the solvent to be degassed under an inert gas (such as nitrogen), optionally, with stirring, at atmospheric pressure for one hour. In addition, it has been found that instead of degassing a solution of, e.g., maleic acid in a water-soluble alcohol, the solvent should be degassed alone in order to avoid
possible side products during the degasification, and the addition of compounds to a reaction mixture should be performed under a blanket of inert gas.

Furthermore, it was found that the amount of impurities (especially the amount of ethyl (2,6-diaminopyridin-3-yl) carbamate maleate or of its precursors) in a flupirtine maleate preparation may be decreased and thus, the purity and color of the flupirtine maleate preparation improved by one or more of the following measures: (1) reducing the amount of redox catalyst; (2) lowering the reaction temperature in the catalytic hydration of ANFP to below 40°C; (3) adding an oxygen scavenger agent in step (ii) and/or step (iii); (4) performing a "two-step crystallization", i.e., crystallizing flupirtine maleate obtained from step (iii) as polymorph B; isolating polymorph B; and converting polymorph B into polymorph A; and (5) washing flupirtine maleate with a water-soluble ketone (preferably acetone) or an aqueous solution of a water-soluble alcohol (such as 10% to 50% water in a water-soluble alcohol (preferably isopropanol)).

While it is not intended to be bound to any theory, it is believed that the difference in impurity removal between crystallizing polymorph A directly from step (iii) and the above two-step crystallization is caused by fundamental crystal stacking differences between the two polymorphs. When polymorph A crystallizes directly from the solution in step (iii), the impurity ethyl (2,6-diaminopyridin-3-yl) carbamate maleate is sufficiently similar to the flupirtine maleate molecule that it can become incorporated in the lattice, and hence is not efficiently removed in the crystallization, while when polymorph B crystallizes from the solution in step (iii) said impurity is excluded from the growing crystal and remains in the mother liquor.
CLAIMS

1. Process for the preparation of flupirtine maleate comprising the steps of:
   (i) reacting 2-amino-3-nitro-6-(4-fluorobenzylamino) pyridine (ANFP) with one or more reducing agents to yield 2,3-diamino-6-(4-fluorobenzylamino) pyridine;
   (ii) reacting 2,3-diamino-6-(4-fluorobenzylamino) pyridine with X-C(0)OCH₂CH₃, wherein X is a leaving group, to yield ethyl {2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamate (flupirtine); and
   (iii) reacting flupirtine with maleic acid to yield flupirtine maleate,
wherein at least one of steps (i) and (ii) is carried out in an ester solvent.

2. The process of claim 1, wherein the ester solvent is selected from the group consisting of acetate esters and carbonate esters.

3. The process of claim 1, wherein the ester solvent is ethyl acetate.

4. The process of any one of claims 1 to 3, wherein the one or more reducing agents comprise dithionite.

5. The process of any one of claims 1 to 4, wherein step (i) is performed at a temperature of 20°C to 80°C, preferably at a temperature of 30°C to 50°C.

6. The process of claim 5, wherein the reaction mixture of step (i) is incubated at a temperature of 30°C to 40°C for 0.5 h to 1.5 h and then heated to a temperature of 40°C to 50°C over a period of time in the range of 15 min to 45 min.

7. The process of any one of claims 1 to 6, further comprising the step of (a) performing a solvent exchange after step (i) and before step (ii).

8. The process of claim 7, wherein step (a) comprises the following steps:
   (a1) removing the volatile components from the reaction mixture of step (i) and
   (a2) adding to the remaining residue one or more solvents in which step (ii) is to be carried out.

9. The process of claim 8, wherein step (i) is carried out in a water-soluble alcohol or a water-soluble nitrogen-containing solvent, and the one or more solvents in which step (ii) is to be carried is an ester solvent.
10. The process of claim 9, further comprising the step of adding water after step (al) and the step of (b) separating the water layer from the ester solvent layer after step (a2).

11. The process of any one of claims 1 to 3, wherein step (i) is performed by using a redox catalyst.

12. The process of claim 11, wherein the redox catalyst is used in an amount of 0.1% to 20% by weight, based on the amount of ANFP.

13. The process of any one of claims 1 to 12, wherein step (i) is performed by using a phase transfer catalyst.

14. The process of any one of claims 1 to 13, wherein the leaving group is selected from the group consisting of -Cl, -Br, -I, and a sulfonyl moiety.

15. The process of any one of claims 1 to 14, wherein in step (ii) a chemical base is added.

16. The process of any one of claims 1 to 15, wherein step (ii) is performed at a temperature of 20°C to 80°C, preferably at a temperature of 20°C to 55°C.

17. The process of any one of claims 1 to 16, wherein step (iii) is performed at a temperature of -10°C to 80°C, preferably at a temperature of 35°C to 45°C.

18. The process of any one of claims 1 to 17, wherein in step (iii) maleic acid is added as aqueous solution and is reacted with flupirtine in an ester solvent.

19. The process of any one of claims 1 to 18, further comprising the step of adding an oxygen scavenger agent in step (ii) and/or step (iii).

20. The process of any one of claims 1 to 19, further comprising the step of filtering the reaction mixture after step (i) and before step (ii) and/or after step (ii) and before step (iii).

21. The process of any one of claims 1 to 20, wherein in each of steps (i) to (iii) degassed solvents are used.
Figure 1

The diagram shows a chemical reaction involving the synthesis of a compound. The reaction starts with two starting materials and proceeds through several steps involving reagents such as HCl, isopropanol, and dioxane. The final products are:

- Crude flupirtine maleate (colored)
- Free flupirtine base
- Purified flupirtine maleate
Figure 2

\[
\begin{align*}
\text{Cl-Pyridine} + \text{F-Benzylamine} & \quad \xrightarrow{-\text{HCl}} \quad \text{F-Benzylamine} \\
\text{step (i)} & \quad \xrightarrow{\text{reducing agent}} \\
\text{step (ii)} & \quad \xrightarrow{\text{XC(O)OEt - HCl}} \\
\text{step (iii)} & \quad \xrightarrow{\text{maleic acid}} \\
\text{Crystallization without seeding} (\text{removal of impurity}) & \quad \xrightarrow{\text{water-soluble alcohol / H}_2\text{O}} \\
\text{Crystallization with seeding} & \quad \xrightarrow{\text{water-soluble alcohol / H}_2\text{O} + \text{crystals of pure polymorph A}} \\
\end{align*}
\]

- Crude Flupirtine Maleate
- Flupirtine Maleate Polymorph B
- Pure Flupirtine Maleate Polymorph A
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061650

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D213/75

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal , CHEM ABS Data, BEI LSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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| X        | DE 197 16 984 Al (ASTA MEDICA AG [DE]) 29 October 1998 (1998-10-29) cited in the application on claim 1 page 2, 11 lines 13-15 pages 6-7; examples 1-2 ----- /

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

13 September 2011

Date of mailing of the international search report

20/09/2011

Name and mailing address of the ISA/

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Guazzelli, Giuditta
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<td>PIPEKE A.J. ET AL.: &quot;Some new methods for preparing 2,3- and 3,4-di aminopyridine&quot;, JOURNAL OF HETEROCYCLIC CHEMISTRY, vol 23, 1986, pages 669-672, XP002607944, page 669, column 1, lines 1-5 scheme II; page 670, column 1; compounds 11, 14, 13 page 672, lines 16-28</td>
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