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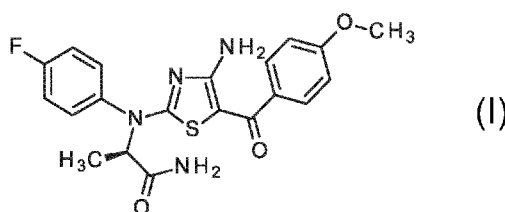
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(54) Title: MICROCRYSTALLINE FORMS OF (R)-2-(N-[4-AMINO-5-(4-METHOXYBENZOYL)THIAZOL-2-YL]-4-FLUOROANILINO)PROPANAMIDE AND PROCESSES FOR THEIR PREPARATION



(57) Abstract: The present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoroanilino)propanamide, (I), (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoroanilino)propanamide, and processes for their preparation, and pharmaceutical compositions comprising them.



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Microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and processes for their preparation

The present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, processes for their preparation, and pharmaceutical compositions comprising them.

BACKGROUND

Among the characteristics of crystalline Active Pharmaceutical Ingredients (APIs) their polymorphic form and particle size are the two most often mentioned. The latter directly determines the dissolution rate (and in turn bioavailability *in vivo*) according to the Noyes–Whitney equation (Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930–934). In order to improve the dissolution rates, APIs often undergo comminution during their manufacturing. One of the widely applied methods is jet-milling (M. Djokić et al., Chemical Engineering Research and Design 2014, 92 (3), 500-508; see also <http://dx.doi.org/10.1016/j.cherd.2013.09.011>). Unfortunately, due to mechanical stress induced by collisions between particles and walls of the chamber, it is possible that surface amorphization of the otherwise fully crystalline input material occurs (M. Djokić et al., Chemical Engineering Research and Design 2014, 92 (3), 500-508; see also <http://dx.doi.org/10.1016/j.cherd.2013.09.011>). The extent of amorphisation generated during processing is often unpredictable and varies between scales of used equipment. As those, even smallest, amounts of amorphous material can change the processing behavior and performance of API (S. Sheokand et al., Journal of Pharmaceutical Sciences 2014, 103, 2264-2276; see also <https://doi.org/10.1002/jps.24160>), it is critical to quantify the extent of amorphisation. Parameters influenced by amorphization: dissolution rate, apparent solubility, solid-state instability (re-crystallisation) and resulting change in dissolution properties over time (S. Sheokand et al., Journal of Pharmaceutical Sciences 2014, 103, 2264-2276; see also <https://doi.org/10.1002/jps.24160>). The quantification of degree of amorphisation remains a significant analytical challenge (S. Sheokand et al., Journal of Pharmaceutical Sciences 2014, 103, 2264-2276; see also <https://doi.org/10.1002/jps.24160>) and generally the partial amorphisation should be avoided.

The suitability of a given particle size distribution range for pharmaceutical development of a given API depends on a variety of parameters, including but not limited to the intended route of administration and the solubility properties of the respective API (see e.g. B. Y. Shekunov et al., Pharmaceutical Research 2007, 24 (2), 203. (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-

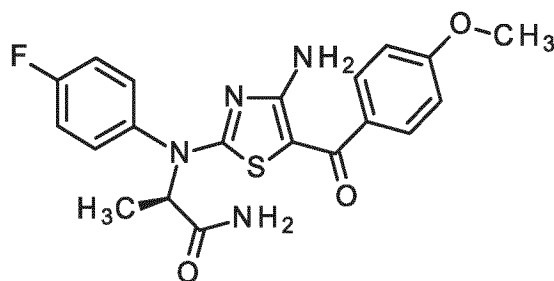
yl]-4-fluoro-anilino)propanamide requires comminution of particles to provide good bioavailability following e.g. oral administration through sufficient solubility and dissolution rate, which correlates with the particle surface and hence also particle size. Given the project specifics, a Particle Size Distribution (PSD) of x10 / x50 / x90: >0.3 / 1-8 / <20 µm was chosen as the target size distribution for micronised (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

During studies aimed at the identification of pharmaceutically useful forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, starting from macrocrystalline material, it was found that mechanical stress during jet-milling micronisation resulted in formation of a solid substance containing significant and varying proportions of amorphous material besides crystalline particles. As partial amorphisation poses a threat to chemical and physical stability of the drug substance, can cause a variability in solubility, dissolution rates and bioavailability and as the quantification of degree of amorphisation remains a significant analytical challenge (S. Sheokand et al., Journal of Pharmaceutical Sciences 2014, 103, 2264-2276; see also <https://doi.org/10.1002/jps.24160>), efforts were undertaken to provide sufficiently small particles with full crystallinity. Despite significant efforts in optimising the jet-milling process, it was not possible to eliminate crystallinity loss upon conducting said jet-milling process to give the desired particle size.

The present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention, processes for their preparation, and pharmaceutical compositions comprising them.

Prior art

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide is a chemical compound known to inhibit the zeta isoform of diacylglycerol kinase (DGKzeta) and is disclosed in the International patent application PCT/EP2021/060167, published as WO 2021/214019, as Example 62.2.



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

However, the state of the art does not describe methods of crystallising said compound (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide to yield crystalline particles of a size favourable for preparing solid pharmaceutical compositions which may in turn be used as drugs, nor does it disclose the resulting microcrystalline forms of said compound, or pharmaceutical compositions comprising them.

It has now been found, and this constitutes the basis of the present invention, that the abovementioned microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention, the processes for their preparation, and pharmaceutical compositions comprising them, have surprising and advantageous properties.

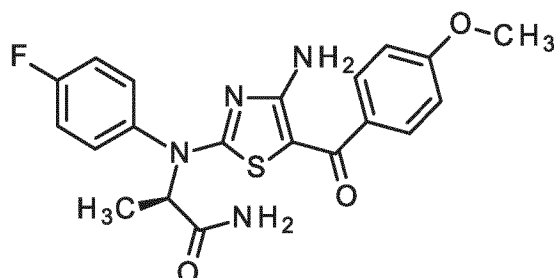
The microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention are, within the accuracy of the analytical methods used, void of amorphous material, feature particle size distributions in the desired range and show substantially improved dissolution properties as compared to macrocrystalline material of the same compound.

The processes for their preparation are robust, highly efficient, and deliver material of excellent chemical and enantiomeric purity. Besides, said processes resolve the risk of racemisation during alkylation of the intermediate [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone with (S)-2-bromopropanamide. The risk of racemisation in such alkylations involving a stereocentre as site of alkylation in alpha-position to a carbonyl group is known to the person skilled in the art. (see e.g. P. S. Dragovich et al., J. Med. Chem. 2003, 46, 4572; L. Chen et al., Organic Process Research & Development 2006, 10 (4), 838). The synthesis of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as disclosed in WO 2021/214019 proceeds via synthesis of rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, followed by an enantiomer separation by means of preparative chiral HPLC. For drug development purposes, such

enantiomer separation is unfavourable as it incurs cost and lengthens process times substantially.

5 DESCRIPTION of the INVENTION

In accordance with a first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

10 in which

the presence of amorphous forms is below 15 %,

and their particle size distribution is as follows: x10 is <5 µm, x50 is <10 µm, and x90 is <35 µm.

DEFINITIONS

15 Enantiomeric excess is frequently abbreviated ee and expressed in percent (%) and is derived from the proportion of the (R)- and (S)- enantiomer in a given mixture of the two enantiomers and is calculated as $ee = [(R)-(S) / (R)+(S)] \times 100$, rendering a racemic mixture as 0 % ee and a pure enantiomer as 100 % ee.

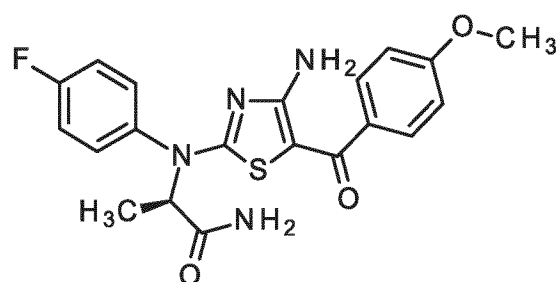
As used herein, the term “leaving group” means an atom or a group of atoms that is displaced
20 in a chemical reaction as stable species taking with it the bonding electrons. In particular, such a leaving group is selected from the group comprising: a halogen atom, in particular a fluorine atom, a chlorine atom, a bromine atom or an iodide atom, being displaced as halide, in particular fluoride, chloride, bromide or iodide; (methylsulfonyl)oxy, [(trifluoromethyl)sulfonyl]oxy, [(nonafluorobutyl)sulfonyl]oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy,
25 [(4-bromophenyl)sulfonyl]oxy, [(4-nitrophenyl)sulfonyl]oxy, [(2-nitrophenyl)sulfonyl]oxy, [(4-isopropylphenyl)sulfonyl]oxy, [(2,4,6-triisopropylphenyl)sulfonyl]oxy, [(2,4,6-trimethylphenyl)sulfonyl]oxy, [(4-*tert*-butylphenyl)sulfonyl]oxy and [(4-methoxyphenyl)sulfonyl]oxy.

As used herein, "microcrystalline" refers to fully crystalline solid forms featuring a particle size distribution in the ranges of x10 / x50 / x90: <5 / <10 / <35 μm , or <3 / 10-15 / <35 μm , or smaller, such as x10 / x50 / x90: <5 / <10 / <20 μm , particularly in the ranges x10 / x50 / x90: 0.3-4 / 4-10 / 10-20 μm , 0.5-2.5 / 3-7 / 8-20 μm , 1-4 / 4-8 / 12-18 μm , 1-2 / 4-5.5 / 10-18 μm , or >0.3 / 1-8 / <20 μm .

As used herein, "macrocrystalline" refers to fully crystalline solid forms featuring a particle size distribution in the range of x10 / x50 / x90: 3 / 10-15 / 35 μm , or larger.

The term "C₁-C₃-alkyl" means a linear or branched, saturated, monovalent hydrocarbon group having 1, 2 or 3 carbon atoms, e.g. a methyl, ethyl, propyl or isopropyl group.

In accordance with a second embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

in which

the presence of amorphous forms is below 15 %,

and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

In accordance with a third embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 15 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a fourth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 15 %,

- 5 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

In accordance with a fifth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

10 in which

the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

15

In accordance with a sixth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

in which

- 20 the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

In accordance with a seventh embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

25 in which

the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

30

In accordance with an eighth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 95 %,

5 the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

In accordance with a ninth embodiment of the first aspect, the present invention covers
10 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

15 and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

In accordance with a tenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

25 In accordance with an eleventh embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

30 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

In accordance with a twelfth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

- 5 and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

In accordance with a thirteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

10 anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

- 15 In accordance with a fourteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

- 20 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

In accordance with a fifteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

25 anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

In accordance with a sixteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

5 the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

In accordance with a seventeenth embodiment of the first aspect, the present invention covers
10 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

15 and their particle size distribution is as follows: x10 is in the range of 1 to 2 µm, x50 is in the range of 4 to 5.5 µm, and x90 is in the range of 10 to 18 µm.

In accordance with an eighteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

25 In accordance with a nineteenth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %,

30 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

In accordance with a twentieth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %,

- 5 and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

In accordance with a twenty-first embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

10 anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

- 15 In accordance with a twenty-second embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry,

- 20 and their particle size distribution is as follows: x10 is in the range of 1 to 2 µm, x50 is in the range of 4 to 5.5 µm, and x90 is in the range of 10 to 18 µm.

In accordance with a twenty-third embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

25 anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm.

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In accordance with a twenty-fourth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD,

and their particle size distribution is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

- 5 In accordance with a twenty-fifth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD,

- 10 and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a twenty-sixth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the presence of amorphous forms is below the detection limits of differential scanning calorimetry according to method DSC1,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

20

In accordance with a twenty-seventh embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 the presence of amorphous forms is below the detection limits of differential scanning calorimetry according to method DSC1,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

- 30 In accordance with a twenty-eighth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD according to method XRPD1,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a twenty-ninth embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD according to method XRPD1,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

Further embodiments of the first aspect of the present invention:

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

5 In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

10 and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8µm, and x90 is in the range of 12 to 18 µm.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

15 anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

20

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

25 and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

30 anilino)propanamide, in which

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

5 In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

10 and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

In accordance with a further embodiment of the first aspect, the present invention covers
15 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is
20 in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

In accordance with a further embodiment of the first aspect, the present invention covers
25 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is
30 in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 99 %,

- 5 the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

- 10 In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

- 15 and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers
20 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to

- 25 20 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 the presence of amorphous forms is below 2.5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

5 the presence of amorphous forms is below 2.5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

10 In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm .

15

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

their particle size distribution as determined according to method PSD2a is as follows: x50 is in the range of 4 to 5.5 μm .

20

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 their particle size distribution as determined according to method PSD4 is as follows: x50 is in the range of 4 to 8 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30

their particle size distribution as determined according to method PSD2a is as follows: x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

5 their particle size distribution as determined according to method PSD4 is as follows: x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the presence of amorphous forms is below 15 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 the presence of amorphous forms is below 10 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 the presence of amorphous forms is below 5 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %.

5

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry.

10

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 the presence of amorphous forms is below the detection limits of XRPD.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the presence of amorphous forms is below the detection limits of differential scanning calorimetry according to method DSC1.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25

the presence of amorphous forms is below the detection limits of XRPD according to method XRPD1.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 99 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 98 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 95 %.

In accordance with a further embodiment of the first aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 90 %.

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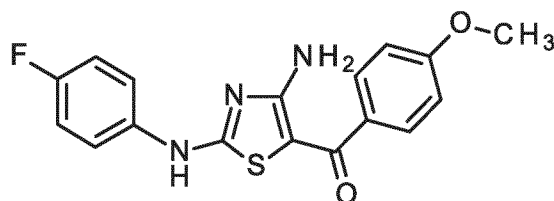
In a particular further embodiment of the first aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading "further embodiments of the first aspect of the present invention".

- 25 The present invention covers any sub-combination within any embodiment or aspect of the present invention of microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, processes for their preparation, and pharmaceutical compositions comprising them.

- 30 The present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention, as described in the Experimental Section herein.

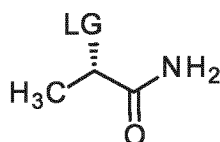
In accordance with a second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 5 i. allowing an intermediate compound of formula (II)



(II)

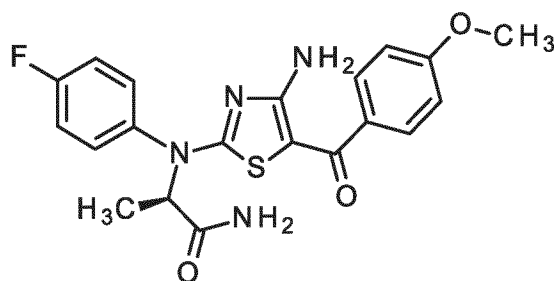
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



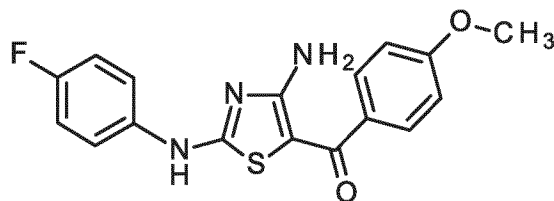
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 15 ii. dissolving the crude product resulting from step i. in a solvent or solvent mixture,
 iii. bringing the solution resulting from step ii. together with an antisolvent, and
 iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

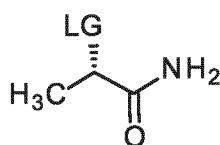
In accordance with a second embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

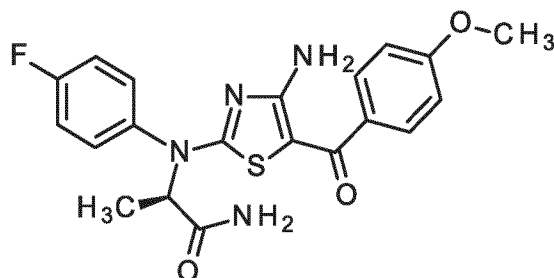
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



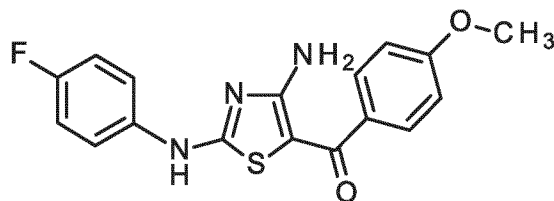
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- ii. dissolving the crude product resulting from step i. in acetone containing water in a range from 0 % to 30 % (v/v),
- iii. bringing the solution resulting from step ii. together with water, and
- iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

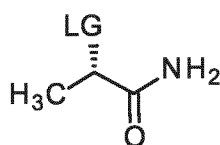
In accordance with a third embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

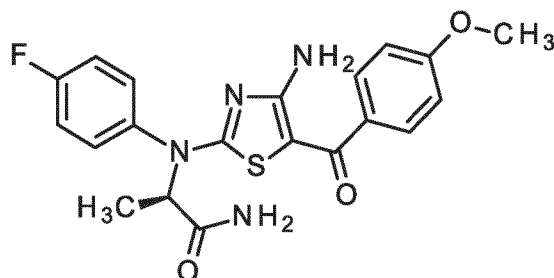
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- ii. dissolving the crude product resulting from step i. in a dipolar aprotic and/or protic solvent with subsequent optional filtering,
 iii. addition of the solution or filtrate resulting from step ii. to an antisolvent, and
 iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

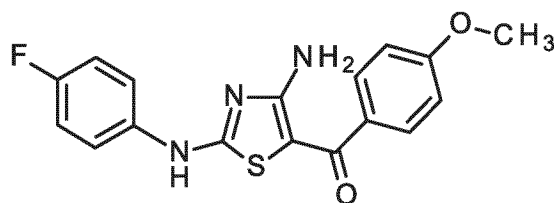
In accordance with a fourth embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- iii. adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a dipolar aprotic and/or protic solvent to an antisolvent, and
- iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

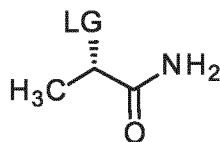
In accordance with a fifth embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

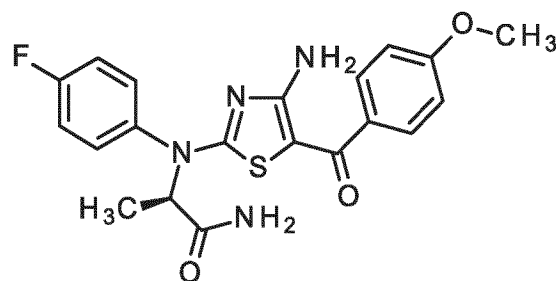


(III)

in which LG is a leaving group as defined *supra*,

in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

thereby giving



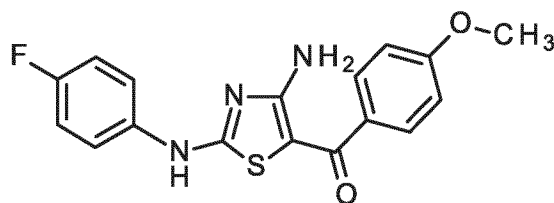
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- ii. dissolving the crude product resulting from step (i) in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone with subsequent filtering,
- iii. addition of the filtrate to water over a time in the range of 20 minutes and 1.5 hours, at a temperature in the range of 0°C to 20°C, and
- iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

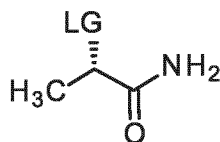
In accordance with a sixth embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

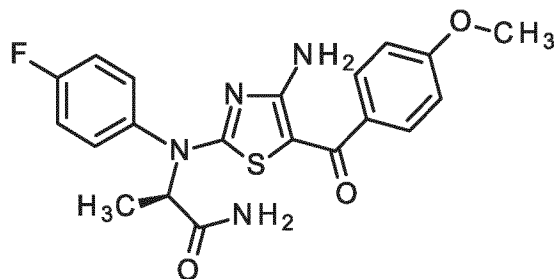


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



5

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

ii. dissolving the crude product resulting from step (i) in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone with subsequent filtering,

10 iii. addition of the filtrate to water over a time range of 30 minutes and 1 hour, at a temperature in the range of 4°C to 10°C, and

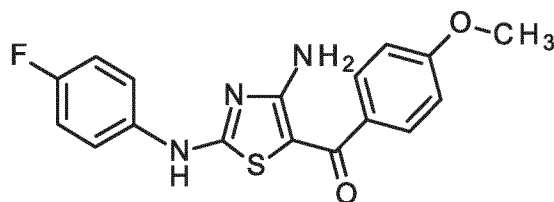
iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

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In accordance with a seventh embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

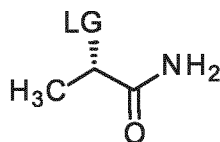
i. allowing an intermediate compound of formula (II)



20

(II)

to react with an intermediate compound of formula (III)

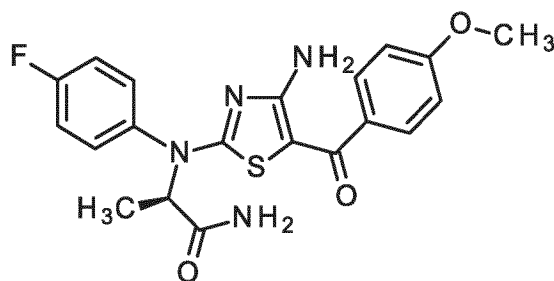


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

ii. dissolving the crude product resulting from step (i) in a mixture of acetone and water in a ratio in the range of 8:1(v/v) to 12:1 (v/v) in favour of acetone with subsequent filtering,

iii. addition of the filtrate to water over a time range of 30 minutes and 1 hour, at a temperature in the range of 4°C to 10°C, and

iv. isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with an eighth embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

iii. adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone to water over a time range of 30 minutes and 1 hour, at a temperature in the range of 4°C to 10°C, and

iv. isolation and drying of the resulting precipitate,
to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

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Further embodiments of the second aspect of the present invention:

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
10 2-yl]-4-fluoro-anilino)propanamide, in which
their particle size distribution is as follows: x10 is in the range of 1 to 2 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
15 2-yl]-4-fluoro-anilino)propanamide, in which
their particle size distribution is as follows: x50 is in the range of 4 to 5.5 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
20 2-yl]-4-fluoro-anilino)propanamide, in which
their particle size distribution is as follows: x50 is in the range of 4 to 8 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
25 2-yl]-4-fluoro-anilino)propanamide, in which
their particle size distribution is as follows: x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
30 2-yl]-4-fluoro-anilino)propanamide, in which
their particle size distribution is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 their particle size distribution as determined according to method PSD2a is as follows: x50 is in the range of 4 to 5.5 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 their particle size distribution as determined according to method PSD4 is as follows: x50 is in the range of 4 to 8 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 their particle size distribution as determined according to method PSD2a is as follows: x90 is in the range of 10 to 18 μm .
- 30

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

5 their particle size distribution as determined according to method PSD4 is as follows: x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

20 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 15 %.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 10 %.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
5 2-yl]-4-fluoro-anilino)propanamide, in which
the presence of amorphous forms is below 5 %.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
10 2-yl]-4-fluoro-anilino)propanamide, in which
the presence of amorphous forms is below 2.5 %.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
15 2-yl]-4-fluoro-anilino)propanamide, in which
the presence of amorphous forms is below the detection limits of differential scanning calorimetry.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
20 2-yl]-4-fluoro-anilino)propanamide, in which
the presence of amorphous forms is below the detection limits of XRPD.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-
25 2-yl]-4-fluoro-anilino)propanamide, in which
the presence of amorphous forms is below the detection limits of differential scanning calorimetry according to method DSC1.

30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD according to method XRPD1.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 99 %.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 98 %.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 95 %.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 90 %.

30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a chlorine atom, a bromine atom or an iodine atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, and [(4-methoxyphenyl)sulfonyl]oxy.

- 5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a chlorine atom, a bromine atom or an iodine atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy and [(4-methylphenyl)sulfonyl]oxy.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a chlorine atom.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a [(4-methylphenyl)sulfonyl]oxy group.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a bromine atom or a [(4-methylphenyl)sulfonyl]oxy group.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step i. is a bromine atom.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

10 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 step i. is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 step i. is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate selected from sodium carbonate, potassium carbonate and cesium carbonate, an alkali bicarbonate selected from sodium bicarbonate, potassium bicarbonate, and cesium

bicarbonate, and an alkali phosphate selected from sodium phosphate, potassium phosphate and cesium phosphate.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

10 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium
15 phosphate.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 step i. is carried out in the presence of a base selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which
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step i. is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the second aspect, the present invention covers
30 methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of 1.5 to 3 equivalents of potassium phosphate.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in the presence of 2 to 6 equivalents of potassium carbonate.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 step i. is carried out at a temperature in the range of 0°C to 100°C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 step i. is carried out at a temperature in the range of 20°C to 90°C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 step i. is carried out at a temperature in the range of 40°C to 80°C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 step i. is carried out at a temperature in the range of 50°C to 70°C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 step i. is carried out at a temperature in the range of 40°C to 80°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step i. is carried out at a temperature in the range of 50°C to 70°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 step i. is carried out at a temperature in the range of 40°C to 80°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 step i. is carried out at a temperature in the range of 50°C to 70°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step i. is carried out in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 step i. is carried out in a solvent selected from N,N-dimethylformamide, acetonitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol in a range of 5:1 (v/v) to 1:5 (v/v).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in a solvent selected from N,N-dimethylformamide and acetonitrile.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in N,N-dimethylformamide as a solvent.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out in acetonitrile as a solvent.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 step i. is carried out over a time in the range of 30 minutes to 24 hours.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 step i. is carried out over a time in the range of 30 minutes to 6 hours.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 step i. is carried out over a time in the range of 30 minutes to 2 hours.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step i. is carried out over a time in the range of 1 to 2 hours.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 step ii. is carried out in one or more dipolar aprotic and/or polar solvent, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step ii. is carried out in one or more solvents selected from dimethylsulfoxide, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, N,N-dimethylformamide, 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 step ii. is carried out in one or more solvents selected from 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step ii. is carried out in one or more solvents selected from isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step ii. is carried out in one or more solvents selected from acetonitrile, diethylketone, methylethylketone, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-10 2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in one or more solvents selected from acetonitrile, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-15 2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-20 2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water in a ratio in the range of 5:1 (v/v) to 20:1 (v/v) in favour of acetone.

25 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water in a ratio in the range of 6:1 (v/v) to 15:1 (v/v) in favour of acetone.

30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water in a ratio in the range of 6:1 (v/v) to 12:1 (v/v) in favour of acetone.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone.

10 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step ii. is carried out in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 10:1 (v/v) in favour of acetone.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 6:1 to 20:1 (w/w; solvent : compound).

25 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 8:1 to 15:1 (w/w; solvent : compound).

30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 10:1 (w/w) to 14:1 (w/w) in favour of the solvent.

- 5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 11:1 (w/w) to 12:1 (w/w) in favour of
10 the solvent.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 8:1 (w/w) to 15:1 (w/w) in favour of the mixture of acetone and water.

- In accordance with a further embodiment of the second aspect, the present invention covers
20 methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 10:1 (w/w) to 14:1 (w/w) in favour of the mixture of acetone and water.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step ii. is in the range of 11:1 (w/w) to 12:1 (w/w) in favour of the mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the solvent in step iii. is one or more dipolar aprotic and/or polar solvent, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is one or more solvents selected from dimethylsulfoxide, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, N,N-dimethylformamide, 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is one or more solvents selected from 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is one or more solvents selected from isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is one or more solvents selected from acetonitrile, diethylketone, methylethylketone, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the solvent in step iii. is one or more solvents selected from acetonitrile, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is a mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is a mixture of acetone and water in a ratio in the range of 5:1 (v/v) to 20:1 (v/v) in favour of acetone.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is a mixture of acetone and water in a ratio in the range of 6:1 (v/v) to 15:1 (v/v) in favour of acetone.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the solvent in step iii. is a mixture of acetone and water in a ratio in the range of 6:1 (v/v) to 12:1 (v/v) in favour of acetone.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the solvent in step iii. is a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the solvent in step iii. is a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 10:1 (v/v) in favour of acetone.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 6:1 to 20:1 (w/w; solvent : compound).

20 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 8:1 to 15:1 (w/w; solvent : compound).

25 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 10:1 (w/w) to 14:1 (w/w) in favour of the solvent.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 11:1 (w/w) to 12:1 (w/w) in favour of the solvent.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 8:1 (w/w) to 15:1 (w/w) in favour of the mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 10:1 (w/w) to 14:1 (w/w) in favour of the mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in the solution employed in step iii. is in the range of 11:1 (w/w) to 12:1 (w/w) in favour of the mixture of acetone and water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is water, or a mixture of water with one or more organic solvents selected from the group comprising methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, acetone, 1,4-dioxane or 2-methyltetrahydrofuran.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the antisolvent in step iii. is hexane, cyclohexane, n-heptane, ethyl acetate, or a mixture thereof with one or more solvents selected from the group comprising ethyl acetate, isopropyl acetate, di-ethyl ether, di-isopropyl ether or methyl-tert-butyl ether.

- 10 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is water, or a mixture of water with one or more organic solvents selected from the group comprising methanol, ethanol, isopropanol, tetrahydrofuran and acetonitrile.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 the antisolvent in step iii. is hexane, cyclohexane, n-heptane, ethyl acetate, or a mixture thereof with one or more solvents selected from the group comprising isopropyl acetate, di-ethyl ether, di-isopropyl ether or methyl-tert-butyl ether.

- 25 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is water, or a mixture of water with one or more organic solvents selected from the group comprising methanol, ethanol and isopropanol.

- 30 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is hexane, cyclohexane, n-heptane or ethyl acetate.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is water.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the antisolvent in step iii. is water and no other antisolvent.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the antisolvent in step iii. is in the range of 1:1 to 1:100 (w/w) in favour of the antisolvent.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the antisolvent in step iii. is in the range of 1:2 to 1:50 (w/w) in favour of the antisolvent.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the antisolvent in step iii. is in the range of 1:4 to 1:40 (w/w) in favour of the antisolvent.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the antisolvent in step iii. is in the range of 1:6 to 1:40 (w/w) in favour of the antisolvent.

5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the antisolvent in step iii. is in the range of 1:10 to 1:30 (w/w) in favour of the antisolvent.

10 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the water used as an antisolvent in step iii. is in the range of 1:4 to 1:40 (w/w) in favour of
15 the water.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the water used as an antisolvent in step iii. is in the range of 1:6 to 1:40 (w/w) in favour of the water.

In accordance with a further embodiment of the second aspect, the present invention covers
25 methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and the water used as an antisolvent in step iii. is in the range of 1:10 to 1:30 (w/w) in favour of the water.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent employed in step ii. and the antisolvent in step iii. is in the range of 1:10 to 10:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent employed in step ii. and the antisolvent in step iii. is in the range of 1:6 to 6:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent employed in step ii. and the antisolvent in step iii. is in the range of 1:4 to 4:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent employed in step ii. and the antisolvent in step iii. is in the range of 1:3 to 2:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent employed in step ii. and the antisolvent in step iii. is in the range of 1:2 to 1:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent used in the solution and the antisolvent in step iii. is in the range of 1:10 to 10:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent used in the solution and the antisolvent in step iii. is in the range of 1:6 to 6:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent used in the solution and the antisolvent in step iii. is in the range of 1:4 to 4:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent used in the solution and the antisolvent in step iii. is in the range of 1:3 to 2:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of solvent used in the solution and the antisolvent in step iii. is in the range of 1:2 to 1:1 (v/v; solvent : antisolvent).

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step iii. is carried out over a time in the range of 20 minutes to 2 hours at a temperature in the range of 0°C to 20 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 step iii. is carried out over a time in the range of 20 minutes to 1.5 hours at a temperature in the range of 0°C to 20 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 step iii. is carried out over a time in the range of 30 minutes to 1 hour at a temperature in the range of 2°C to 15 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step iii. is carried out over a time in the range of 30 minutes to 1 hour at a temperature in the range of 4°C to 10 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 step iii. is carried out over a time in the range of 30 to 45 minutes at a temperature in the range of 2°C to 15 °C.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step iii. is carried out over a time in the range of 35 to 40 minutes at a temperature in the range of 4°C to 10 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 20 minutes to 2 hours at a temperature in the range of 0°C to 20 °C.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 20 minutes to 1.5 hours at a temperature in the range of 0°C to 20 °C.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 30 minutes to 1 hour at a temperature in the range of 2°C to 15 °C.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 30 minutes to 1 hour at a temperature in the range of 2°C to 15 °C.

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In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 30 minutes to 1 hour at a temperature in the range of 4°C to 10 °C.

- 5 In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 30 minutes to 1 hour at

- 10 a temperature in the range of 4°C to 10 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 30 to 45 minutes at a temperature in the range of 2°C to 15 °C.

In accordance with a further embodiment of the second aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in step iii. is carried out over a time in the range of 35 to 40 minutes at a temperature in the range of 4°C to 10 °C.

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In a particular further embodiment of the second aspect, the present invention covers combinations of two or more of the above mentioned embodiments under the heading "further embodiments of the second aspect of the present invention".

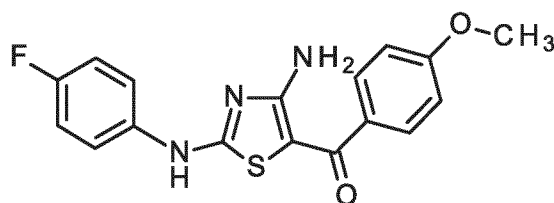
- 30 The present invention covers any sub-combination within any embodiment or aspect of the present invention of microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, processes for their preparation, and pharmaceutical compositions comprising them.

The present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention, said methods comprising the steps as described in the Experimental Section herein.

5

In accordance with a third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

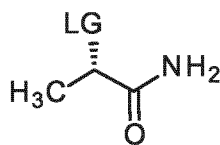
allowing an intermediate compound of formula (II)



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(II)

to react with an intermediate compound of formula (III)

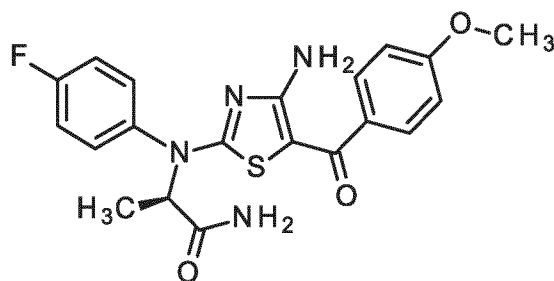


(III)

15

in which LG is a leaving group as defined *supra*,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

dissolving the resulting crude product in a solvent or solvent mixture, followed by

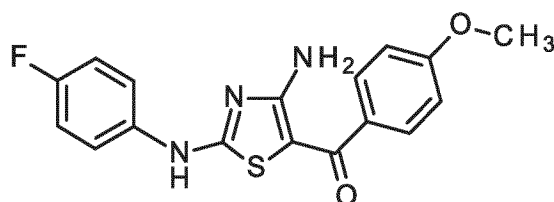
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bringing the resulting solution together with an antisolvent, followed by

isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

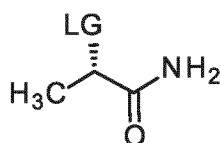
- 5 In accordance with a second embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of
- allowing an intermediate compound of formula (II)



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(II)

to react with an intermediate compound of formula (III)

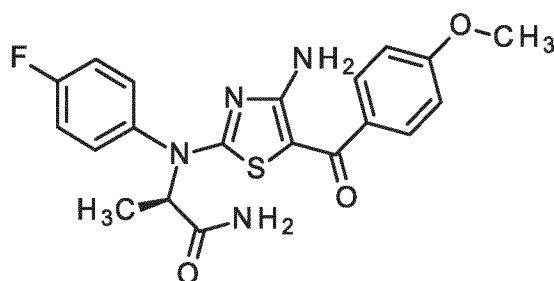


(III)

in which LG is a leaving group as defined *supra*,

15

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

dissolving the resulting crude product in acetone containing water in a range from 0 % to 30 % (v/v), followed by

20

bringing the resulting solution together with water, followed by isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with a third embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a solvent or solvent mixture, followed by

bringing the resulting solution together with an antisolvent, followed by

isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with a fourth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in acetone containing water in a range from 0 % to 30 % (v/v), followed by

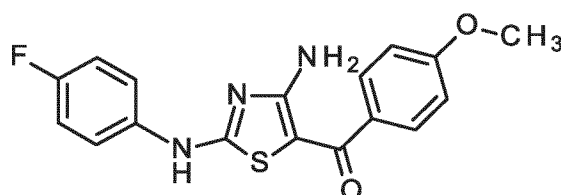
bringing the resulting solution together with water, followed by

isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

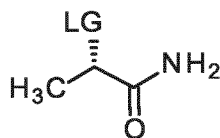
In accordance with a fifth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

1) allowing an intermediate compound of formula (II)



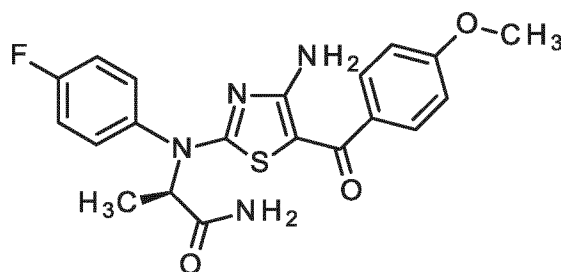
(II)

to react with an intermediate compound of formula (III)



(III)

- 5 in which LG is a leaving group as defined *supra*,
thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in a solvent,
- 10 3) creating a supersaturation,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,
- 5) followed by one or more of the sub-steps selected from
- 15 a. cooling
- b. addition of antisolvent, and
- c. evaporating solvent,
- 6) isolation and drying of the resulting precipitate,

20 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

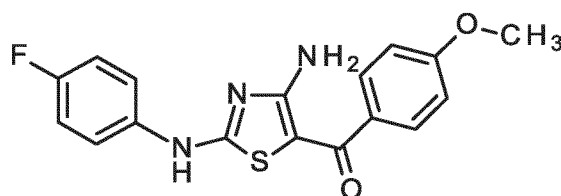
In accordance with a sixth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a solvent,
- 3) creating a supersaturation,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,
- 5) followed by one or more of the sub-steps selected from
 - a. cooling
 - b. addition of antisolvent, and
 - c. evaporating solvent,
- 6) isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

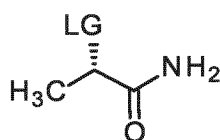
- 15 In accordance with a seventh embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

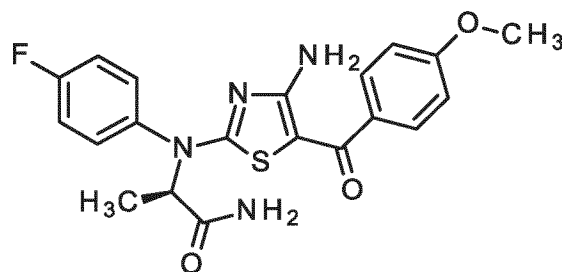
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

2) dissolving the crude product resulting from step 1) in a dipolar aprotic and/or protic solvent with optional filtering,

5 3) creating a supersaturation via one or more of the sub-steps selected from

a. cooling

b. addition of antisolvent, and

c. evaporating solvent,

10 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,

5) followed by one or more of the sub-steps selected from

a. cooling

b. addition of antisolvent, and

15 c. evaporating solvent,

6) isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

20 In accordance with an eighth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a dipolar aprotic and/or protic solvent with optional filtering,

25 3) creating a supersaturation via one or more of the sub-steps selected from

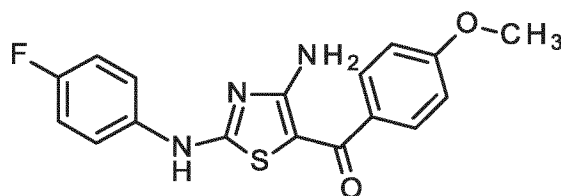
a. cooling

b. addition of antisolvent, and

- c. evaporating solvent,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,
- 5) followed by one or more of the sub-steps selected from
- cooling
 - addition of antisolvent, and
 - evaporating solvent,
- 6) isolation and drying of the resulting precipitate,
- 10 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

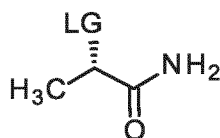
In accordance with a ninth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

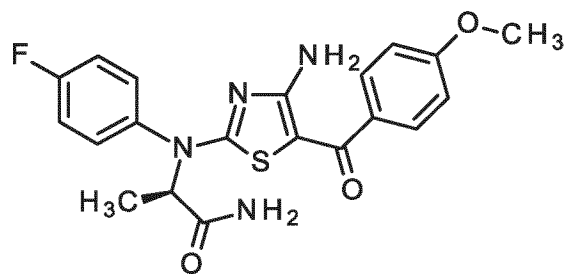
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in a dipolar aprotic and/or protic solvent with optional filtering,
- 3) creating a supersaturation via cooling,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,
- 5) followed by
 - a. cooling, followed by
 - b. addition of antisolvent,
- 6) isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with a tenth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

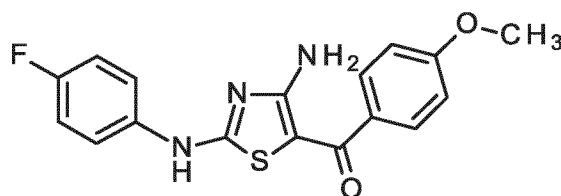
- 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a dipolar aprotic and/or protic solvent with optional filtering,
- 3) creating a supersaturation via cooling,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,
- 5) followed by
 - a. cooling, followed by
 - b. addition of antisolvent,

6) isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

5 In accordance with an eleventh embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

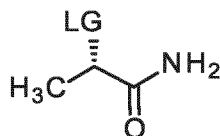
1) allowing an intermediate compound of formula (II)



10

(II)

to react with an intermediate compound of formula (III)



(III)

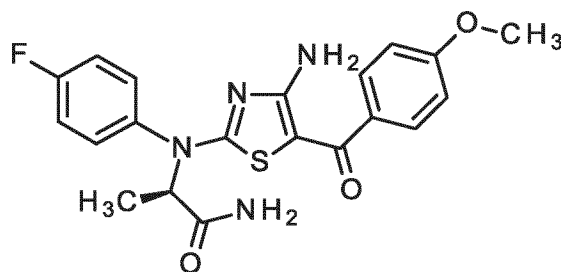
in which LG is a leaving group as defined *supra*,

15

in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

20

thereby giving

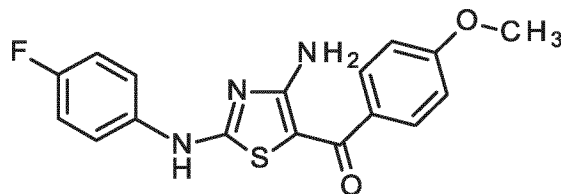


(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in acetone containing water in the range from 10 to 30 % v/v, with optional filtering,
 - 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 5°C to 30°C,
 - 5 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, water, at least one surfactant and at least two polymers,
 - 5) followed by
 - a. cooling, followed by
 - 10 b. addition of water,
 - 6) isolation and drying of the resulting precipitate,
- to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.
- 15 In accordance with a twelfth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of
- 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in acetone containing water in the range from 10 to 30 % v/v, with optional filtering,
 - 20 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 5°C to 30°C,
 - 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, water, at least one surfactant and at least two polymers,
 - 25 5) followed by
 - a. cooling, followed by
 - b. addition of water,
 - 6) isolation and drying of the resulting precipitate,
- 30 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

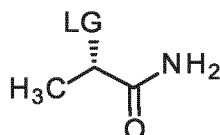
In accordance with a thirteenth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

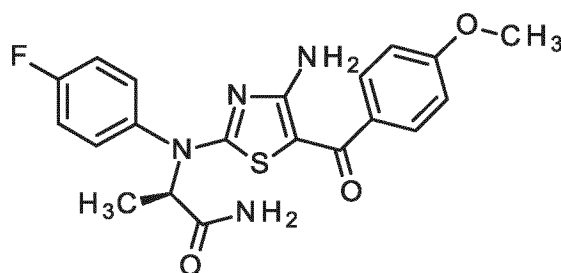


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 15°C to 25°C,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (5 – 20 % w/w), water (60

– 90 % w/w), at least one surfactant (0.05-1 % w/w) and at least two polymers (0.5-15 % w/w each), wherein the quantity of said nanosuspension is in the range of 0.1 to 20 % w/w of the supersaturated solution resulting from step 3),

5) followed by

- 5 a. cooling, the reduction of the temperature being in the range from 5°C to 25°C, followed by
- b. addition of water,

6) isolation and drying of the resulting precipitate,

10 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with a fourteenth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

15 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C, with optional filtering,

3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 15°C to 25°C,

20 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (5 – 20 % w/w), water (60 – 90 % w/w), at least one surfactant (0.05-1 % w/w) and at least two polymers (0.5-15 % w/w each), wherein the quantity of said nanosuspension is in the range of 0.1 to 20 % w/w of the supersaturated solution resulting from step 3),

25 5) followed by

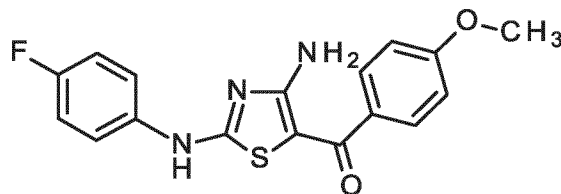
- a. cooling, the reduction of the temperature being in the range from 5°C to 25°C, followed by
- b. addition of water,

6) isolation and drying of the resulting precipitate,

30 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

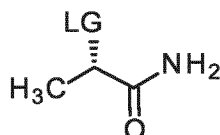
In accordance with an fifteenth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

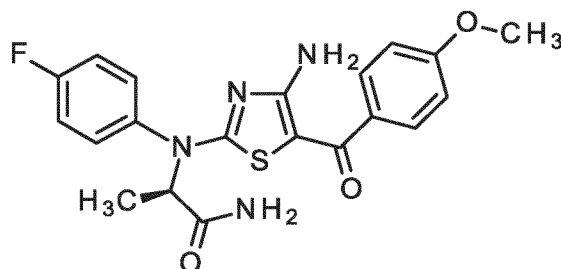


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 15°C to 25°C,

- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (5 – 20 % w/w), water (60 – 90 % w/w), at least one surfactant (0.05-1 % w/w) and at least two polymers (independently from each other 0.5-15 % w/w each), wherein
- 5 the at least one surfactant comprises an alkali salt of a C₈-C₂₀-alkylsulfuric acid, and the at least two polymers comprise hydroxypropylcellulose and polyvinylpyrrolidone, and wherein the quantity of said nanosuspension is in the range of 1 to 6 % w/w of the supersaturated solution resulting from step 3),
- 10 5) followed by
- a. cooling the reduction of the temperature being in the range from 5°C to 25°C, followed by
- b. addition of water,
- 6) isolation and drying of the resulting precipitate,
- 15 to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with an sixteenth embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said methods comprising the steps of

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- 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 15°C to 25°C,
- 25 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (5 – 20 % w/w), water (60 – 90 % w/w), at least one surfactant (0.05-1 % w/w) and at least two polymers (independently from each other 0.5-15 % w/w each), wherein
- 30 the at least one surfactant comprises an alkali salt of a C₈-C₂₀-alkylsulfuric acid, and the at least two polymers comprise hydroxypropylcellulose and polyvinylpyrrolidone,

and wherein the quantity of said nanosuspension is in the range of 1 to 6 % w/w of the supersaturated solution resulting from step 3),

5) followed by

a. cooling the reduction of the temperature being in the range from 5°C to 25°C,
followed by

b. addition of water,

6) isolation and drying of the resulting precipitate,

to give microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

Further embodiments of the third aspect of the present invention:

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which their particle size distribution is as follows: x10 is in the range of 1 to 2 µm.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which their particle size distribution is as follows: x50 is in the range of 4 to 5.5 µm.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which their particle size distribution is as follows: x50 is in the range of 4 to 8 µm.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which their particle size distribution is as follows: x90 is in the range of 10 to 18 µm.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 their particle size distribution is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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their particle size distribution as determined according to method PSD2a is as follows: x50 is in the range of 4 to 5.5 μm .

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

their particle size distribution as determined according to method PSD4 is as follows: x50 is in the range of 4 to 8 μm .

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

5 their particle size distribution as determined according to method PSD2a is as follows: x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 their particle size distribution as determined according to method PSD4 is as follows: x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 15 %.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 10 %.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 5 %.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below 2.5 %.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 the presence of amorphous forms is below the detection limits of XRPD.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry according to method DSC1.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the presence of amorphous forms is below the detection limits of XRPD according to method XRPD1.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 99 %.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 98 %.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 95 %.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide has an enantiomeric excess of at least 90 %.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a chlorine atom, a bromine atom or an iodine atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy, [(4-methylphenyl)sulfonyl]oxy, [(4-bromophenyl)sulfonyl]oxy, and [(4-methoxyphenyl)sulfonyl]oxy.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a chlorine atom, a bromine atom or an iodine atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy and [(4-methylphenyl)sulfonyl]oxy.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a chlorine atom.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a [(4-methylphenyl)sulfonyl]oxy group.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a bromine atom or a [(4-methylphenyl)sulfonyl]oxy group.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-

5 2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in step 1) is a bromine atom.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-

10 2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-

15 2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 step 1) is carried out in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

30 step 1) is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step 1) is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 step 1) is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate selected from sodium carbonate, potassium carbonate and cesium carbonate, an alkali bicarbonate selected from sodium bicarbonate, potassium bicarbonate, and cesium bicarbonate, and an alkali phosphate selected from sodium phosphate, potassium phosphate and cesium phosphate.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step 1) is carried out in the presence of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 step 1) is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

- 30 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out in the presence of a base selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step 1) is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 step 1) is carried out in the presence of 1.5 to 3 equivalents of potassium phosphate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 step 1) is carried out in the presence of 2 to 6 equivalents of potassium carbonate.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step 1) is carried out at a temperature in the range of 0°C to 100°C.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 step 1) is carried out at a temperature in the range of 20°C to 90°C.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 step 1) is carried out at a temperature in the range of 40°C to 80°C.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out at a temperature in the range of 50°C to 70°C.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out at a temperature in the range of 40°C to 80°C, optionally followed by

10 lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 step 1) is carried out at a temperature in the range of 50°C to 70°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step 1) is carried out at a temperature in the range of 40°C to 80°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step 1) is carried out at a temperature in the range of 50°C to 70°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

30 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol.

- 5 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out in a solvent selected from N,N-dimethylformamide, acetonitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol in a range of

- 10 5:1 (v/v) to 1:5 (v/v).

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 step 1) is carried out in a solvent selected from N,N-dimethylformamide and acetonitrile.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step 1) is carried out in N,N-dimethylformamide as a solvent.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 step 1) is carried out in acetonitrile as a solvent.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step 1) is carried out over a time in the range of 30 minutes to 24 hours.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out over a time in the range of 30 minutes to 6 hours.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out over a time in the range of 30 minutes to 2 hours.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 1) is carried out over a time in the range of 1 to 2 hours.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 step 2) is carried out in one or more dipolar aprotic and/or polar solvent, optionally mixed with water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

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step 2) is carried out in one or more solvents selected from dimethylsulfoxide, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, N,N-dimethylformamide, 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

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In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 2) is carried out in one or more solvents selected from 1,2-dimethoxyethane, methanol, ethanol, n-propanol, isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-methyltetrahydrofuran, optionally mixed with water.

- 5 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

step 2) is carried out in one or more solvents selected from isopropanol, tetrahydrofuran, acetonitrile, diethylketone, methylethylketone, acetone, 1,4-dioxane and 2-
10 methyltetrahydrofuran, optionally mixed with water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 step 2) is carried out in one or more solvents selected from acetonitrile, diethylketone, methylethylketone, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 step 2) is carried out in one or more solvents selected from acetonitrile, acetone and 1,4-dioxane, optionally mixed with water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 step 2) is carried out in a mixture of acetone and water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 step 2) is carried out in a mixture of acetone and water, the acetone containing water in the range from 0 to 50 % v/v.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 step 2) is carried out in a mixture of acetone and water, the acetone containing water in the range from 10 to 30 % v/v.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 step 2) is carried out in a mixture of acetone and water, the acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 4:1 to 10:1 (w/w; solvent : compound).

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 4:1 to 8:1 (w/w; solvent : compound).

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 5:1 (w/w) to 7:1 (w/w) in favour of the solvent.
- 30

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

5 the ratio of the solvent and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 5.5:1 (w/w) to 6:1 (w/w) in favour of the solvent.

10 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 4:1 (w/w) to 8:1 (w/w) in favour of the mixture of acetone and water.

15 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 5:1 (w/w) to 7:1 (w/w) in favour of the mixture of acetone and water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 the ratio of the mixture of acetone and water and (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed in step 2) is in the range of 5.5:1 (w/w) to 6:1 (w/w) in favour of the mixture of acetone and water.

30 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by adding an antisolvent.

5

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by evaporating solvent.

10

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling, the reduction of the temperature being in the range from 5°C to 30°C.

15

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling, the reduction of the temperature being in the range from 15°C to 25°C.

20

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling, the reduction of the temperature being in the range from 5°C to 30°C, and in which the solvent is acetone containing water in the range from 10 to 30 % v/v.

25

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling, the reduction of the temperature being in the range from 15°C to 25°C, and in which the solvent is acetone containing water in the range from 10 to 30 % v/v.

30

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-

2-yl]-4-fluoro-anilino)propanamide, in which creating of a supersaturation in step 3) is accomplished by cooling, the reduction of the temperature being in the range from 15°C to 25°C, and in which the solvent is acetone containing water in the range from 10 to 30 % v/v.

5

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) comprises (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a range
10 from 5 to 20 % w/w.

15

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the antisolvent in the nanosuspension employed in
step 4) is water.

20

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) comprises
water in a range from 60 to 90 % w/w.

25

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) comprises
at least one surfactant in a range from 0.05 to 1 % w/w.

30

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) contains
one surfactant in a range from 0.05 to 1 % w/w.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) contains

one surfactant in a range from 0.05 to 1 % w/w, and in which said surfactant is an alkali salt of a C₈-C₂₀-alkylsulfuric acid.

5 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) contains one surfactant in a range from 0.05 to 1 % w/w, and in which said surfactant is a sodium or potassium salt of a C₁₀-C₁₆-alkylsulfuric acid.

10 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) contains one surfactant in a range from 0.05 to 1 % w/w, and in which said surfactant is sodium dodecyl sulfate.

15

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) comprises at least two polymers, independently from each other in a range from 0.5 to 15 % w/w.

20

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) comprises at least two polymers, independently from each other in a range from 0.5 to 15 % w/w, in which
25 one polymer is hydroxypropyl cellulose and one polymer is polyvinylpyrrolidone.

30

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the nanosuspension employed in step 4) contains two polymers, independently from each other in a range from 0.5 to 15 % w/w, in which one polymer is hydroxypropyl cellulose and one polymer is polyvinylpyrrolidone.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-

2-yl]-4-fluoro-anilino)propanamide, in which the quantity of the nanosuspension employed in step 4) is in the range of 0.1 to 20 % w/w of the supersaturated solution resulting from step 3).

5 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the quantity of the nanosuspension employed in step 4) is in the range of 0.25 to 10 % w/w of the supersaturated solution resulting from step 3).

10 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the quantity of the nanosuspension employed in step 4) is in the range of 1 to 6 % w/w of the supersaturated solution resulting from step 3).

15 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the quantity of the nanosuspension employed in step 4) is in the range of 2 to 4 % w/w of the supersaturated solution resulting from step 3).

20 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which the quantity of the nanosuspension employed in step 4) is in the range of 2.5 to 3.0 % w/w of the supersaturated solution resulting from step 3).

25 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which step 5) is accomplished by cooling, followed by the addition of an antisolvent.

30 In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which step 5) is accomplished by cooling, followed by the addition of water.

In accordance with a further embodiment of the third aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which step 5) is accomplished by cooling, the reduction of the temperature being in the range from 5°C to 25°C, followed by the addition of water.

5

The present invention covers any sub-combination within any embodiment or aspect of the present invention of microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, processes for their preparation, and pharmaceutical compositions comprising them.

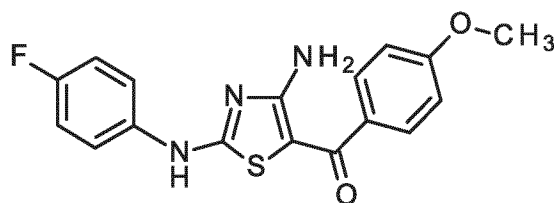
10

The present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention, said methods comprising the steps as described in the Experimental Section herein.

15

In accordance with a fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide said methods comprising the step of

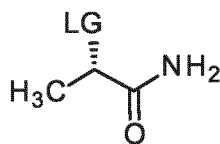
allowing an intermediate compound of formula (II)



20

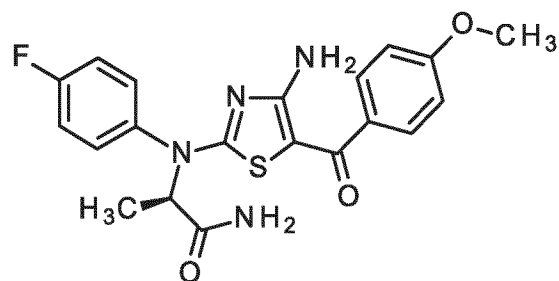
(II)

to react with an intermediate compound of formula (III)



(III)

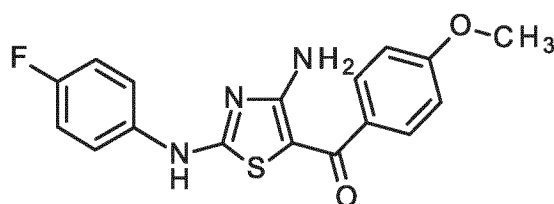
25 in which LG is a leaving group as defined *supra*,
thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

In accordance with a second embodiment of the fourth aspect, the present invention covers
 5 methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 80 %, said methods comprising the step of

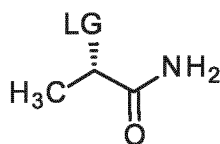
allowing an intermediate compound of formula (II)



10

(II)

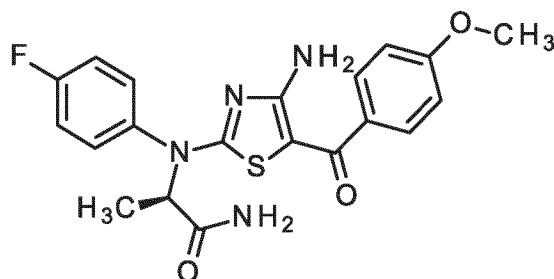
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

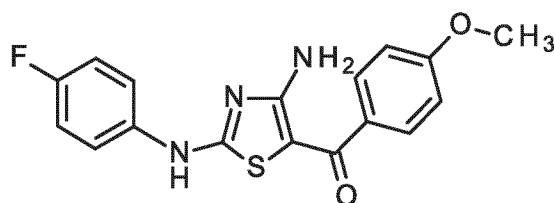
15 thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 80 %.

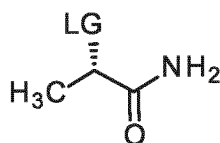
In accordance with a third embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

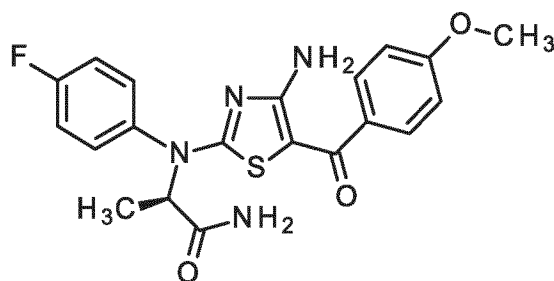
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving

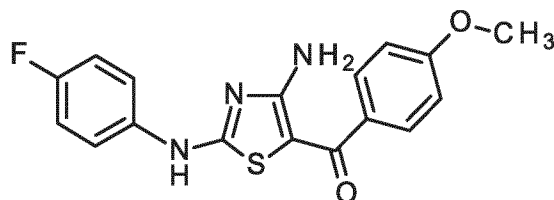


(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

In accordance with a fourth embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

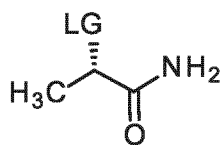
allowing an intermediate compound of formula (II)



5

(II)

to react with an intermediate compound of formula (III)

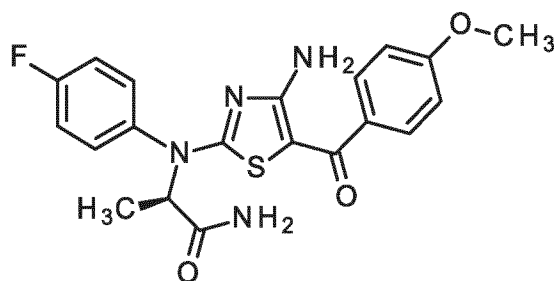


(III)

in which LG is a leaving group as defined *supra*,

10 in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

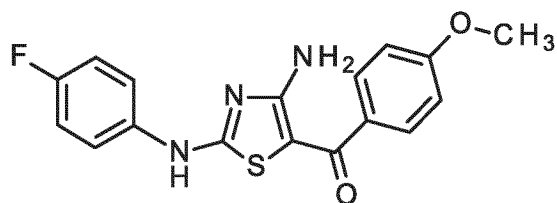
15 thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

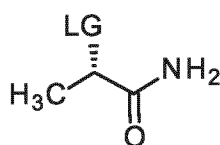
20 In accordance with a fifth embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



5

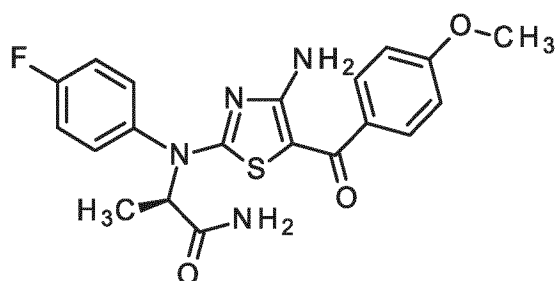
(III)

in which LG is a bromine atom,

in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate, at a temperature in the range of 40 to 80 °C, in a solvent selected from

10 N,N-dimethylformamide and acetonitrile, for a time in the range of 30 minutes to 6 hours,

thereby giving

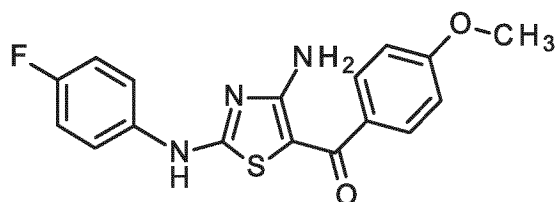


(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

15

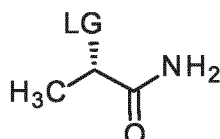
In accordance with a sixth embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

20 allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



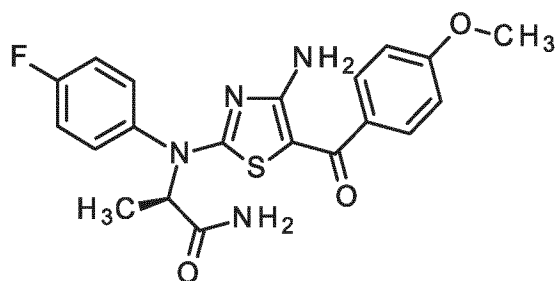
(III)

5

in which LG is a bromine atom,

in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate, at a temperature in the range of 40 to 80 °C, in a solvent selected from N,N-dimethylformamide and acetonitrile, for a time in the range of 30 minutes to 6 hours,
 10 optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

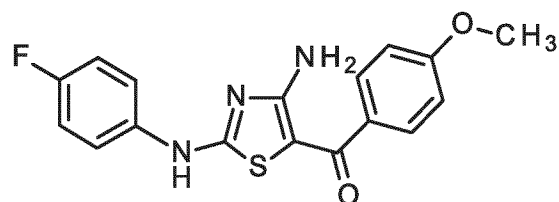
thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an
 15 enantiomeric excess of at least 90 %.

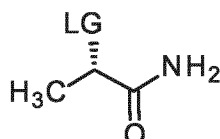
In accordance with a seventh embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %, said methods comprising the
 20 step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



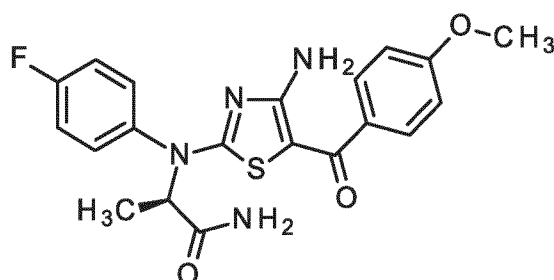
(III)

5

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving

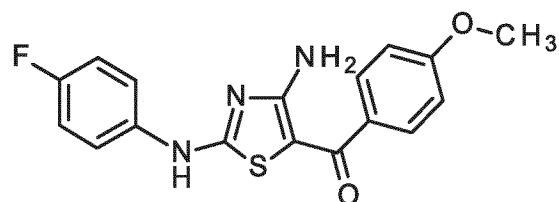


10

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %.

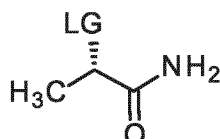
15 In accordance with an eighth embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

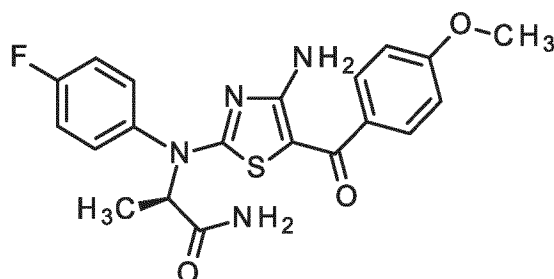


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %.

Further embodiments of the fourth aspect of the present invention:

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a chlorine atom, a bromine atom or an iodine atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy and [(4-methylphenyl)sulfonyl]oxy.

- 5 In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a chlorine atom.

- 10 In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a [(4-methylphenyl)sulfonyl]oxy group.

- 15 In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a bromine atom or a [(4-methylphenyl)sulfonyl]oxy group.

20

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a bromine atom.

25

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 the step comprised therein is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate selected from sodium carbonate, potassium carbonate and cesium carbonate, an alkali bicarbonate selected from sodium bicarbonate, potassium bicarbonate, and cesium bicarbonate, and an alkali phosphate selected from sodium phosphate, potassium phosphate and cesium phosphate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out in the presence of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

- 10 In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

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In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 the step comprised therein is carried out in the presence of a base selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate.

- 30 In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 3 equivalents of potassium phosphate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 2 to 6 equivalents of potassium carbonate.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 0°C to 100°C.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 20°C to 90°C.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 40°C to 80°C.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 50°C to 70°C.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 40°C to 80°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out at a temperature in the range of 50°C to 70°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-
10 anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 40°C to 80°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-
15 anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 50°C to 70°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

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In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-
30 anilino)propanamide, in which

the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide, acetonitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol in a range of 5:1 to 1:5.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide and acetonitrile.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

10 anilino)propanamide, in which

the step comprised therein is carried out in N,N-dimethylformamide as a solvent.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

15 anilino)propanamide, in which

the step comprised therein is carried out in acetonitrile as a solvent.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

20 anilino)propanamide, in which

the step comprised therein is carried out over a time in the range of 30 minutes to 24 hours.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

25 anilino)propanamide, in which

the step comprised therein is carried out over a time in the range of 30 minutes to 6 hours.

In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

30 anilino)propanamide, in which

the step comprised therein is carried out over a time in the range of 30 minutes to 2 hours.

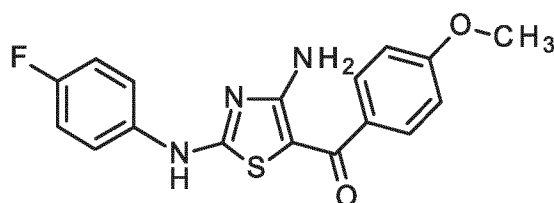
In accordance with a further embodiment of the fourth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out over a time in the range of 1 to 2 hours.

In accordance with a fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-

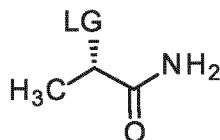
10 anilino)propanamide said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

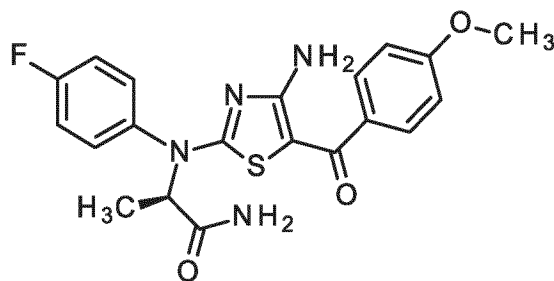


15

(III)

in which LG is a leaving group as defined *supra*,

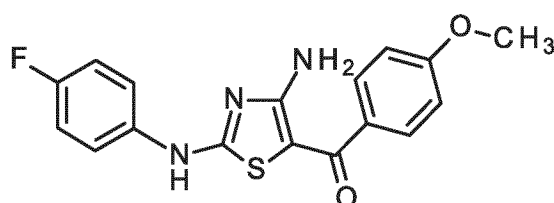
thereby giving



20 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

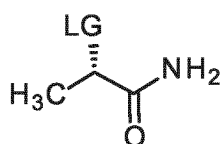
In accordance with a second embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 80 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

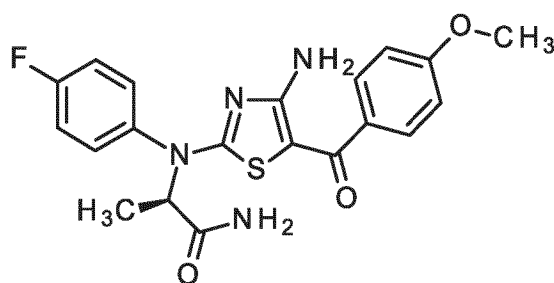
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

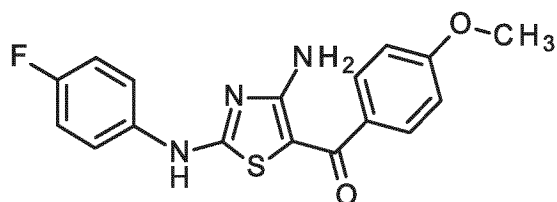
thereby giving



microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 80 %.

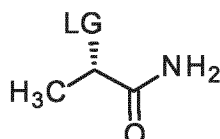
In accordance with a third embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

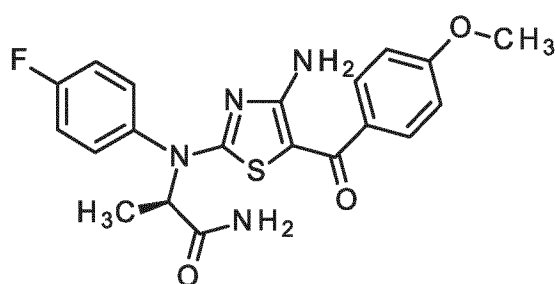


5

(III)

in which LG is a leaving group as defined *supra*,

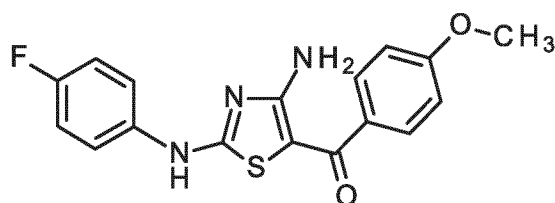
thereby giving



microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

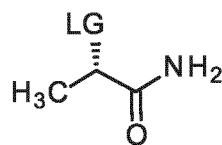
In accordance with a fourth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

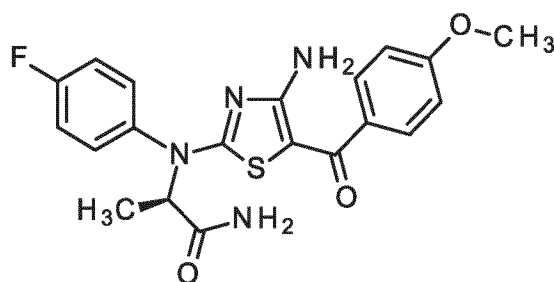


(III)

in which LG is a leaving group as defined *supra*,

- 5 in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

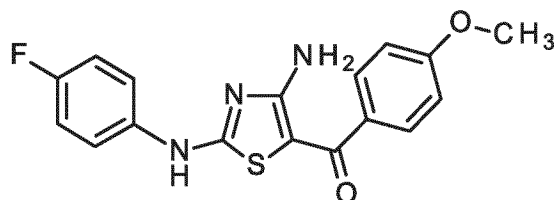
- 10 thereby giving



microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

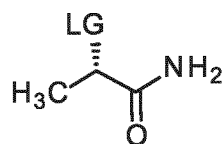
- 15 In accordance with a fifth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

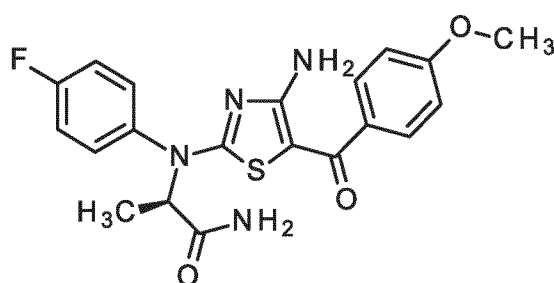
to react with an intermediate compound of formula (III)



(III)

in which LG is a bromine atom,

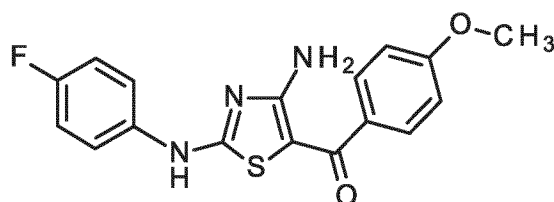
in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and
 5 potassium phosphate, at a temperature in the range of 40 to 80 °C, in a solvent selected from N,N-dimethylformamide and acetonitrile, for a time in the range of 30 minutes to 6 hours,
 thereby giving



microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-
 10 anilino)propanamide in an enantiomeric excess of at least 90 %.

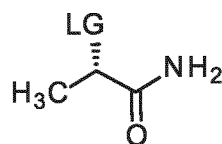
In accordance with a sixth embodiment of the fifth aspect, the present invention covers methods
 of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-
 fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %, said methods comprising
 15 the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

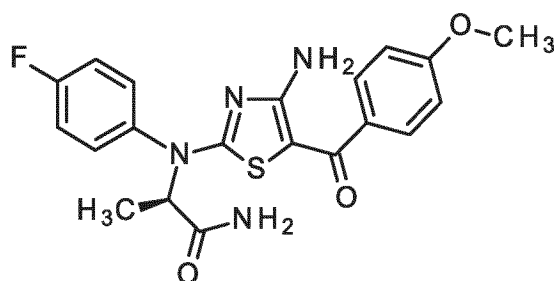


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and potassium phosphate, at a temperature in the range of 40 to 80 °C, in a solvent selected from N,N-dimethylformamide and acetonitrile, for a time in the range of 30 minutes to 6 hours, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving



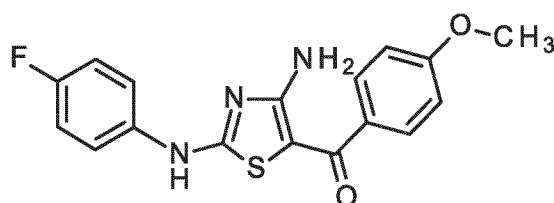
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microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 90 %.

In accordance with a seventh embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %, said methods comprising the step of

15

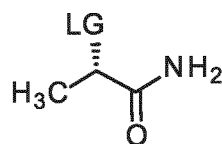
allowing an intermediate compound of formula (II)



(II)

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to react with an intermediate compound of formula (III)



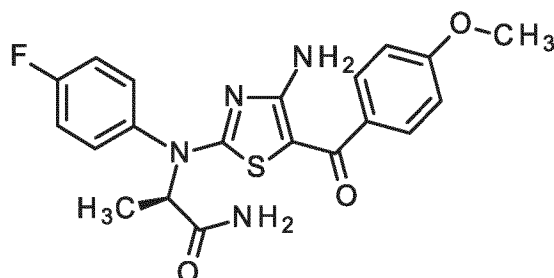
(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of

5 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving

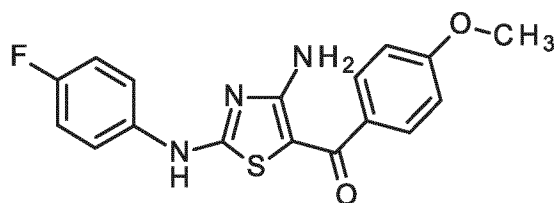


microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %.

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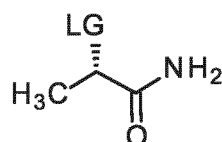
In accordance with an eighth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %, said methods comprising the step of

15 allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



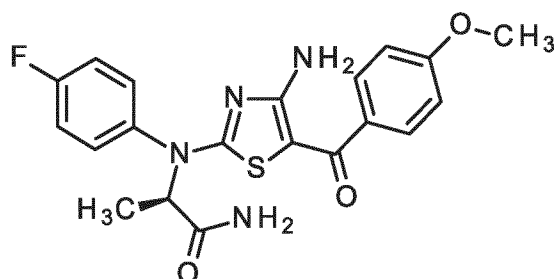
(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, optionally followed by lowering

5 the temperature to 20°C over a time in the range of up to one hour,

thereby giving

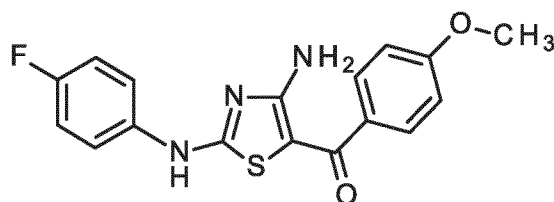


microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %.

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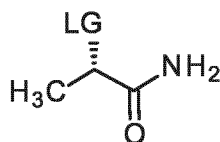
In accordance with a ninth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %, said methods comprising the step of

15 allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



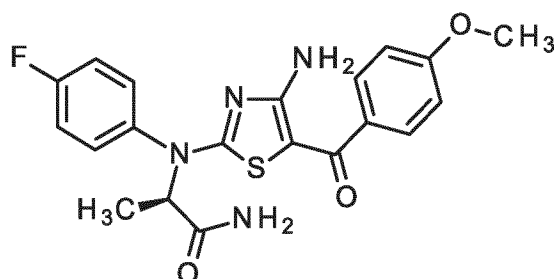
(III)

in which LG is a bromine atom,

20

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

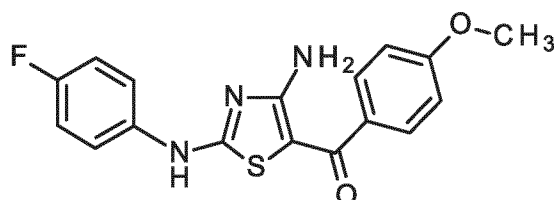
thereby giving



- 5 microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %.

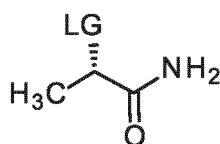
In accordance with a tenth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

- 15 to react with an intermediate compound of formula (III)

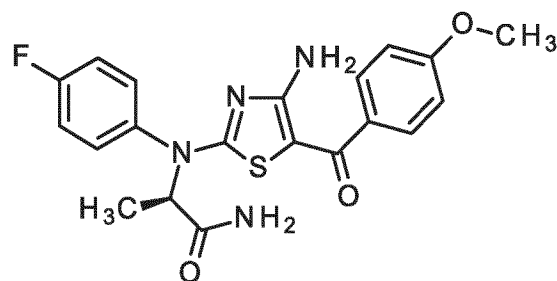


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



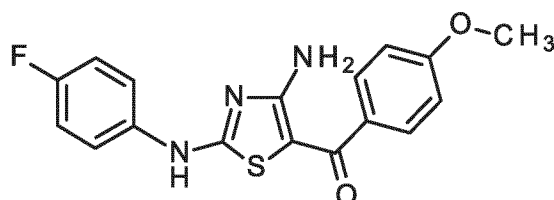
microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %, in which

the presence of amorphous forms is below 5 %,

- 5 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

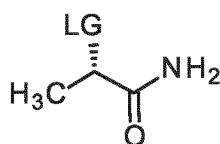
In accordance with an eleventh embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

- 15 to react with an intermediate compound of formula (III)

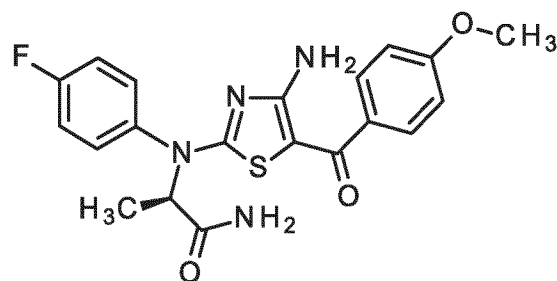


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 $^{\circ}\text{C}$ in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



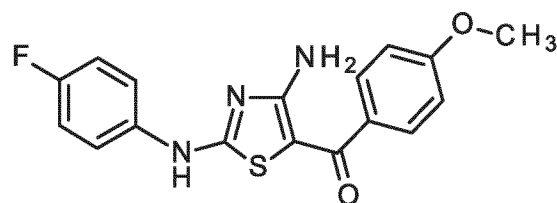
microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 98 %, in which

the presence of amorphous forms is below 5 %,

- 5 and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

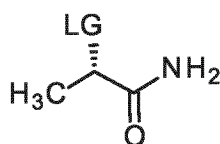
In accordance with a twelfth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

- 15 to react with an intermediate compound of formula (III)

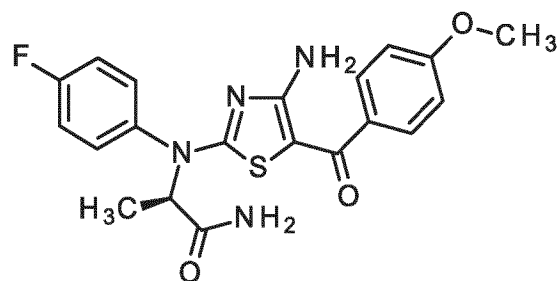


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 $^{\circ}\text{C}$ in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



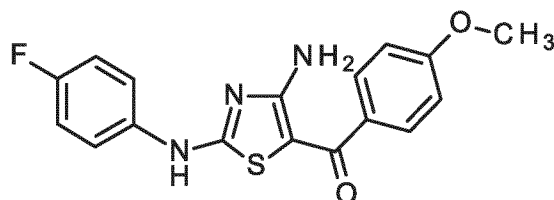
microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

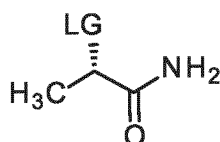
In accordance with a thirteenth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

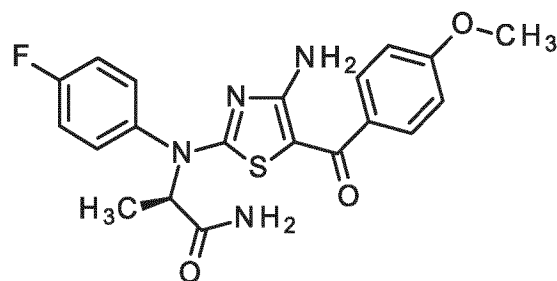


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 $^{\circ}\text{C}$ in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



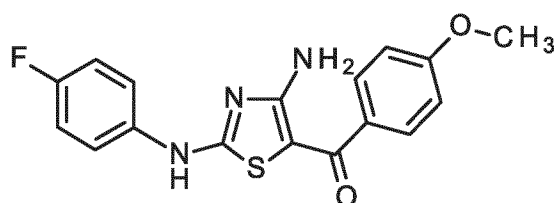
microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, in which

the presence of amorphous forms is below the detection limits of differential scanning calorimetry,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

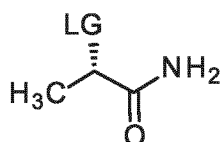
In accordance with a fourteenth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

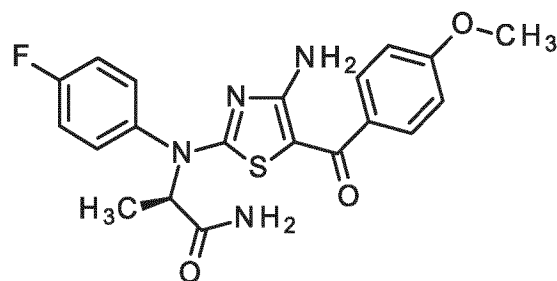


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 $^{\circ}\text{C}$ in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



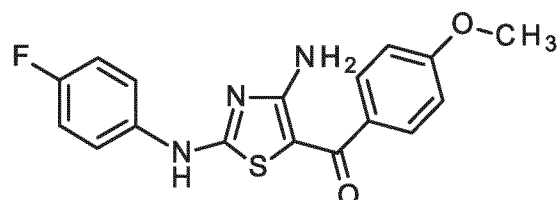
microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, in which

the presence of amorphous forms is below the detection limits of XRPD,

- 5 and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

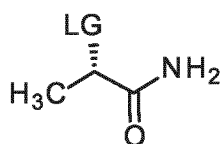
In accordance with a fifteenth embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, said methods comprising the step of

allowing an intermediate compound of formula (II)



(II)

- 15 to react with an intermediate compound of formula (III)

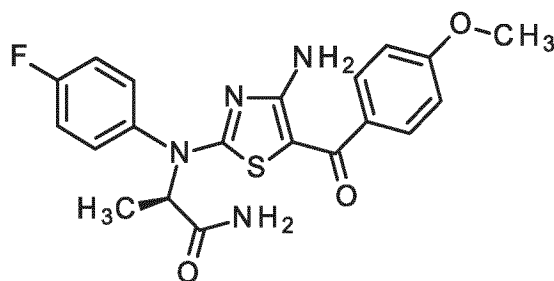


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 $^{\circ}\text{C}$ in acetonitrile for a time in the range of 1 to 2 hours,

thereby giving



microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 99 %, in which

the presence of amorphous forms is below the detection limits of XRPD,

- 5 and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

Further embodiments of the fifth aspect of the present invention:

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In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the leaving group LG in the step comprised therein is a chlorine atom, a bromine atom or an iodide atom, or a group selected from (methylsulfonyl)oxy, (phenylsulfonyl)oxy and [(4-methylphenyl)sulfonyl]oxy.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20

the leaving group LG in the step comprised therein is a chlorine atom.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25

the leaving group LG in the step comprised therein is a [(4-methylphenyl)sulfonyl]oxy group.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the leaving group LG in the step comprised therein is a bromine atom or a
5 [(4-methylphenyl)sulfonyl]oxy group.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 the leaving group LG in the step comprised therein is a bromine atom.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15

the step comprised therein is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20

the step comprised therein is carried out in the presence of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25

the step comprised therein is carried out in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

30

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate, an alkali phosphate and N, N, N, N-tetra (C₁-C₃-alkyl)guanidine.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from an alkali carbonate selected from sodium carbonate, potassium carbonate and cesium carbonate, an alkali bicarbonate selected from sodium bicarbonate, potassium bicarbonate, and cesium bicarbonate, and an alkali phosphate selected from sodium phosphate, potassium phosphate and cesium phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate, cesium carbonate, potassium bicarbonate, cesium bicarbonate, and potassium phosphate.

- 5 In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in the presence of a base selected from potassium carbonate and potassium phosphate.

10

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- the step comprised therein is carried out in the presence of 1.5 to 6 equivalents of a base
15 selected from potassium carbonate and potassium phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 the step comprised therein is carried out in the presence of 1.5 to 3 equivalents of potassium phosphate.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25

the step comprised therein is carried out in the presence of 2 to 6 equivalents of potassium carbonate.

- 30 In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out at a temperature in the range of 0°C to 100°C.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out at a temperature in the range of 20°C to 90°C.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 10 the step comprised therein is carried out at a temperature in the range of 40°C to 80°C.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 15 the step comprised therein is carried out at a temperature in the range of 50°C to 70°C.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 20 the step comprised therein is carried out at a temperature in the range of 40°C to 80°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 25 the step comprised therein is carried out at a temperature in the range of 50°C to 70°C, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 30 the step comprised therein is carried out at a temperature in the range of 40°C to 80°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

- 5 the step comprised therein is carried out at a temperature in the range of 50°C to 70°C, followed by lowering the temperature to 20°C over a time in the range of up to one hour.

10 In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol.

15

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide, acetonitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, or a mixture of acetone and iso-propanol in a range of 5:1 (v/v) to 1:5 (v/v).

25 In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in a solvent selected from N,N-dimethylformamide and acetonitrile.

30 In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in N,N-dimethylformamide as a solvent.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

the step comprised therein is carried out in acetonitrile as a solvent.

5

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

10 the step comprised therein is carried out over a time in the range of 30 minutes to 24 hours.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

15 the step comprised therein is carried out over a time in the range of 30 minutes to 6 hours.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

20 the step comprised therein is carried out over a time in the range of 30 minutes to 2 hours.

In accordance with a further embodiment of the fifth aspect, the present invention covers methods of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, in which

25 the step comprised therein is carried out over a time in the range of 1 to 2 hours.

In accordance with a sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and one or more pharmaceutically acceptable excipients.

30

In accordance with a second embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the presence of amorphous forms is below 15 %,

- 5 and their particle size distribution is as follows: x10 is <5 µm, x50 is <10 µm, and x90 is <35 µm.
and one or more pharmaceutically acceptable excipients.

In accordance with a third embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

10

the presence of amorphous forms is below 15 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm,

and one or more pharmaceutically acceptable excipients.

15

In accordance with a fourth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the presence of amorphous forms is below 15 %,

- 20 and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm,

and one or more pharmaceutically acceptable excipients.

In accordance with a fifth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

25

the presence of amorphous forms is below 15 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm,

- 30 and one or more pharmaceutically acceptable excipients.

In accordance with a sixth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 95 %,

5 the presence of amorphous forms is below 10 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm ,

and one or more pharmaceutically acceptable excipients.

10 In accordance with a seventh embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

15 and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm ,

and one or more pharmaceutically acceptable excipients.

In accordance with an eighth embodiment of the sixth aspect, the present invention covers

20 pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 95 %,

the presence of amorphous forms is below 10 %,

25 and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm ,

and one or more pharmaceutically acceptable excipients.

In accordance with a ninth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-

30 methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm ,
and one or more pharmaceutically acceptable excipients.

- 5 In accordance with a tenth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
the presence of amorphous forms is below 5 %,
and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the
10 range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm ,
and one or more pharmaceutically acceptable excipients.

- In accordance with an eleventh embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
15 the presence of amorphous forms is below 5 %,
and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm ,
and one or more pharmaceutically acceptable excipients.

20

- In accordance with a twelfth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
the enantiomeric excess is at least 98 %,
25 the presence of amorphous forms is below 5 %,
and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm ,
and one or more pharmaceutically acceptable excipients.

- 30 In accordance with a thirteenth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm,

5 and one or more pharmaceutically acceptable excipients.

In accordance with a fourteenth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

10 the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm,

and one or more pharmaceutically acceptable excipients.

15

In accordance with a fifteenth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 99 %,

20 the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 2 µm, x50 is in the range of 4 to 5.5 µm, and x90 is in the range of 10 to 18 µm,

and one or more pharmaceutically acceptable excipients.

25 In accordance with a sixteenth embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

30 and their particle size distribution is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm,

and one or more pharmaceutically acceptable excipients.

Further embodiments of the sixth aspect of the present invention:

- 5 In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
- the enantiomeric excess is at least 95 %,
- the presence of amorphous forms is below 10 %,
- 10 and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm,
- and one or more pharmaceutically acceptable excipients.
- 15 In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
- the enantiomeric excess is at least 95 %,
- the presence of amorphous forms is below 10 %,
- 20 and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm,
- and one or more pharmaceutically acceptable excipients.
- 25 In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which
- the enantiomeric excess is at least 95 %,
- the presence of amorphous forms is below 10 %,
- 30 and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18 µm,

and one or more pharmaceutically acceptable excipients.

In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-

5 methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to

10 20 µm,

and one or more pharmaceutically acceptable excipients.

In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-

15 methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20

20 µm,

and one or more pharmaceutically acceptable excipients.

In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-

25 methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 µm, x50 is in the range of 4 to 8 µm, and x90 is in the range of 12 to 18

30 µm,

and one or more pharmaceutically acceptable excipients.

In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 99 %,

5 the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD2a is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm ,

and one or more pharmaceutically acceptable excipients.

10

In accordance with a further embodiment of the sixth aspect, the present invention covers pharmaceutical compositions comprising microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in which

the enantiomeric excess is at least 99 %,

15 the presence of amorphous forms is below 5 %,

and their particle size distribution as determined according to method PSD4 is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm ,

and one or more pharmaceutically acceptable excipients.

20

The microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention can be utilized to inhibit, block, reduce or decrease DGK ζ activity resulting in the modulation of dysregulated immune responses e.g. to block immunosuppression and increase immune cell activation and infiltration in the context of cancer and cancer immunotherapy that will eventually lead to reduction of tumour growth.

25

This method comprises administering to a mammal in need thereof, including a human, an amount of a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide; which is effective to treat the disorder.

The present invention also provides methods of treating a variety of other disorders wherein

30

DGK ζ is involved such as, but not limited to, disorders with dysregulated immune responses, inflammation, vaccination for infection & cancer, virus infections, lymphoproliferative disorders, asthma, eye diseases, and type 2 diabetes/ insulin resistance.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

5 In accordance with a further aspect, the present invention covers microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, for use in the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling.

10 The pharmaceutical activity of the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention can be explained by the activity of the underlying compound (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as DGK ζ inhibitor.

15 In accordance with a further aspect, the present invention covers the use of microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, for the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling, particularly liquid and solid tumours.

20

In accordance with a further aspect, the present invention covers the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, for the use in the treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant
25 DGK ζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers the use of microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, in a method of treatment or prophylaxis of diseases, in particular cancer or
30 conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers the use of a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as
35 described *supra*, in a method of treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers use of a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, for the preparation of a pharmaceutical composition, preferably a medicament, for the prophylaxis or treatment of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling, particularly liquid and solid tumours.

In accordance with a further aspect, the present invention covers a method of treatment or prophylaxis of diseases, in particular cancer or conditions with dysregulated immune responses or other disorders associated with aberrant DGK ζ signaling, particularly liquid and solid tumours, using an effective amount of a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*.

In accordance with a further aspect, the present invention covers pharmaceutical compositions, in particular a medicament, comprising a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, as described *supra*, and one or more excipients, in particular one or more pharmaceutically acceptable excipient(s). Conventional procedures for preparing such pharmaceutical compositions in appropriate dosage forms can be utilized.

The present invention furthermore covers pharmaceutical compositions, in particular medicaments, which comprise at least one microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention, conventionally together with one or more pharmaceutically suitable excipients, and to their use for the above mentioned purposes.

It is possible for the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention to have systemic and/or local activity. For this purpose, they can be administered in a suitable manner, such as, for example, via the oral, parenteral, pulmonary, nasal, sublingual, lingual, buccal, rectal, vaginal, dermal, transdermal, conjunctival, otic route or as an implant or stent.

For these administration routes, it is possible for the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention to be administered in suitable administration forms.

For oral administration, it is possible to formulate the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention to dosage forms known in the art that deliver (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-

4-fluoro-anilino)propanamide of the invention rapidly and/or in a modified manner, such as, for example, tablets (uncoated or coated tablets, for example with enteric or controlled release coatings that dissolve with a delay or are insoluble), orally-disintegrating tablets, films/wafers, films/lyophilisates, capsules (for example hard or soft gelatine capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions or aerosols.

Parenteral administration can be effected with avoidance of an absorption step (for example intravenous, intraarterial, intracardial, intraspinal or intralumbal) or with inclusion of absorption (for example intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal).

Administration forms which are suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of suspensions, emulsions, lyophilisates or sterile powders.

Examples which are suitable for other administration routes are pharmaceutical forms for inhalation [inter alia powder inhalers, nebulizers], nasal drops, nasal sprays; tablets/films/wafers/capsules for lingual, sublingual or buccal administration; suppositories; eye drops, eye ointments, eye baths, ocular inserts, ear drops, ear sprays, ear powders, ear-rinses, ear tampons; vaginal capsules, aqueous suspensions (lotions, mixturae agitandae), lipophilic suspensions, emulsions, ointments, creams, transdermal therapeutic systems (such as, for example, patches), milk, pastes, foams, dusting powders, implants or stents.

The microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention can be incorporated into the stated administration forms. This can be effected in a manner known per se by mixing with pharmaceutically suitable excipients. Pharmaceutically suitable excipients include, inter alia,

- fillers and carriers (for example cellulose, microcrystalline cellulose (such as, for example, Avicel®), lactose, mannitol, starch, calcium phosphate (such as, for example, Di-Cafos®)),
- ointment bases (for example petroleum jelly, paraffins, triglycerides, waxes, wool wax, wool wax alcohols, lanolin, hydrophilic ointment, polyethylene glycols),
- bases for suppositories (for example polyethylene glycols, cacao butter, hard fat),
- solvents (for example water, ethanol, isopropanol, glycerol, propylene glycol, medium chain-length triglycerides fatty oils, liquid polyethylene glycols, paraffins),
- surfactants, emulsifiers, dispersants or wetters (for example sodium dodecyl sulfate), lecithin, phospholipids, fatty alcohols (such as, for example, Lanette®), sorbitan fatty acid esters (such as, for example, Span®), polyoxyethylene sorbitan fatty acid esters (such as, for example, Tween®), polyoxyethylene fatty acid glycerides (such as, for example,

Cremophor®), polyoxethylene fatty acid esters, polyoxyethylene fatty alcohol ethers, glycerol fatty acid esters, poloxamers (such as, for example, Pluronic®),

- buffers, acids and bases (for example phosphates, carbonates, citric acid, acetic acid, hydrochloric acid, sodium hydroxide solution, ammonium carbonate, trometamol, triethanolamine),

- isotonicity agents (for example glucose, sodium chloride),

- adsorbents (for example highly-disperse silicas),

- viscosity-increasing agents, gel formers, thickeners and/or binders (for example polyvinylpyrrolidone, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose-sodium, starch, carbomers, polyacrylic acids (such as, for example, Carbopol®); alginates, gelatine),

- disintegrants (for example modified starch, carboxymethylcellulose-sodium, sodium starch glycolate (such as, for example, Explotab®), cross-linked polyvinylpyrrolidone, croscarmellose-sodium (such as, for example, AcDiSol®)),

- flow regulators, lubricants, glidants and mould release agents (for example magnesium stearate, stearic acid, talc, highly-disperse silicas (such as, for example, Aerosil®)),

- coating materials (for example sugar, shellac) and film formers for films or diffusion membranes which dissolve rapidly or in a modified manner (for example polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohol, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, hydroxypropylmethylcellulose phthalate, cellulose acetate, cellulose acetate phthalate, polyacrylates, polymethacrylates such as, for example, Eudragit®)),

- capsule materials (for example gelatine, hydroxypropylmethylcellulose),

- synthetic polymers (for example polylactides, polyglycolides, polyacrylates, polymethacrylates (such as, for example, Eudragit®), polyvinylpyrrolidones (such as, for example, Kollidon®), polyvinyl alcohols, polyvinyl acetates, polyethylene oxides, polyethylene glycols and their copolymers and blockcopolymers),

- plasticizers (for example polyethylene glycols, propylene glycol, glycerol, triacetine, triacetyl citrate, dibutyl phthalate),

- penetration enhancers,

- stabilisers (for example antioxidants such as, for example, ascorbic acid, ascorbyl palmitate, sodium ascorbate, butylhydroxyanisole, butylhydroxytoluene, propyl gallate),

- preservatives (for example parabens, sorbic acid, thiomersal, benzalkonium chloride, chlorhexidine acetate, sodium benzoate),
- colourants (for example inorganic pigments such as, for example, iron oxides, titanium dioxide),
- 5 • flavourings, sweeteners, flavour- and/or odour-masking agents.

The present invention furthermore relates to a pharmaceutical composition which comprises at least one microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to the invention, conventionally together with one or more
10 pharmaceutically suitable excipient(s), and to their use according to the present invention.

Based upon standard laboratory techniques known to evaluate microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide useful for the treatment of cancer or conditions with dysregulated immune responses or other disorders
15 associated with aberrant DGK ζ signaling, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known active ingredients or medicaments that are used to treat these conditions, the effective dosage of the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of
20 the present invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient
25 treated, and the nature and extent of the condition treated.

The total amount of the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide to be administered will generally range from about 0.001 mg/kg to about 200 mg/kg body weight per day, and preferably from
30 about 0.01 mg/kg to about 20 mg/kg body weight per day. Clinically useful dosing schedules will range from one to three times a day dosing to once every four weeks dosing. In addition, it is possible for "drug holidays", in which a patient is not dosed with a drug for a certain period of time, to be beneficial to the overall balance between pharmacological effect and tolerability. It is possible for a unit dosage to contain from about 0.5 mg to about 1500 mg of active ingredient,
35 and can be administered one or more times per day or less than once a day. The average daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and

- parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The average daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The average daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.
- Of course the specific initial and continuing dosage regimen for each patient will vary according to the nature and severity of the condition as determined by the attending diagnostician, the activity of the microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide employed, the age and general condition of the patient, time of administration, route of administration, rate of excretion of the drug, drug combinations, and the like. The desired mode of treatment and number of doses of a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide of the present invention or a pharmaceutically acceptable salt or ester or composition thereof can be ascertained by those skilled in the art using conventional treatment tests.

Description of the Figures

Figure 1: XRPD (Method XRPD1) of the material obtained in Example 2

Figure 2: DSC (Method DSC1) of the material obtained in Example 2

Figure 3: XRPD (Method XRPD1) of Material obtained in Example 3 (lower graph with peak picking)

5

Table 1: Peak listing corresponding to Figure 3, lower graph:

No.	Position	Intensity
1	7.3	160
2	7.6	181
3	7.9	584
4	8.2	136
5	9.2	288
6	12.2	92
7	12.5	129
8	13.5	232
9	14.0	209
10	14.2	40
11	14.6	368
12	14.9	161
13	15.2	154
14	15.3	184
15	15.8	124
16	16.3	137
17	18.4	79
18	19.0	112
19	19.4	89
20	19.5	66
21	20.0	44
22	20.2	63
23	20.6	246
24	21.2	329
25	21.5	46
26	22.7	78
27	22.8	149
28	22.9	131
29	23.8	43
30	24.5	79
31	25.1	37
32	25.8	37
33	26.1	51
34	26.6	83
35	27.1	71
36	28.3	53

37	28.4	42
38	31.2	45
39	31.7	50
40	32.6	38
41	33.6	32
42	38.7	28

Figure 4: DSC (Method DSC1) of Material obtained in Example 3

Figure 5. Comparison of dissolution profiles in phosphate buffer (pH 6.8) + 0.1 % SDS; the thermodynamic solubility of crystalline material being about 20 %; 100% dissolution equals 201.5 µg / mL. Materials profiled are (i) material from Reference Example 1 after jet milling (— — — — —), (ii) material from Example 3 (— • — • — •), and (iii) material from Reference Example 2 (— — — — —). The Y axis relates to the dissolved amount (%), the X-axis relates to the time in minutes.

Figure 6. Zoom-in showing the first hour of the comparison of dissolution profiles as shown in Figure 5, the y-axis being cropped to 30%

Figure 7. XRPD (Method XRPD2) of Material as obtained from Reference Example 1, prior to jet milling

Figure 8. DSC (Method DSC2) of Material as obtained from Reference Example 1, prior to jet milling

Figure 9. DSC (Method DSC2) of Material as obtained from Reference Example 1, after jet milling

Figure 10 Comparative XRPD (Method XRPD2) of material from Reference Example 1 before jet milling (upper diffractogram), and thereafter (lower diffractogram)

Figure 11: XRPD (Method XRPD 3) of Material as obtained from Reference Example 2

Figure 12: DSC (Method DSC3) of Material as obtained from Reference Example 2

Figure 13: Particle size distribution of Material as obtained from Example 4 (Method PSD 4)

Figure 14: DSC (Method DSC1) of Material as obtained from Example 4

Figure 15: XRPD (Method XRPD 1) of Material as obtained from Example 4

Figure 16: Comparison of dissolution profiles of tablets containing equal amounts of microcrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide obtained as described in Example 3 (-▲-) and Example 4 (-◆-). The Y axis relates to the dissolved amount (%), the X-axis relates to the time in minutes.

EXPERIMENTAL SECTION

Table 2: Abbreviations

The following table lists the abbreviations used herein.

5	XRPD	X-Ray Powder Diffraction
	DSC	Differential Scanning Calorimetry
	PSD	Particle Size Distribution
	HPLC	High Performance Liquid Chromatography
	UPLC	Ultra Performance Liquid Chromatography
10	ee or ee	Enantiomeric excess
	w/w	Weight to weight
	v/v	Volume to volume
	ELSD	Evaporative Light Scattering Detector
	MS	Mass Spectrometry
15	NMR	Nuclear Magnetic Resonance
	RT, rt	Room temperature
	t _R	Retention time
	SDS	Sodium dodecyl sulfate
	PMMA	Poly(methyl methacrylate)

20

The various aspects of the invention described in this application are illustrated by the following examples which are not meant to limit the invention in any way.

The example testing experiments described herein serve to illustrate the present invention and the invention is not limited to the examples given.

25 **EXPERIMENTAL SECTION – MATERIALS AND METHODS****HPLC and LC/MS methods:****Method HPLC1: Preparative HPLC :**

Instrument: pump: Labomatic HD-5000 or HD-3000, head HDK 280, low pressure gradient module ND-B1000; manual injection valve: Rheodyne 3725i038; detector: Knauer Azura UVD

2.15; collector: Labomatic Labocol Vario-4000; column: Chromatorex RP C-18 10 µm, 125x30mm; eluent: solvent A: water + 0.2 vol-% ammonia (32%), solvent B: acetonitrile; gradient: 0.00-0.50 min 15% B (150 ml/min), 0.50–6.00 min 15-55% B (150 ml/min), 6.00-6.10 min 55-100% B (150 ml/min), 6.10-8.00 min 100% B (150 ml/min); UV: 361 nm

5

Method HPLC2: Analytical UPLC/MS:

Instrument: Waters Acquity UPLC-MS SQD 3001; column: Acquity UPLC BEH C18 1.7 50x2.1mm; eluent: solvent A: water + 0.2 vol% aqueous ammonia (32%), eluent solvent B: acetonitrile; gradient: 0-1.6 min 1-99% B, 1.6-2.0 min 99% B; flow 0.8 mL/min; temperature: 60°C; injection: 2 µL; DAD scan: 210-400 nm; ELSD

10

Method HPLC3: Analytical chiral HPLC:

Instrument: Thermo Fisher UltiMate 3000; Column: YMC Cellulose SB 3µ, 100x4.6; eluent solvent A: hexane + 0.1 vol % diethylamine; eluent solvent B: 2-propanol; isocratic: 60%A+40%B; flow: 1.4 ml/min; temperature: 25°C; UV: 254 nm

15

Method HPLC4: Chemical purity, Examples 3 and 4, and Reference Example 2:

Equipment: High-performance liquid chromatograph (with a pressure range of up to 600 bar and a dwell volume of approx. 850 µL) with a thermostatically controlled column oven, UV detector and data evaluation system (e.g. Agilent 1260)

Column:

*Waters Acquity BEH
Shield C18
Length: 50 mm, inner
diameter: 2.1 mm,
particle size: 1.7 µm*

Maximum pressure: 600 bar

Typical starting pressure: 500 bar

Eluents:

A: 1580mg Ammonium
bicarbonate + 80µL
formic acid (98+%) / 1L
Milli-Q water
(compressibility: Use
Solvent Types)

B: Acetonitrile
(compressibility: Use
Solvent Types)

Gradient:	Time (min)	B (%)
	0,00	5,0
	1,00	5,0
	4,50	45,0
	7,50	60,0
	8,50	80,0
	9,50	80,0
	10,00	5,0
	11,00	5,0
The percentage of mobile phase A is the difference between B (%) and 100%.		
Equilibration time:	1 min (at starting condition)	
Flow rate:	0.7 mL/min	
Draw speed:	200 µL/min	
Injection volume:	2.5 µL (RT)	
Needle wash:	Flush port period (7 sec)	
	Solvent: <u>Methanol</u>	
Column temperature:	40 °C	
Data sampling rate:	20 Hz (> 0.013 min (0.25 s response time))	
Detection wavelength:	270 nm, band width: 4 nm	
Margin for negative absorbance:	100 mAU	
Detector cell path:	10 mm	
Slit:	4 nm	
Sample solvent:	Acetonitrile	
Sample/Calibration solution:	Dissolve sample at a concentration of approx. 0.25 mg/mL (e.g. weigh exactly 25 mg and dissolve in 100 mL) of the substance with sample solvent and fill up to the calibration mark.	

Method HPLC5: Enantiomeric excess, Examples 3 and 4, and Reference Example 2:

Equipment: Ultrahigh-performance liquid chromatograph with a thermostatically controlled column oven, UV detector and data evaluation system, dwell volume approx. 200 µL (e.g. Agilent 1290)

Column:***Daicel Chiralpak IB N-3****Length: 150 mm, inner**diameter: 4.6 mm,**particle size: 3.0 µm*

Maximum pressure: 300 bar

Typical starting pressure: 210 bar

**Column
temperature:**

25 °C

Mobile phase:

A: n-Heptane / Ethanol+

0.1 % TFA (50 % +

50 %; V:V)

(compressibility: use

Solvent-Type)

Flow rate

1.50 mL/min

Isocratic: A (%): 100**Runtime:** 8.0 min**Detector cell path:** 10 mm**Detection
wavelength:** 265 nm, band width: 4 nm**Data sampling rate:** 2.5 Hz (> 0.1 min (2 s response time))**Margin for negative
absorbance:** 100 mAU**Slit:** 4 nm**Injection volume:** 3.0 µL (RT)**Draw speed:** 200 µL/min**Needle wash:** Flush port period (7 sec)

Solvent: Ethanol

Sample solvent: Ethanol**Sample solution:** Dissolve sample at a concentration of approx. 1.0 mg/mL (e.g. weigh exactly 25 mg and dissolve in 25 mL) of the substance with sample solvent and fill up to the calibration mark.**Method HPLC6: Preparative chiral HPLC:**

Instrument: Labomatic HD3000, Knauer Pump 100, Labcol Vario 4000 Plus, Knauer DAD

2600; Column: amylose SB 5µ 250x50mm Nr.34; eluent A: hexane + 0.1 Vol-% diethylamine

5 (99%); eluent B: 2-propanol; isocratic: 60%A + 40%B; flow 150.0 ml/min, from 16 min

180ml/min; UV @ 254 nm

Particle Size Distribution (PSD)

Method PSD1 : The Particle Size Distribution (PSD) was measured by laser diffraction using the Malvern Panalytical Mastersizer 3000. 0.1 % Span 85 in Heptane was used as dispersant medium. Samples were sonicated for 40% intensity for 45 seconds.

Method PSD2a : The Particle Size Distribution (PSD) was measured by laser diffraction using the Sympatec Helos device. Water with a small amount of surfactant was used as dispersant medium. Samples were sonicated for 240 seconds.

Method PSD2b : The Particle Size Distribution (PSD) was measured by laser diffraction using the Sympatec Helos device. Paraffin was used as dispersant medium. Samples were sonicated for 240 seconds.

Method PSD 3 : Particle size analysis was performed by laser diffraction using Sympatec (HELOS) with Baysilone (Element 14 PDMS 10-A) as dispersion medium. The samples were sonicated for 90 seconds with an intensity of 80% (60 sec break) and stirred with a magnetic stirrer at 800 rpm. The measurements were carried out 3 times (30 sec break) and the arithmetic mean value was calculated.

Method PSD 4 : Particle size analysis was measured by laser diffraction using the Malvern Panalytical Mastersizer 3000. Water with one drop of Tween 80 was used as dispersant medium. Samples were sonicated for 180 seconds.

Differential Scanning Calorimetry (DSC)

Method DSC1 :

Differential Scanning Calorimetry (DSC) was performed with a Mettler Toledo TGA/DSC 3+. The instrument was purged with nitrogen gas at a flow rate of 20 ml min⁻¹. Approximately 1 - 15 mg of each sample was placed into an aluminum crucible and heated at a heating rate of 20 °C min⁻¹ starting from 25°C. No sample preparation.

Method DSC2 :

Differential Scanning Calorimetry (DSC) was performed with a Mettler Toledo TGA/DSC 3+. The instrument was purged with nitrogen gas at a flow rate of 30 ml min⁻¹. Approximately 1 – 15 mg of each sample was placed into an aluminum crucible and heated at a heating rate of 10 or 20 °C min⁻¹ starting from 25°C. No sample preparation.

Method DSC 3 :

Differential scanning calorimetry (DSC) was performed with a Mettler Toledo DSC3. The calorimeter was purged with nitrogen gas at a flow rate of 50 ml.min⁻¹. Approximately 3 – 5 mg of sample was placed into an aluminum crucible without sample preparation. The temperature range was -10 – 230°C at a heating rate of 20°C.min⁻¹.

X-Ray Powder Diffraction (XRPD)**Method XRPD1 :**

The X-Ray Powder Diffraction (XRPD) data was recorded on a Bruker D2 PHASER diffractometer with a LYNXEYE-2 detector using Cu K α 1 radiation (1.54060 Å). All samples were prepared and measured at ambient temperature, on Si-single-crystal low background sample holders, either open or with a PMMA dome. The data were collected in the Bragg-Brentano ($\theta/2\theta$) horizontal geometry between either 3 and 40° (2 θ) or 4 and 40° (2 θ), in 0.02° steps at 0.3 s step⁻¹. The X-ray tube was operated at 30 kV and 10 mA.

Method XRPD2 :

X-ray powder diffraction (XRPD) data were recorded on a PANalytical X'Pert PRO diffractometer using monochromatized Cu-K alpha 1 radiation, at generator settings of 40 kV and 40 mA. The samples were collected in transmission mode, being prepared as a thin layer between two foils. The scanning range was between 2° and 40° 2 theta with a 0.013° step at 25 seconds/step.

Method XRPD3 :

X-ray powder diffraction (XRPD) data were recorded on a STOE STADI P diffractometer using monochromatized Cu-K alpha 1 radiation, a position sensitive detector, at generator settings of 40 kV and 40 mA. The samples were collected in transmission mode, being prepared as a thin layer between two foils. The scanning range was between 2° and 40° 2 theta with a 0.5° step at 15 seconds/step.

Comparison of dissolution

Dissolution properties of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, material from Example 3 as compared to material from Reference Examples 1 and 2

5

Methodology

Samples

The following batches were supplied for the comparison experiment:

- 10 Product resulting from **Example 3**, that is, microcrystalline (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide manufactured using processes according to the present invention

- 15 Product resulting from **Reference Example 1**, that is, a batch of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, manufactured via jet milling of a crystalline batch and containing partially amorphous material

- Product resulting from **Reference Example 2**, that is, a macrocrystalline batch of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

20

Setting

- 25 Phosphate buffer pH 6.8 with 0.1% SDS was used as the dissolution medium. The 100% level was set at 201.5 µg/ml. Based on previous solubility data of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, the thermodynamic solubility of the compound from a crystalline batch should results in roughly 20% release. The higher weigh in was used to be able to detect a possible supersaturation of the investigated batches.

Calibration

- 30 Calibration and measurement were performed with the µDissolver from PION, a small-scale dissolution apparatus with in-situ UV probes, which allow high time resolution. A five point calibration was recorded from 0 to 207 µg/ml in phosphate buffer pH 6.8 with 2% SDS. Detection wavelength was set to 255-268 nm (method range, second derivative).

Measurement

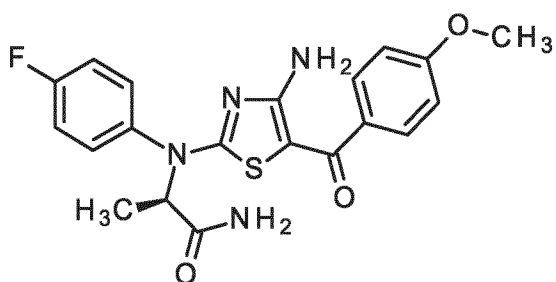
- 35 2.015 mg (±0.1mg) of the respective drug substance batch were transferred into the µDiss vessel and 10 ml of phosphate buffer pH 6.8 with 0.1% SDS were added. The dissolution profile was recorded over roughly five and a half hours. Each sample was measured as a duplicate (n=2). For the batch from Reference Example 2, the in-situ UV-probe of one vessel was blocked with

particles during the measurement, therefore this batch was only investigated from a single vessel (n=1).

5 EXPERIMENTAL SECTION – EXAMPLES

Example 1: Preparation of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (screening of process variants)

10 (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide



Example 1a

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (100 mg, 0.29 mmol, CAS 697232-63-6, WO2021/214019, see also Reference Example 1, step 1, below) was dissolved in N,N-dimethylformamide (2.1 mL), followed by the addition of potassium carbonate (K₂CO₃, 201 mg, 1.46 mmol) and (2S)-2-bromopropanamide (53.1 mg, 0.35 mmol, CAS 41137-34-2, purchased from Enamine). The reaction mixture was stirred at rt for 24 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 73.8 mg (0.18 mmol, 61% yield) of the title compound in 88% ee.

Example 1b

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (50 mg, 0.145 mmol) were dissolved in iso-propanol/acetone 3/1 (1.2 mL), followed by the addition of N,N,N,N-tetramethylguanidine (25 mg, 0.22 mmol) and (2S)-2-bromopropanamide (26.6 mg, 0.17 mmol). The reaction mixture was stirred at rt for 48 h and at 50°C for 2 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 22.7 mg (0.05 mmol, 38% yield) of the title compound in 61% ee.

30 Example 1c

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (50 mg, 0.145 mmol) were dissolved in 1-methyl-2-pyrrolidone (1.3 mL), followed by the addition of potassium carbonate (100 mg, 0.73 mmol) and (2S)-2-bromopropanamide (26.6 mg, 0.17 mmol). The reaction mixture was stirred at rt for 48 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 27 mg (0.06 mmol, 44% yield) of the title compound in 76% ee.

Example 1d

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (50 mg, 0.145 mmol) were dissolved in N,N-dimethylformamide (1.2 mL), followed by the addition of potassium bicarbonate (KHCO₃, 73 mg, 0.73 mmol) and (2S)-2-bromopropanamide (26.6 mg, 0.17 mmol). The reaction mixture was stirred at rt for 48 h and at 50°C for 2 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 27 mg (0.06 mmol, 44% yield) of the title compound in 63% ee.

Example 1e

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (100 mg, 0.29 mmol) were dissolved in N,N-dimethylformamide (2.1 mL), followed by the addition of potassium carbonate (201 mg, 1.46 mmol) and (2S)-2-bromopropanamide (53.1 mg, 0.35 mmol). The reaction mixture was stirred at rt for 5 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 73.8 mg (0.18 mmol, 61% yield) of the title compound in 91% ee.

Example 1f

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (50 mg, 0.145 mmol) were dissolved in N,N-dimethylformamide (1.2 mL), followed by the addition of N,N,N,N-tetramethylguanidine (25 mg, 0.22 mmol) and (2S)-2-bromopropanamide (26.6 mg, 0.17 mmol). The reaction mixture was stirred at rt for 24 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 26 mg (0.06 mmol, 43.6% yield) of the title compound in 86% ee.

Example 1g

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (65 mg, 0.19 mmol) were dissolved in N,N-dimethylformamide (1.4 mL), followed by the addition of potassium carbonate (133 mg, 0.96 mmol) and (S)-1-amino-1-oxopropan-2-yl 4-methylbenzenesulfonate (56 mg, 0.23 mmol). The reaction mixture was stirred at rt for 24 h and 60°C for 2 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 46 mg (0.11 mmol, 58% yield) of the title compound in 88% ee.

Example 1h

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (71.5 mg, 0.21 mmol) were dissolved in N,N-dimethylformamide (1.4 mL), followed by the addition of potassium carbonate (144 mg, 1.04 mmol) and (S)-1-amino-1-oxopropan-2-yl 4-methylbenzenesulfonate (61 mg, 0.25 mmol). The reaction mixture was stirred at rt for 4 h and 60°C for 1 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 24 mg (0.06 mmol, 28% yield) of the title compound in 94% ee.

Example 1i

[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (71.5 mg, 0.21 mmol) were dissolved in N,N-dimethylformamide (1.4 mL), followed by the addition of N,N,N,N-tetramethylguanidine (36 mg, 0.31 mmol) and (S)-1-amino-1-oxopropan-2-yl 4-methylbenzenesulfonate (61 mg, 0.25 mmol). The reaction mixture was stirred at rt for 2 h and 60°C for 1 h, filtrated and purified by preparative HPLC (Method HPLC1) to give 24 mg (0.06 mmol, 28% yield) of the title compound in 95% ee.

Analytical data of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as obtained in Examples 1a – 1i:

LC/MS (Method HPLC2): t_R = 1.06 min/MS (ESIpos): m/z = 415.5 $[M+H]^+$

Analytical Chiral HPLC (Method HPLC3): t_R = 5.92 min (Example 1a; t_R for Examples 1b – 1i being in the range from 5.9 to 6.2 minutes; the (S)-enantiomer was found to elute at t_R 3.49 to 3.55 minutes)

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ ppm = 1.16 (d, 3 H), 3.75 (s, 3 H), 5.06 (q, 1 H), 6.93 (d, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (dd, 2 H), 7.48 (d, 2 H), 7.57 (s, 1 H), 7.64 (dd, 2 H), 7.79 - 8.38 (m, 2 H).

Example 2: Crystallisation of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide to give a microcrystalline form of the present invention

2.5 g of solid (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide was weighed into a 100 mL crystallisation vessel. 26.74 g of acetone and 2.98 g of water were added. The suspension was stirred at 20 °C for 10 minutes, resulting in an API solution. In a second 100 mL crystallisation vessel, 59.42 g of water was pre-cooled to 5 °C and stirred. The API solution was dosed onto the pre-cooled water over 30 minutes, while the temperature was maintained at 5 °C. The resulting suspension was isolated through filtration and the filter cake

was rinsed with a displacement wash of Acetone/H₂O 70wt% (5.0 g) and afterwards with a displacement wash of H₂O (5.0 g). The wet filter cake was dried in vacuum at 60 °C. Yield: 89.9%.

XRPD analysis (Method XRPD1) of the thus obtained (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide did not show any evidence of the presence of amorphous material or a difference in crystalline form (Figure 1) as compared to WO 2021/214019 (see Figure 9, Table 16 therein). DSC (Method DSC1) indicated full crystallinity and did not show any evidence of the presence of amorphous material either (Figure 2). PSD as determined with Method PSD1 was found to be x10 / x50 / x90 is 1.8 / 4.3 / 12.6 µm.

Example 3: Preparation of microcrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

A suspension of [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-methoxyphenyl)methanone (120 g, 349 mmol), (2S)-2-bromopropanamide (63.7 g, 419 mmol, 1.2 equiv, 95% enantiomeric excess) and potassium phosphate (K₃PO₄, 148 g, 699 mmol, 2.0 equiv) in acetonitrile (1200 mL) was heated to 60 °C and stirred at that temperature for 1 h. The temperature was subsequently lowered to 20 °C within 40 min, and water (1200 mL) was simultaneously added within 20 min. The resulting triphasic mixture was stirred at 20 °C for 3 h, filtered, and the filter cake was washed with water (3 x 240 mL), affording (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as a light yellow solid (124 g wet, 99.14 % purity, 99.2% enantiomeric excess). The water content of the wet filter cake was determined and found to be 16%, corresponding to 20 mL of residual water in the wet filter cake. This amount was considered in the subsequent microcrystallization step.

The wet filter cake was dissolved in a mixture of acetone (1350 mL) and water (130 mL) at ambient temperature, resulting in a solution with a small amount of residual solid. The mixture was filtered, and the filtrate was added to water (2000 mL) at 4–10 °C within 38 min. The resulting disperse, off-white suspension was filtered and the filter cake was washed with water (2 x 150 mL) and dried in vacuo at 50 °C, furnishing (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (90.3 g, 216 mmol, 62% yield, 99.12% purity, 99.3% enantiomeric excess) as an off-white, lumped powder. PSD as determined with Method PSD2a was found to be (x10 / x50 / x90): 1.2 / 4.6 / 16.1 µm).

The chemical purity and enantiomeric excess were determined as specified above according to HPLC methods 4 and 5, *supra*.

Chemical purity (HPLC method 4): t_R = 5.4 min.

Enantiomeric excess (HPLC method 5):

t_R = 2.9 min ((2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide)

5 t_R = 2.3 min ((2S)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide)

10 XRPD analysis (Method XRPD1) of the thus obtained (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide did not show any evidence of the presence of amorphous material or a difference in crystalline form as compared to WO 2021/214019 (Figure 3). DSC (Method DSC1) indicated full crystallinity and did not show any evidence of the presence of amorphous material either (Figure 4). The dissolution of the material was only minimally slower as compared to the dissolution of the material obtained from jet milling of macrocrystalline material (see Reference Example 1) but substantially faster as compared to the macrocrystalline comparator disclosed in Reference Example 2 (Figures 5, 6).

15

Preparation of starting materials for Example 3:

Preparation of [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-methoxyphenyl)methanone:

20 A mixture of 1-fluoro-4-isothiocyanato-benzene (300 g, 1.96 mol) and triethylamine (297 g, 2.94 mol, 1.5 equiv) in acetonitrile (0.90 L) was warmed to 60 °C. To this mixture was added a solution of cyanamide (90.6 g, 2.15 mol, 1.1 equiv) in acetonitrile (1.35 L) within 1 h. After an additional 1 h, a solution of 2-bromo-1-(4-methoxyphenyl)ethanone (449 g, 1.96 mol, 1.0 equiv) in acetonitrile (2.25 L) was added at 60 °C within 75 min. After an additional 15 min, the suspension was cooled to 20 °C within 0.5 h and stirred at that temperature for an additional
25 0.5 h. The mixture was filtered, the precipitate was washed with H₂O and dried at 50 °C in vacuum to yield [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-methoxyphenyl)methanone (606 g, 1.75 mol, 89% yield, 99.0% purity) as a yellow to orange solid.

Preparation of (2S)-2-bromopropanamide:

30 A mixture of (2S)-2-bromopropanoic acid (200 g, 1.31 mol, 88% ee, purchased from ABCR) and thionyl chloride (218 g, 1.83 mol, 1.4 equiv) were heated to 50 °C. After 18 h, the resulting crude acyl chloride was diluted with 2-methyltetrahydrofuran (1.85 L) and added to 30% aqueous ammonia solution (381 g, 3.27 mol, 2.5 equiv) at -15 to 7 °C within 75 min. After completion of the addition, the temperature was raised to 20 °C and water (200 mL) was
35 added. The layers were separated and the aqueous layer was extracted with 2-methyltetrahydrofuran. The combined organic layers were washed with saturated aqueous

sodium chloride solution and part of the solvent was removed in vacuo at 40 °C. n-Heptane was added, the resulting suspension was cooled to 0-5 °C, kept at that temperature for 1 h, filtered, and the precipitate was washed with n-heptane. Drying of the filter cake in vacuum at 35 °C afforded (2S)-2-bromopropanamide (147 g, 967 mmol, 74% yield, 99.65% purity, 95% enantiomeric excess) as a colourless solid.

Example 4: Preparation of microcrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

(2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide powder (essentially anhydrous, prepared according to the protocol described in Example 3) (180 g) was added to a mixture of acetone (877 g) and water (175.5 g) and heated up to 55 °C, resulting in a solution with a small amount of residual solid. The mixture was filtered with a K300 20 µm filter cloth, and the filtrate was cooled down to 35 °C in 1 hour. 35 g of a nanosuspension (prepared via method described in European patent application No. 22196150.1, published as EP4154872A1, EXAMPLES 1.1) containing 79.8 wt% water, 10 wt% (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, 8 wt% PVP K12, 2 wt% HPC Klucel ELF and 0.2 wt% SDS was added as seeding material. Subsequently the suspension was cooled down to 20 °C in 1 hour. To increase the yield, 1165.5 g of water was continuously added over 1 hour with a subsequent stirring time of 1 hour. The resulting disperse, white suspension was filtered in a pressure filter and a PP 2703 filter cloth. The filter cake was washed with water (2 x 800 mL) and dried in vacuum at 50 °C, furnishing (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (164.55 g, 91.4% yield, 99.59% purity, 99.74% enantiomeric excess) as an white, lumped powder. PSD as determined with Method PSD4 was found to be (x10 / x50 / x90): 3.22 / 6.87 / 13.2 µm (Figure 13).

XRPD analysis (Method XRPD1) of the thus obtained (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide did not show any evidence of the presence of amorphous material or a difference in crystalline form as compared to the disclosure of WO 2021/214019 (Figure 15); likewise, DSC analysis (Method DSC1) did not show any evidence of the presence of amorphous material (Figure 14).

The dissolution of the material was minimally faster or equal as compared to the dissolution of the material obtained from Example 3. Specifically, dissolution of tablets containing equal amounts of microcrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide obtained as described in Example 3 (-▲-) and Example 4 (-◆-) was determined according to PH. Eur. 2.9.3., using acetate buffer pH 4.5 containing 2% SDS (sodium dodecyl sulfate) as dissolution medium (Figure 16). A paddle apparatus as specified in the U.S. pharmacopeia (USP Apparatus 2 (paddle)) was used with a stirrer speed of 50 rpm and with a total medium volume of 900 mL.

EXPERIMENTAL SECTION – REFERENCE EXAMPLES FOR COMPARISON TO EXAMPLES ACCORDING TO THE PRESENT INVENTION

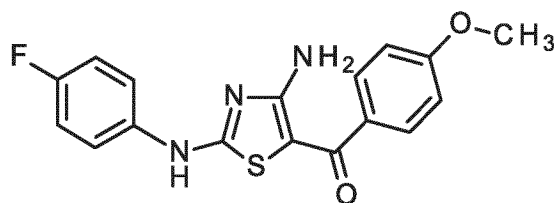
- 5 **Reference Example 1:** Partial Amorphisation of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as a result of jet-milling

Protocol of jet-milling

- 10 For the micronisation of the compound a LSM Zero air jet mill was used.
- The compound prepared as shown below (4.00 g) was sieved through a 1 mm manual sieve and added in small fractions to the air jet mill. Micronisation was carried out at room temperature (23°C, 40% relative humidity) with an injector pressure of 8 bar, a grinding pressure of 6 bar and nitrogen as air jet medium for a duration of about 1 h.
- 15 Particle size analysis (Method PSD3), DSC (Method DSC2) and XRPD analysis (Method XRPD2) of the compound were performed after the micronisation process and the yield was determined (3.78 g, 94.5%). PSD of the material thus obtained, as determined with Method PSD3, was found to be (x10 / x50 / x90): 2.55 / 11.08 / 25.95 µm.
- 20 (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as obtained by chemical synthesis described below and as employed for jet milling is a crystalline solid, characterised by a diffractogram shown in Figure 7 (obtained with method XRPD2) and a thermal behaviour as characterised with method DSC2 (Figure 8), where a single endothermic event (melting) occurs at 195 °C (onset).
- 25 The partial amorphisation which occurred during jet milling could be clearly detected through Differential Scanning Calorimetry (DSC, method DSC2), where a re-crystallisation of partially amorphous material is seen in an exothermic event between 100 and 140 °C (Figure 9). A direct comparison of XRPD data (obtained with Method XRPD2) of the material prior and after jet-
- 30 milling also shows the reduced level of crystallinity (Fig. 10) being present in the jet-milled material (the latter resulting in the lower graph in Figure 10).

The material used for jet-milling was prepared as follows:

Step 1: [4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone



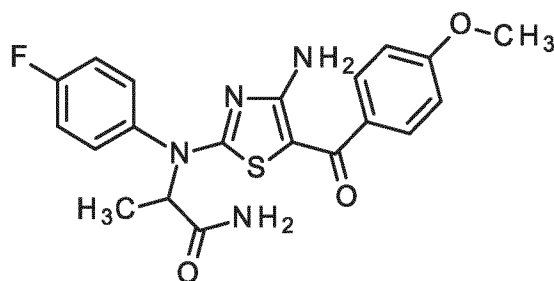
1-Fluoro-4-isothiocyanatobenzene (51.175 g, 98%, 327.4 mmol, CAS 1544-68-9, Aldrich) was dissolved in acetonitrile (1930 mL, Honeywell). Cyanamide (16.52 g, 393 mmol, CAS 420-04-2, Aldrich) was added at room temperature, followed by DBU (48.9 mL, 327.4 mmol, Sigma-Aldrich). The reaction mixture was stirred for 45 minutes, then additional DBU (24.4 mL, 163.7 mmol), followed by 2-bromo-1-(4-methoxyphenyl) ethan-1-one (75 g, 327.4 mmol, CAS 2632-13-5, Fluka and Aldrich) as a solution in acetonitrile (570 mL), were added at room temperature. The reaction mixture was stirred for 48 h at rt upon formation of a suspension. Plenty of water was added, the precipitate was filtered off, washed with water, suspended in water, and dried by lyophilization to yield 122.57 g (quant. yield, 91% pure) of a solid that was employed in the next step without further purification.

^1H NMR (400 MHz, DMSO- d_6) δ ppm= 3.81 (s, 3 H) 7.01 (d, 2 H) 7.21 (dd, 2 H) 7.59 - 7.65 (m, 2 H) 7.66 (d, 2 H) 8.12 (br s, 2 H) 10.76 (br s, 1 H).

LC/MS (Method HPLC2): t_R = 1.07 min; MS(ESIpos) m/z = 344.2 $[\text{M}+\text{H}]^+$.

20

Step 2: rac-2-(N-[4-Amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

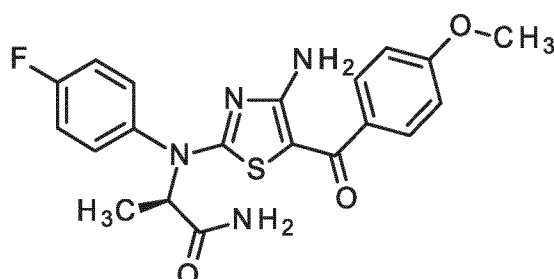


[4-amino-2-(4-fluoroanilino)-1,3-thiazol-5-yl](4-methoxyphenyl)methanone (87.36 g, 254.4 mmol) were dissolved in N,N-dimethylformamide (1863 mL, Aldrich), followed by the addition of potassium carbonate (175.8 g, 1272 mmol, Riedel-de-Haen) and rac-2-bromopropanamide (46.4 g, 305.3 mmol, CAS 5875-25-2, Aldrich). The reaction mixture was stirred at rt for 3 days. Water was added and the precipitate was filtered off, washed with water, suspended in water, and dried by lyophilization to give 82.6 g (199.29 mmol, 78% yield) of the title compound.

¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm = 1.16 (d, 3 H), 3.75 (s, 3 H), 5.06 (q, 1 H), 6.93 (d, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (dd, 2 H), 7.48 (d, 2 H), 7.57 (s, 1 H), 7.64 (dd, 2 H), 7.79 - 8.38 (m, 2 H).

5 LC/MS (Method HPLC2): *t*_R = 1.06 min/MS (ESIpos): *m/z* = 415.5 [M+H]⁺

Step 3: (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide



10

rac-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (82.60 g, 199.3 mmol) was separated by chiral HPLC to yield 33.0 g (79.62 mmol, 39.95 %) of S-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 1 and 38.8 g (93.61 mmol, 46.97 %) of R-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, enantiomer 2 with slight impurities. R-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide was suspended in methyl tert.-butylether (500 mL, Aldrich) and stirred for 16 days. The suspension was filtered and the solid was washed with methyl tert.-butylether. Water was added and the precipitate was filtered off, washed with water, suspended in water, and dried by lyophilization to give 35.7 g (84.44 mmol, 42.4% yield) of the title compound as crystalline material which was characterised as shown below, and as discussed above in context of Figures 7 and 8.

15

20

Preparative chiral HPLC (Method HPLC6)

Enantiomer 1 *t*_R = 10.2 – 12.1 min

25

Enantiomer 2 *t*_R = 14.6 – 21.4 min

Analytical chiral HPLC (Method HPLC3): Enantiomer 2, (R), *t*_R = 5.99 min

30

¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm = 1.16 (d, 3 H), 3.75 (s, 3 H), 5.06 (q, 1 H), 6.93 (d, 2 H), 7.22 - 7.27 (m, 1 H), 7.34 (dd, 2 H), 7.48 (d, 2 H), 7.57 (s, 1 H), 7.64 (dd, 2 H), 7.79 - 8.38 (m, 2 H).

$[\alpha]_D^{20} = +150.65^\circ$ (chloroform)

Reference Example 2: Macrocrystalline (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

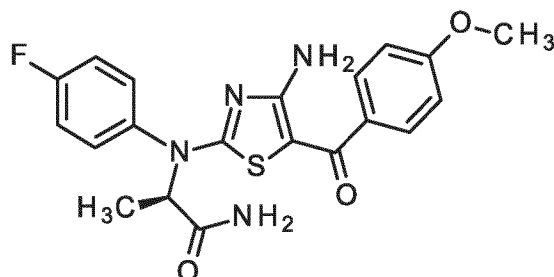
Macrocrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide was produced by thorough mixing to homogeneity of solids of three qualitatively equivalent sub-batches of (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, each produced according to the following procedure:

A suspension of [4-amino-2-(4-fluoroanilino)thiazol-5-yl]-(4-methoxyphenyl)methanone (120 g, 349 mmol), (2S)-2-bromopropanamide (63.7 g, 419 mmol, 1.2 equiv, 90% enantiomeric excess) and potassium phosphate (K_3PO_4 , 148 g, 699 mmol, 2.0 equiv) in acetonitrile (1200 mL) was heated to 60 °C and stirred at that temperature for 1 h. The temperature was subsequently lowered to 20 °C within 40 min, and water (1200 mL) was simultaneously added within 20 min. The resulting triphasic mixture was stirred at 20 °C for 3 h and filtered. The filter cake was washed with water (3 x 240 mL) and dried in vacuo at 50 °C, affording (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide as a light yellow solid (105 g, 252 mmol, 72% yield, 99.74% purity, 99.0% enantiomeric excess). PSD as determined with Method PSD2b was found to be (x10 / x50 / x90): 5.6 / 34 / 131 μm .

XRPD analysis (Method XRPD3) of the thus obtained macrocrystalline (2R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide did not show any evidence of the presence of amorphous material or a difference in crystalline form as compared to WO 2021/214019 (Figure 11). DSC (Method DSC3) indicated full crystallinity and did not show any evidence of the presence of amorphous material either (Figure 12).

CLAIMS

1. A microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,



5 (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide

in which

the presence of amorphous forms is below 15 %,

and the particle size distribution is as follows: x10 is <5 µm, x50 is <10 µm, and x90 is <35 µm.

10 2. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1,

in which

the particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 µm, x50 is in the range of 3 to 7 µm, and x90 is in the range of 8 to 20 µm.

15

3. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1,

in which

the particle size distribution is as follows: x10 is in the range of 0.3 to 4 µm, x50 is in the range of 4 to 10 µm, and x90 is in the range of 10 to 20 µm.

20

4. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 2 or 3

in which

25 the enantiomeric excess is at least 95 %.

5. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 2, 3 or 4,

in which

the presence of amorphous forms is below 5 %.

5

6. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 2, 3, 4 or 5,

in which

the particle size distribution is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

10

7. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 3, 4 or 5,

in which

the particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

15

8. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 2, 4 or 5,

in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 0.5 to 2.5 μm , x50 is in the range of 3 to 7 μm , and x90 is in the range of 8 to 20 μm .

20

25

9. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 3, 4 or 5,

in which

the enantiomeric excess is at least 98 %,

the presence of amorphous forms is below 5 %,

30

and their particle size distribution is as follows: x10 is in the range of 0.3 to 4 μm , x50 is in the range of 4 to 10 μm , and x90 is in the range of 10 to 20 μm .

10. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 2, 3, 4, 5, 6 or 8,

in which

the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 2 μm , x50 is in the range of 4 to 5.5 μm , and x90 is in the range of 10 to 18 μm .

11. The microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to claim 1, 3, 4, 5, 7 or 9,

in which

the enantiomeric excess is at least 99 %,

the presence of amorphous forms is below 5 %,

and their particle size distribution is as follows: x10 is in the range of 1 to 4 μm , x50 is in the range of 4 to 8 μm , and x90 is in the range of 12 to 18 μm .

12. A method of preparing microcrystalline forms of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said method comprising the steps of

dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a solvent or solvent mixture, followed by

bringing of the resulting solution together with an antisolvent, followed by

isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

13. The method according to claim 12, said method comprising the steps of

adding an optionally filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a dipolar aprotic and/or protic solvent to an antisolvent, and

isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

- 5 14. The method according to claim 12 or 13, said method comprising the steps of
- adding a filtered solution of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone to water over a time range of 30 minutes and 1 hour, at a temperature in the range of 4°C to 10°C, and
- 10 isolation and drying of the resulting precipitate,
- to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

15. The method according to claim 12, said method comprising the steps of

- 15 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in a solvent,
- 3) creating a supersaturation,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one
- 20 surfactant and at least one polymer,
- 5) followed by one or more of the sub-steps selected from
- a. cooling
- b. addition of antisolvent, and
- c. evaporating solvent,
- 25 6) isolation and drying of the resulting precipitate,
- to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

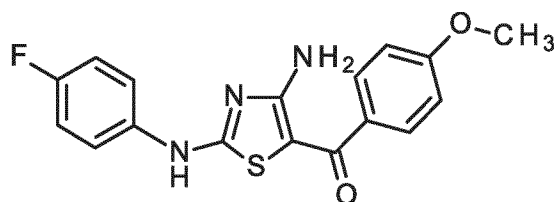
16. The method according to claim 12 or 15, said method comprising the steps of, said methods
- 30 comprising the steps of

- 2) dissolving (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in acetone containing water in the range from 10 to 30 % v/v, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 5°C to 30°C,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, water, at least one surfactant and at least two polymers,
- 5) followed by
 - a. cooling, followed by
 - b. addition of water,
- 6) isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

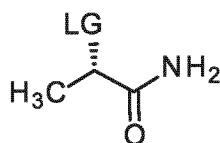
17. The method according to claim 12 or 13, said method comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

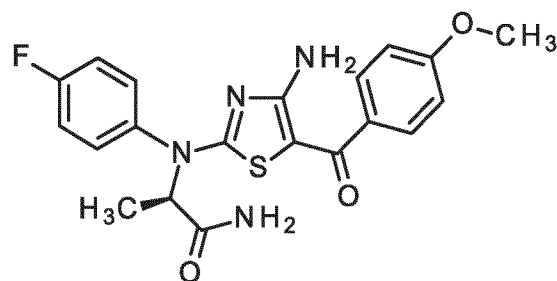
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



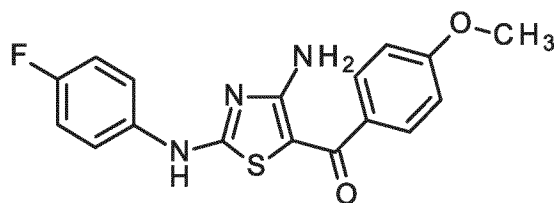
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- ii. dissolving the crude product resulting from step i. in a dipolar aprotic and/or protic solvent with subsequent optional filtering,
- 5 iii. addition of the solution or filtrate resulting from step ii. to an antisolvent, and
- iv. isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

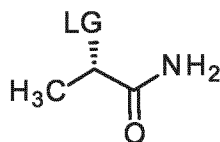
10 18. The method according to claim 12, 13 or 17, said method comprising the steps of

- i. allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)



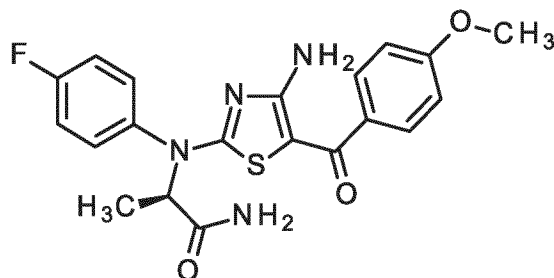
(III)

in which LG is a leaving group as defined *supra*,

in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-

dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

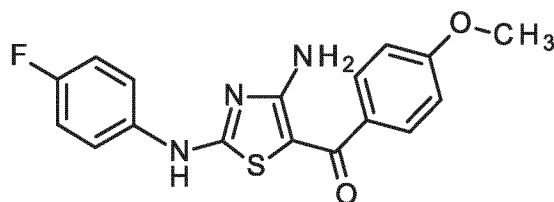
thereby giving



- 5 (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,
- ii. dissolving the crude product resulting from step (i) in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone with subsequent filtering,
- iii. addition of the filtrate to water over a time in the range of 20 minutes and 1.5 hours,
- 10 at a temperature in the range of 0°C to 20°C, and
- iv. isolation and drying of the resulting precipitate,

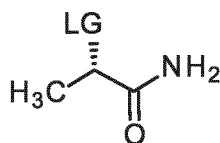
to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

- 15 19. The method according to claim 12, 13, 14, 17 or 18, said method comprising the steps of
- i. allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

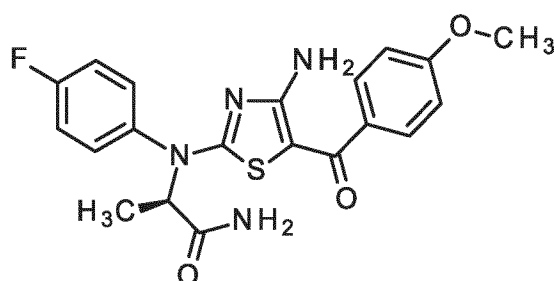


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving



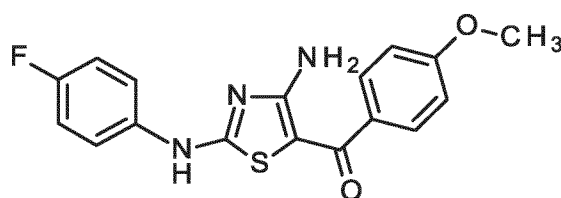
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- ii. dissolving the crude product resulting from step (i) in a mixture of acetone and water in a ratio in the range of 8:1 (v/v) to 12:1 (v/v) in favour of acetone with subsequent filtering,
- iii. addition of the filtrate to water over a time range of 30 minutes and 1 hour, at a temperature in the range of 4°C to 10°C, and
- iv. isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

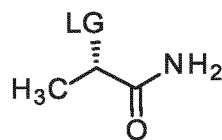
20. The method according to claim 12 or 15, said method comprising the steps of, said method comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

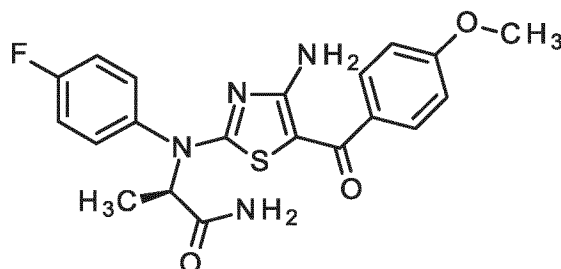
to react with an intermediate compound of formula (III)



(III)

in which LG is a leaving group as defined *supra*,

thereby giving



5

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

2) dissolving the crude product resulting from step 1) in a solvent,

3) creating a supersaturation,

10

4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, antisolvent, at least one surfactant and at least one polymer,

5) followed by one or more of the sub-steps selected from

a. cooling

b. addition of antisolvent, and

15

c. evaporating solvent,

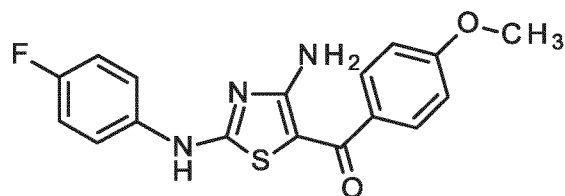
6) isolation and drying of the resulting precipitate,

to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

20

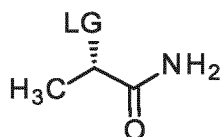
21. The method according to claim 12, 15, 16 or 20, said method comprising the steps of

1) allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

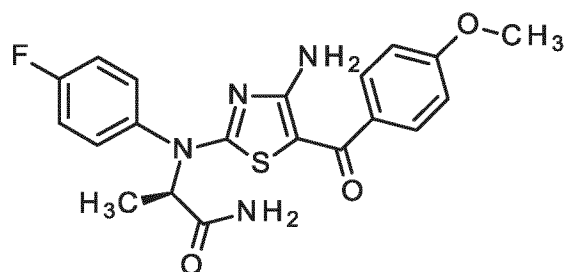


(III)

in which LG is a leaving group as defined *supra*,

in the presence of at least 1 equivalent of a base selected from an alkali carbonate, an alkali bicarbonate and an alkali phosphate, at a temperature in the range of 20 to 80 °C, in a solvent selected from N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, propionitrile, N-methyl pyrrolidinone, acetone, and iso-propanol, for a time in the range of 30 minutes to 24 hours,

thereby giving



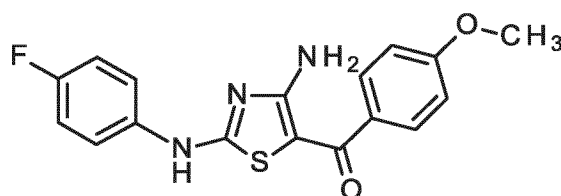
(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in acetone containing water in the range from 10 to 30 % v/v, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 5°C to 30°C,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, water, at least one surfactant and at least two polymers,
- 5) followed by

- a. cooling, followed by
 - b. addition of water,
 - 6) isolation and drying of the resulting precipitate,
- to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

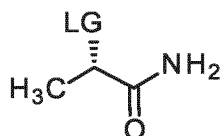
22. The method according to claim 12, 15, 16, 20 or 21, said method comprising the steps of

- 1) allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

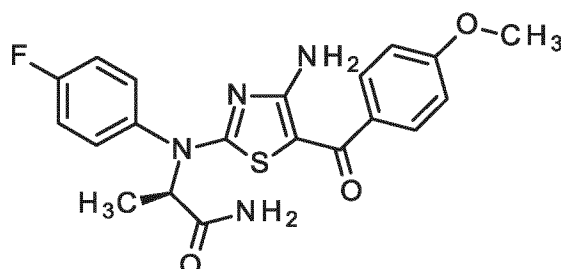


(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, optionally followed by lowering the temperature to 20°C over a time in the range of up to one hour,

thereby giving

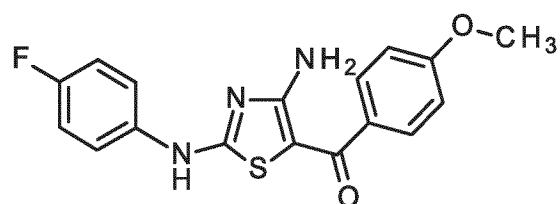


(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide,

- 2) dissolving the crude product resulting from step 1) in acetone containing water in the range from 10 to 30 % v/v, at a temperature in the range from 40°C to 70°C, with optional filtering,
- 3) creating a supersaturation via cooling, the reduction of the temperature being in the range from 15°C to 25°C,
- 4) adding a nanosuspension comprising further (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide (5 – 20 % w/w), water (60 – 90 % w/w), at least one surfactant (0.05-1 % w/w) and at least two polymers (independently from each other 0.5-15 % w/w each), wherein
- the at least one surfactant comprises an alkali salt of a C₈-C₂₀-alkylsulfuric acid, and the at least two polymers comprise hydroxypropylcellulose and polyvinylpyrrolidone,
- and wherein the quantity of said nanosuspension is in the range of 1 to 6 % w/w of the supersaturated solution resulting from step 3),
- 5) followed by
- a. cooling the reduction of the temperature being in the range from 5°C to 25°C, followed by
- b. addition of water,
- 6) isolation and drying of the resulting precipitate,
- to give a microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

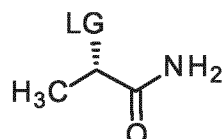
23. A pharmaceutical composition comprising the microcrystalline form of (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide according to any one of claim 1 to 11 and one or more pharmaceutically acceptable excipients.

24. A method of preparing (R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide, said method comprising the step of allowing an intermediate compound of formula (II)



(II)

to react with an intermediate compound of formula (III)

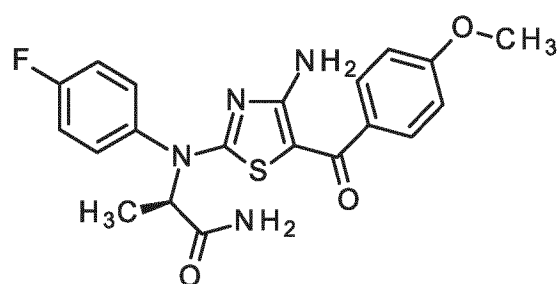


5

(III)

in which LG is a leaving group as defined *supra*,

thereby giving

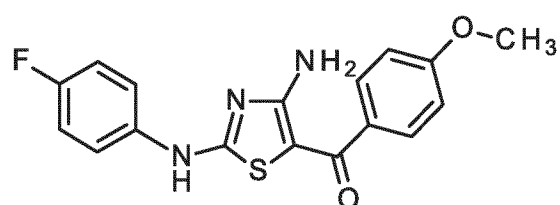


(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide.

10

25. A method according to claim 24, said method comprising the step of

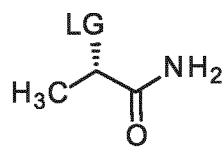
allowing an intermediate compound of formula (II)



(II)

15

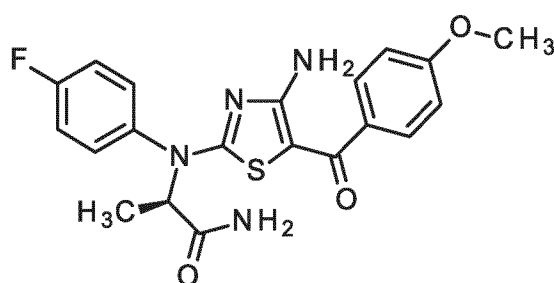
to react with an intermediate compound of formula (III)



(III)

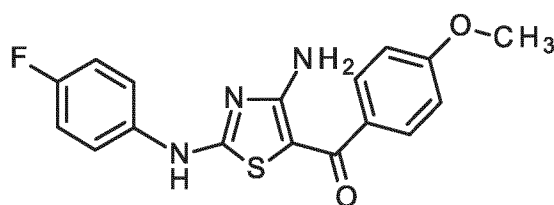
in which LG is a bromine atom,

in the presence of 1.5 to 6 equivalents of a base selected from potassium carbonate and
 5 potassium phosphate, at a temperature in the range of 40 to 80 °C, in a solvent selected from N,N-dimethylformamide and acetonitrile, for a time in the range of 30 minutes to 6 hours,
 thereby giving



(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an
 10 enantiomeric excess of at least 90 %.

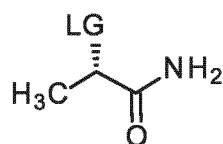
26. A method according to claim 24 or 25, said method comprising the step of
 allowing an intermediate compound of formula (II)



15

(II)

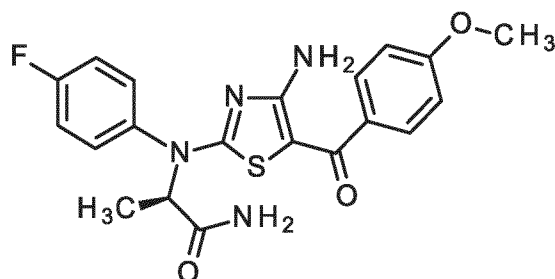
to react with an intermediate compound of formula (III)



(III)

in which LG is a bromine atom,

in the presence of 1.5 to 5 equivalents of potassium phosphate, at a temperature in the range of 50 to 70 °C in acetonitrile for a time in the range of 1 to 2 hours, followed by lowering the temperature to 20°C over a time in the range of up to one hour, thereby giving



5

(R)-2-(N-[4-amino-5-(4-methoxybenzoyl)thiazol-2-yl]-4-fluoro-anilino)propanamide in an enantiomeric excess of at least 95 %.

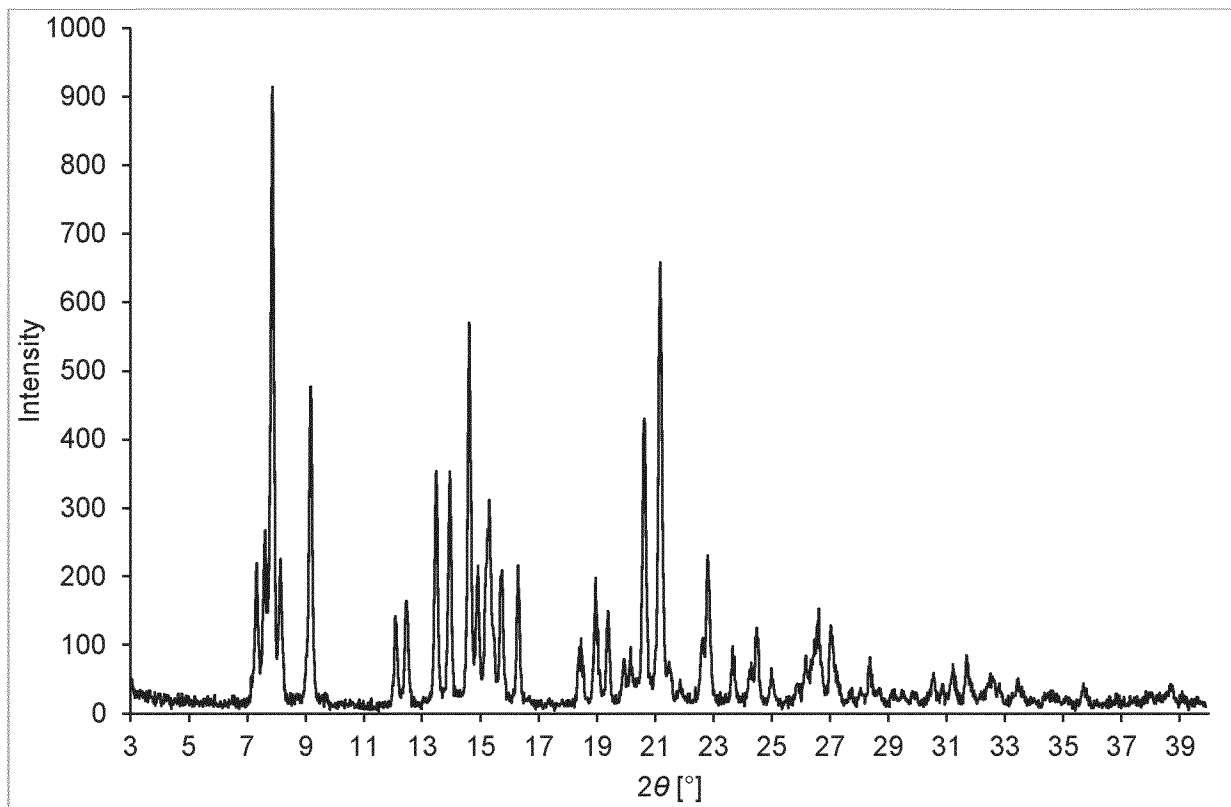


Figure 1

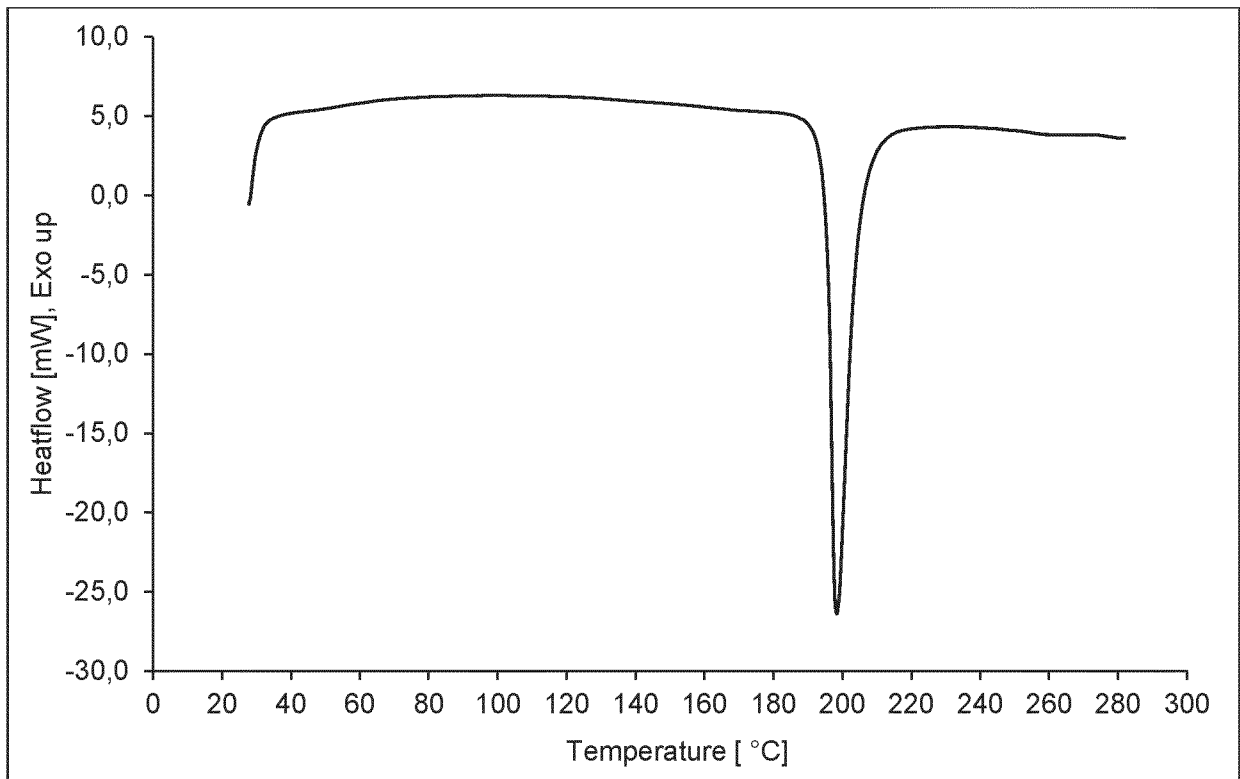


Figure 2

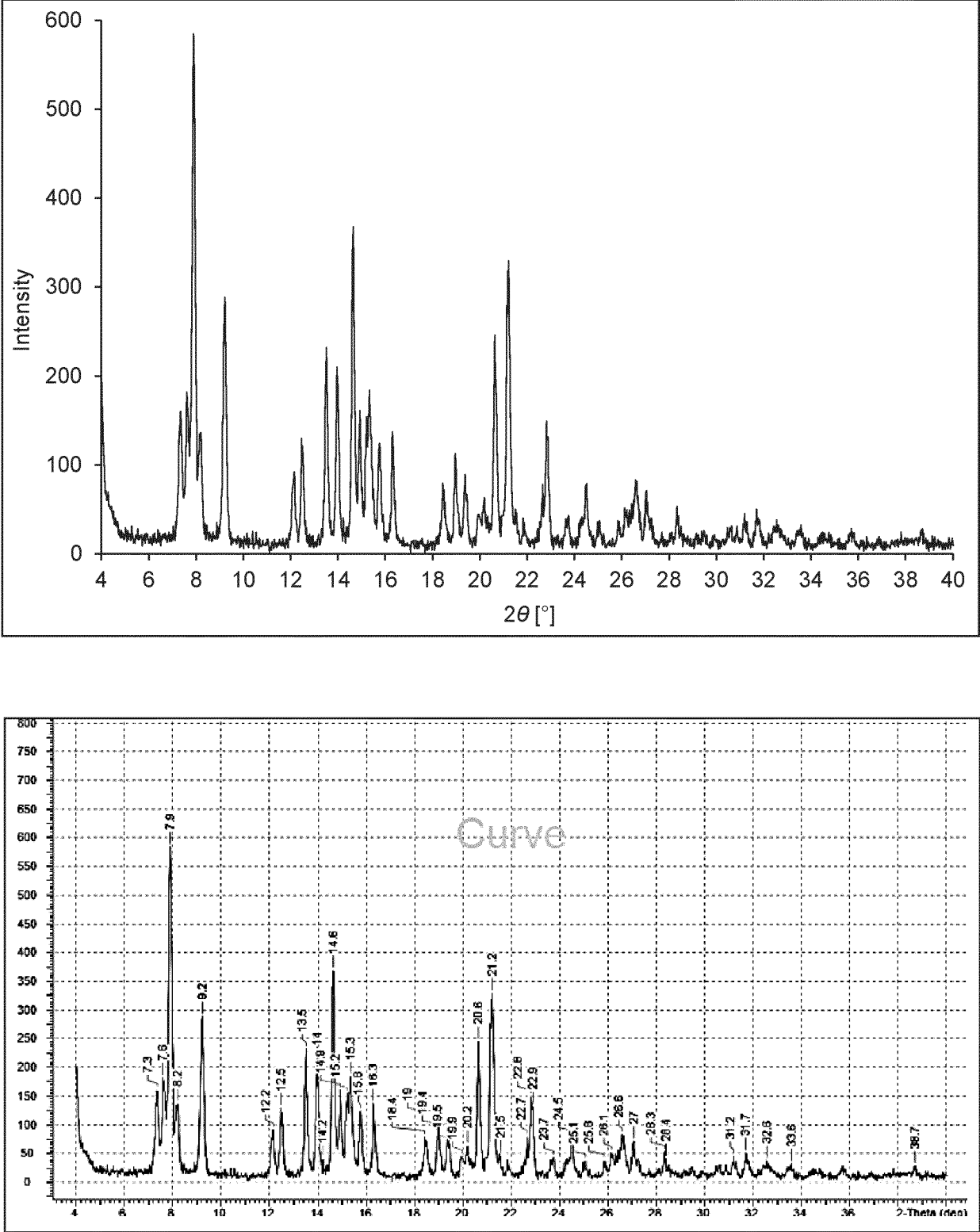


Figure 3

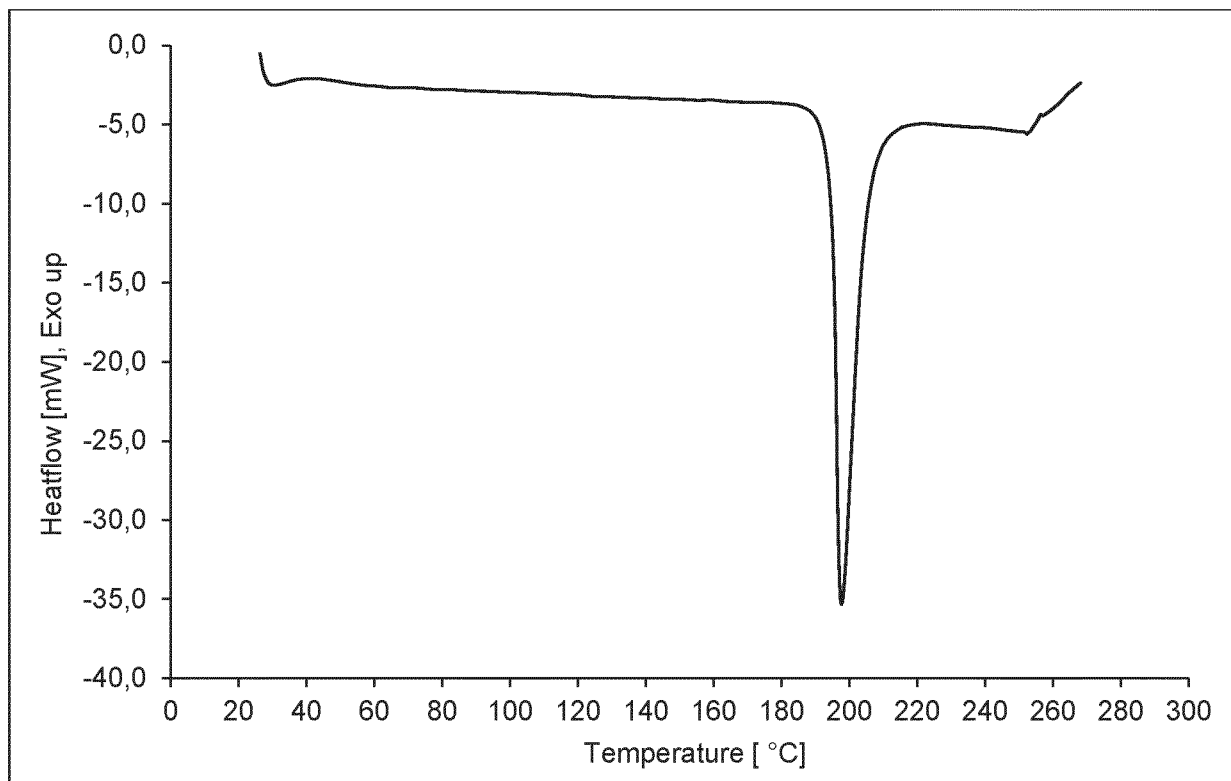


Figure 4

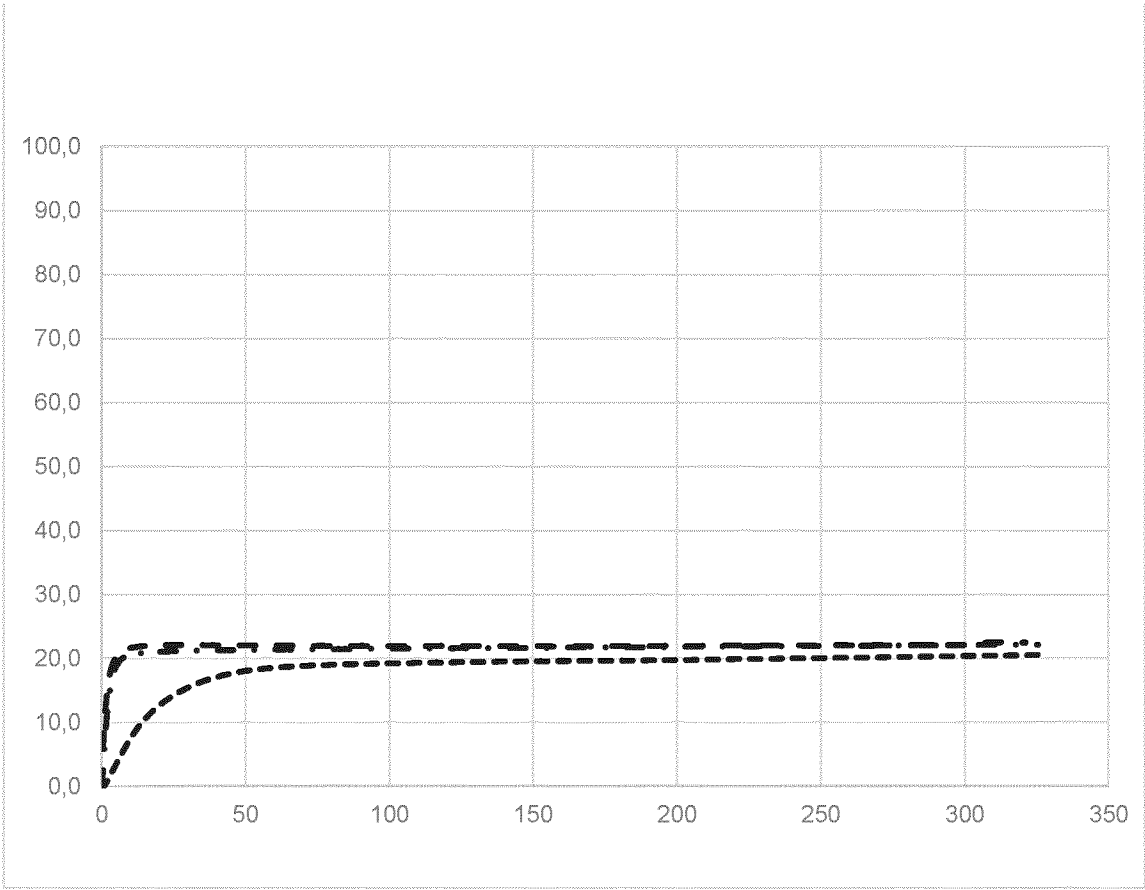


Figure 5

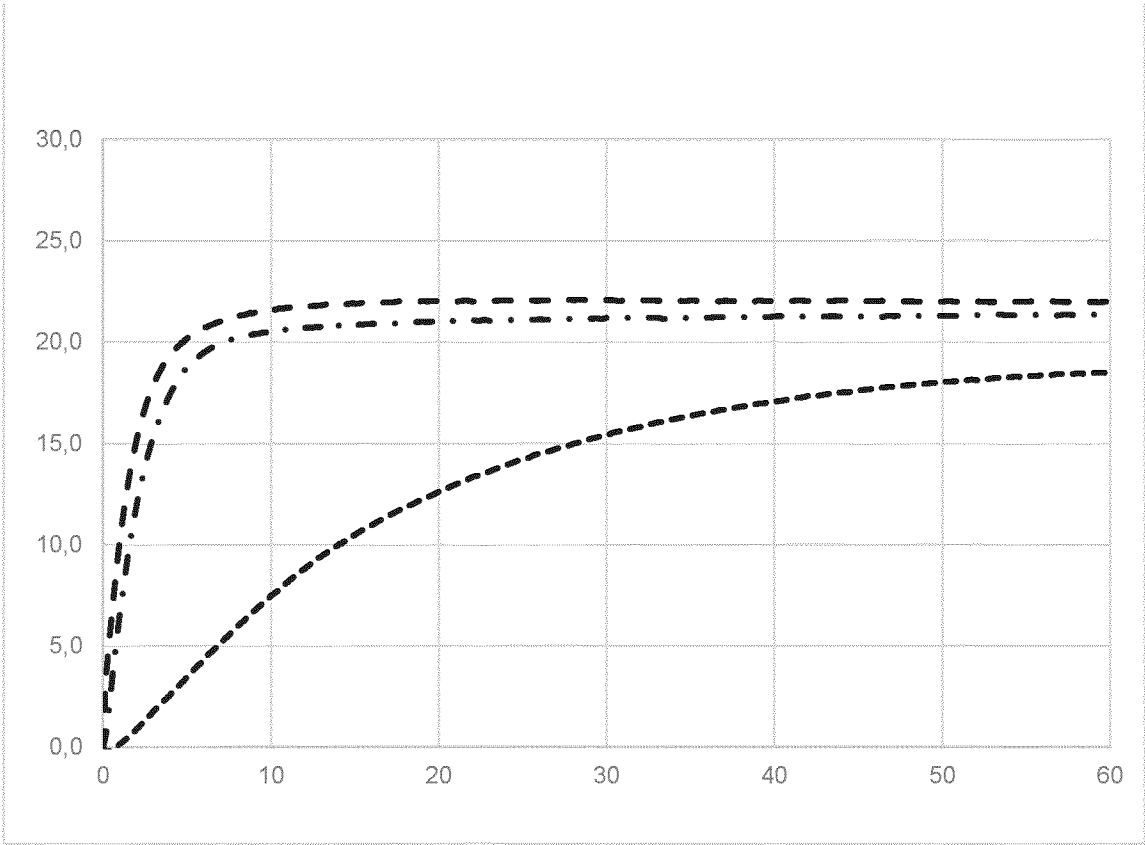


Figure 6

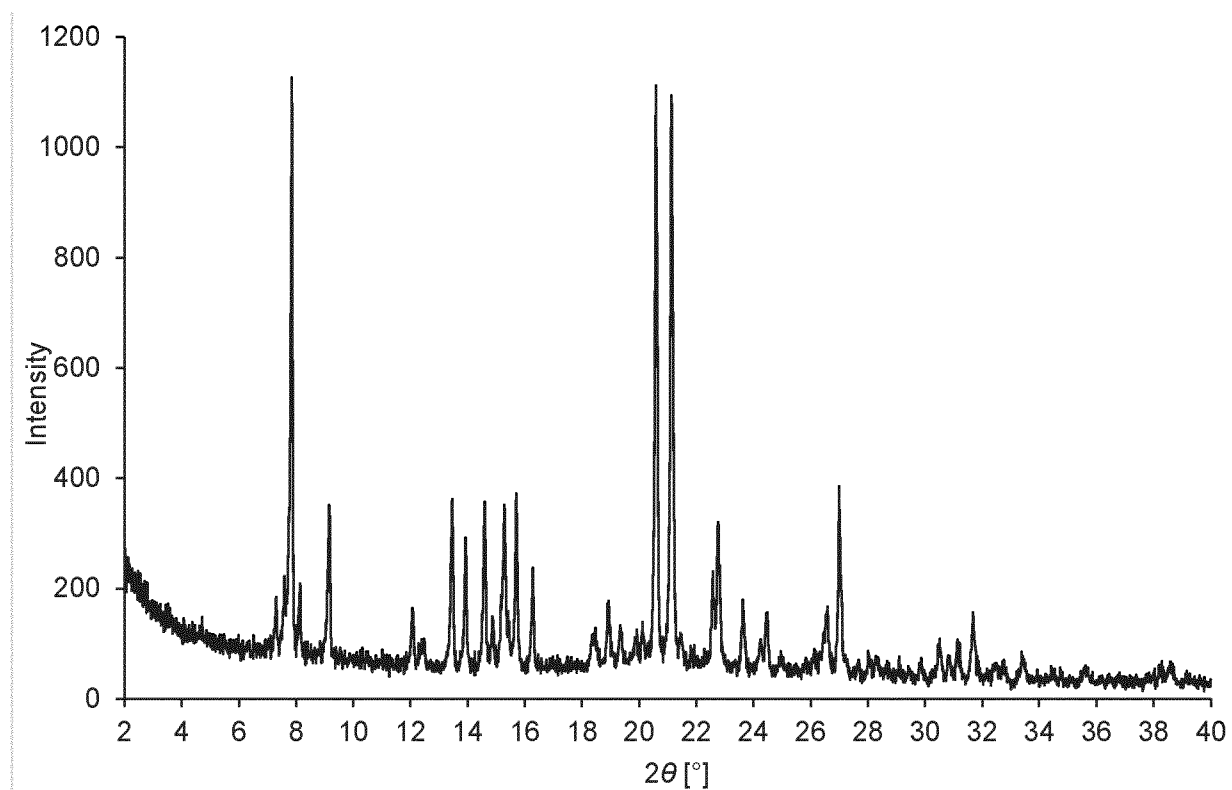


Figure 7

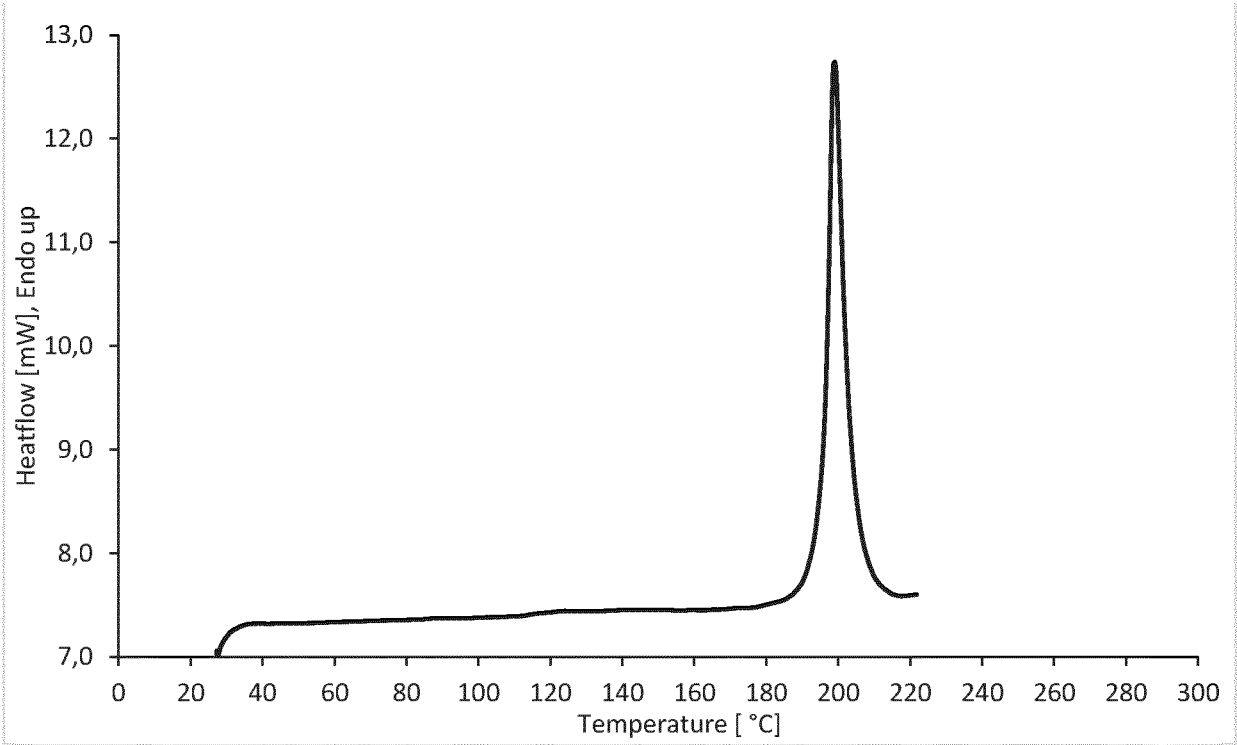


Figure 8

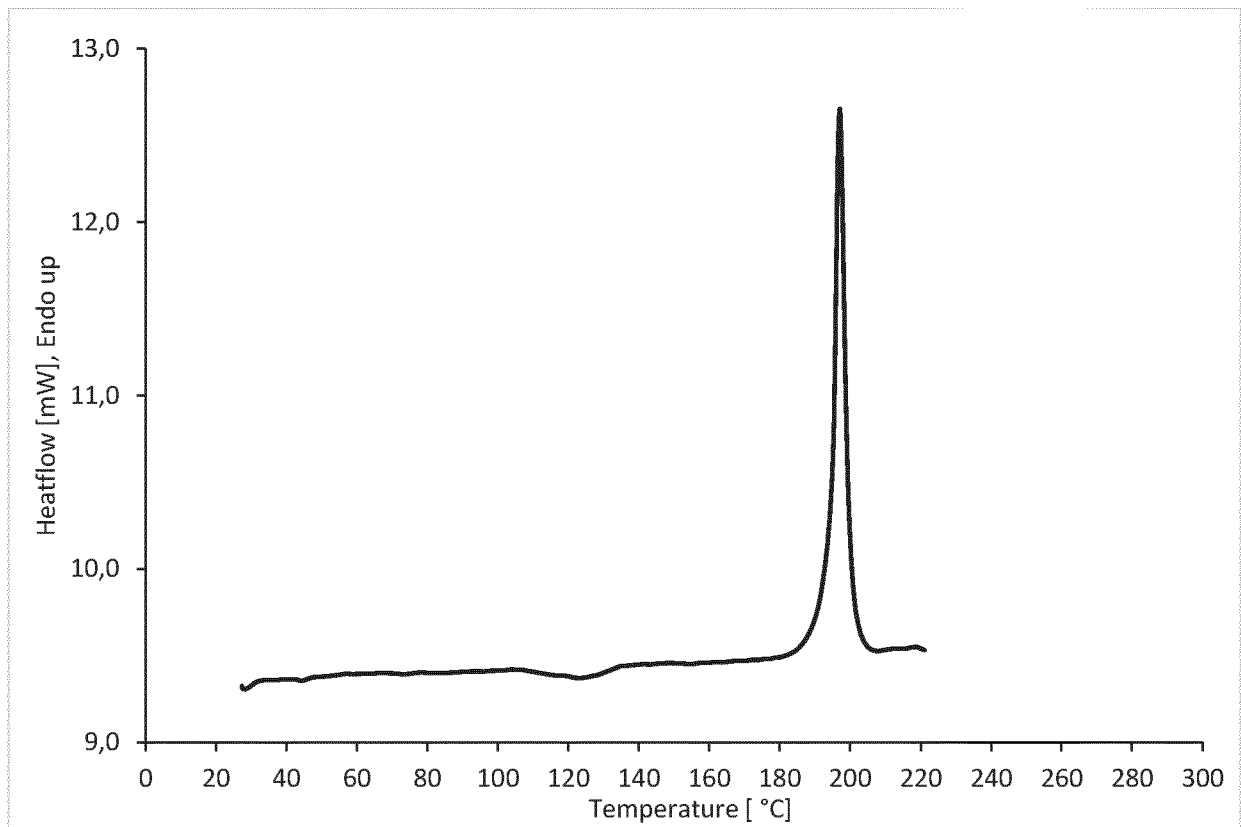


Figure 9

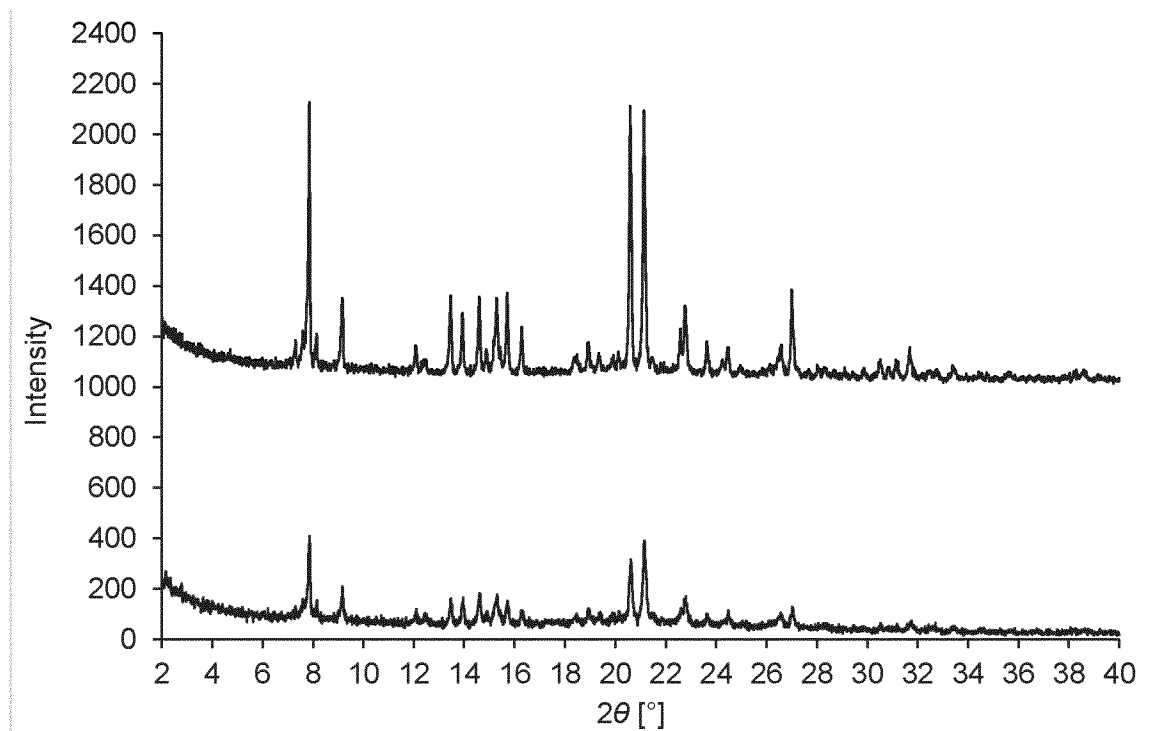


Figure 10

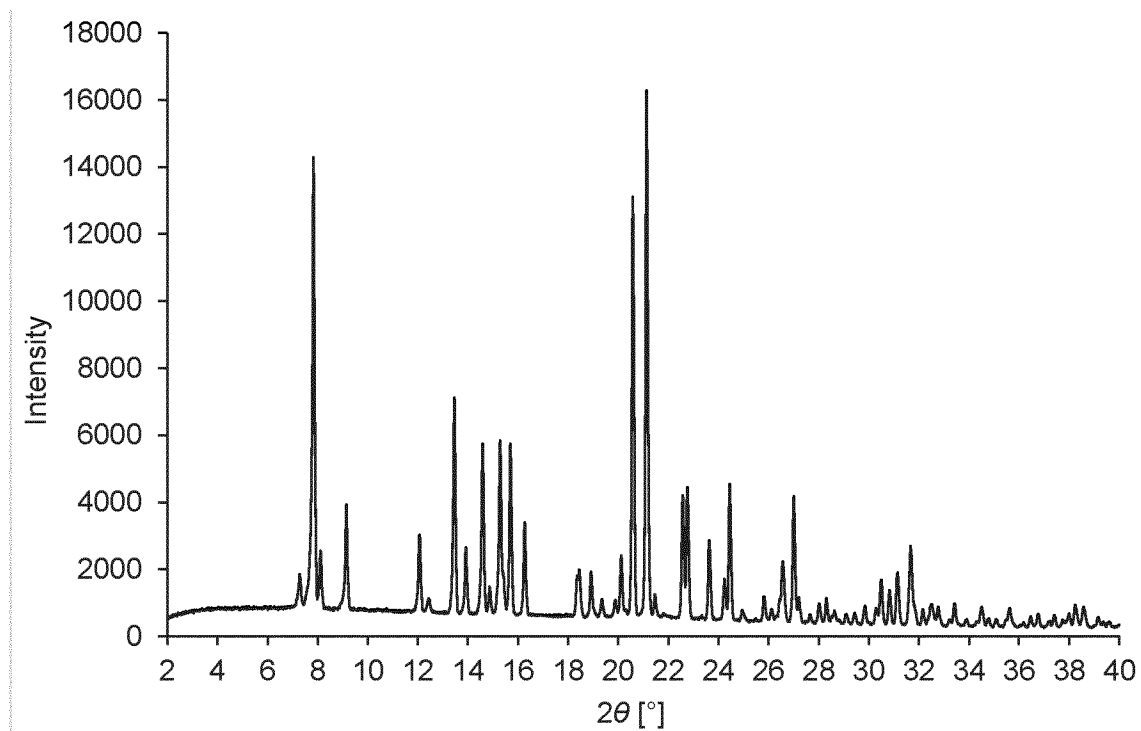


Figure 11

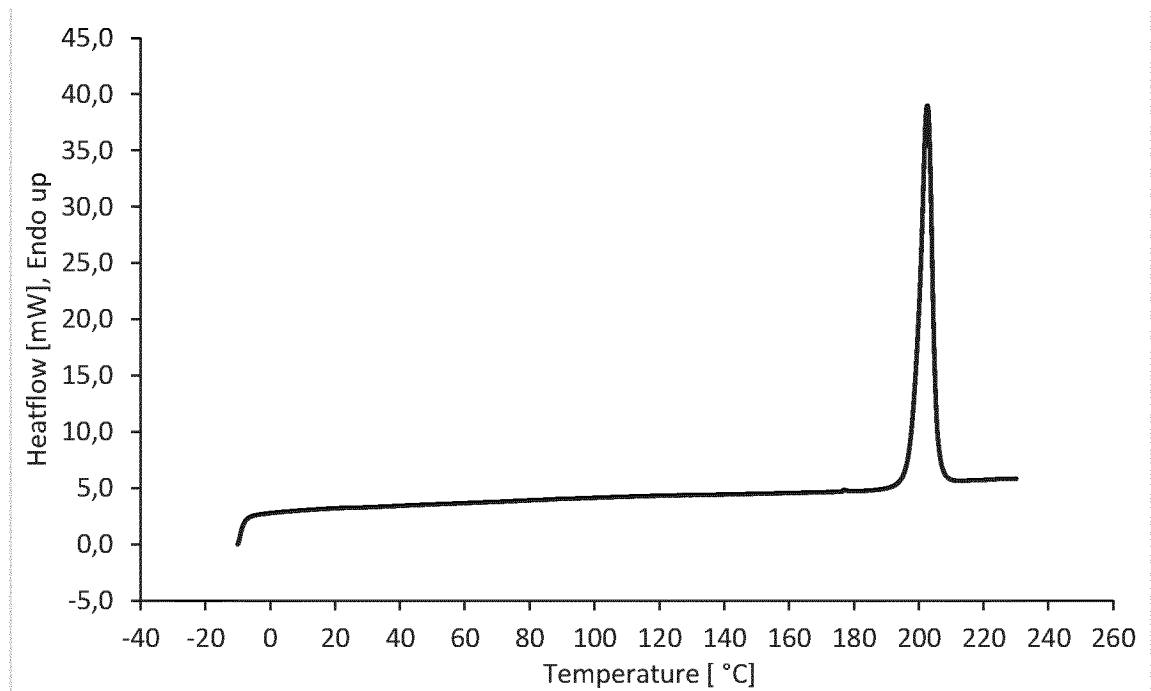


Figure 12

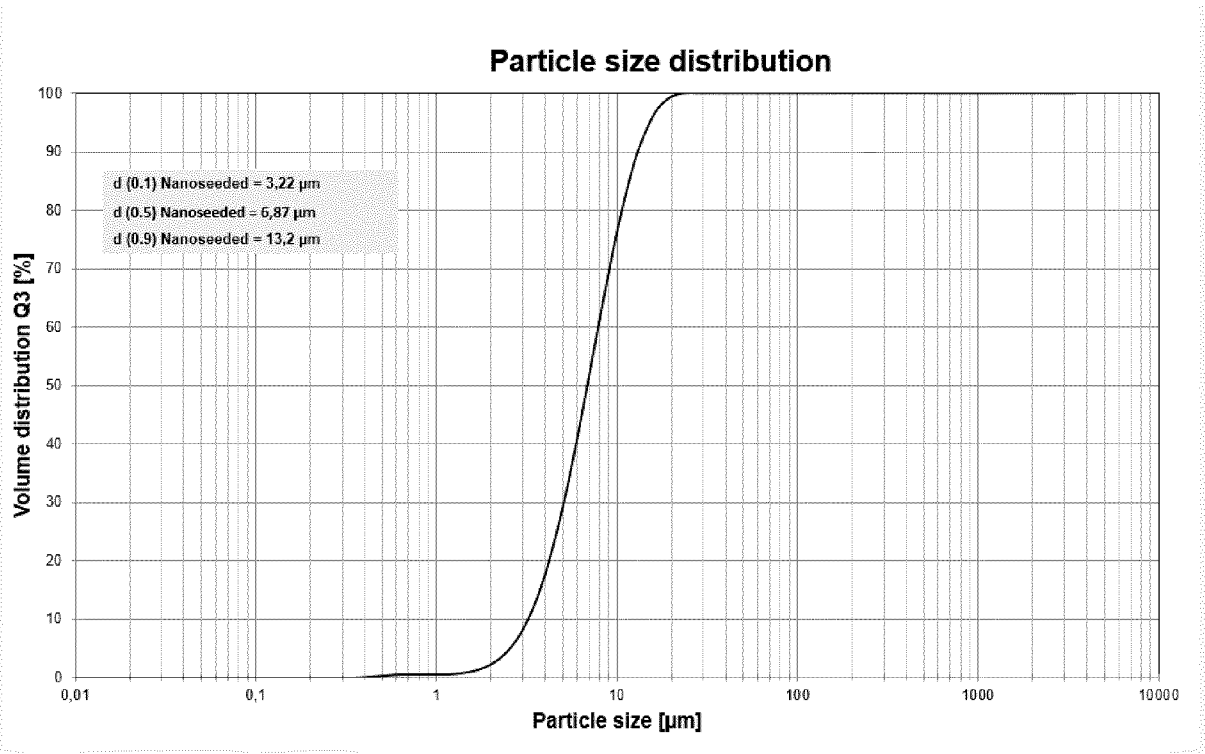


Figure 13

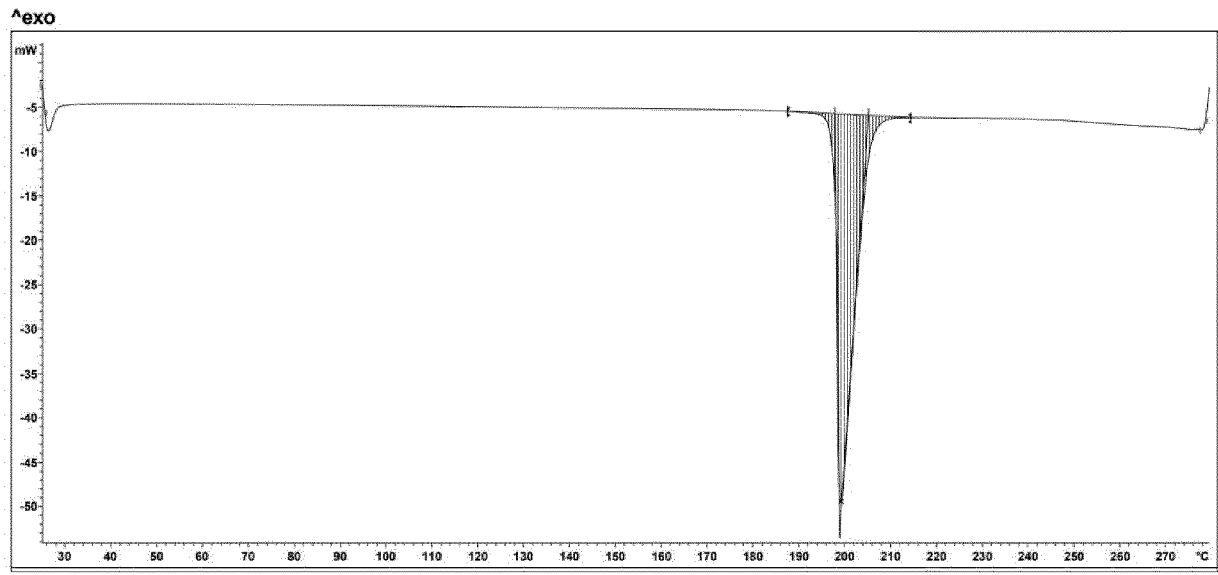


Figure 14

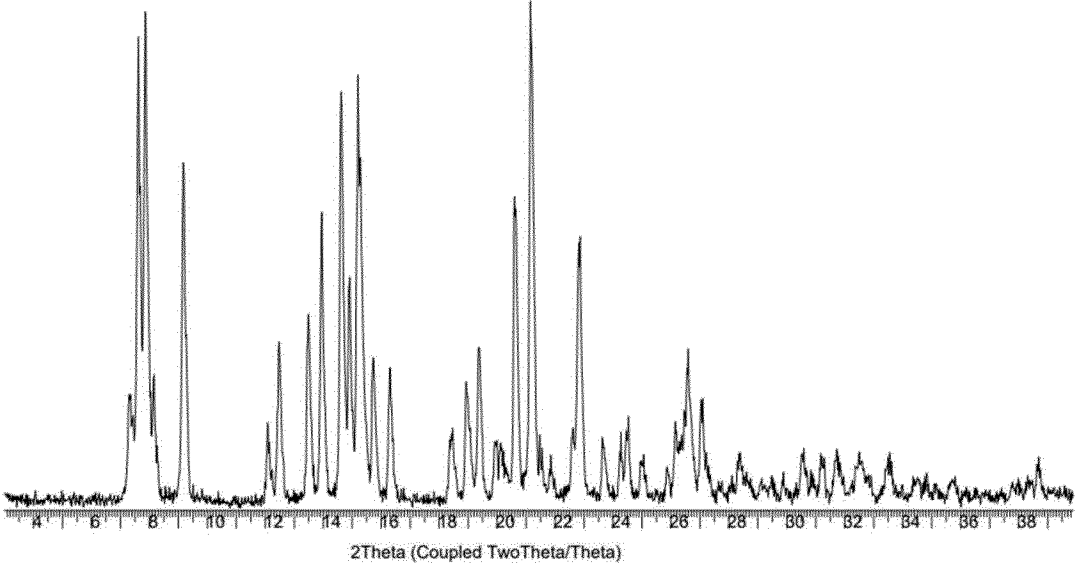


Figure 15

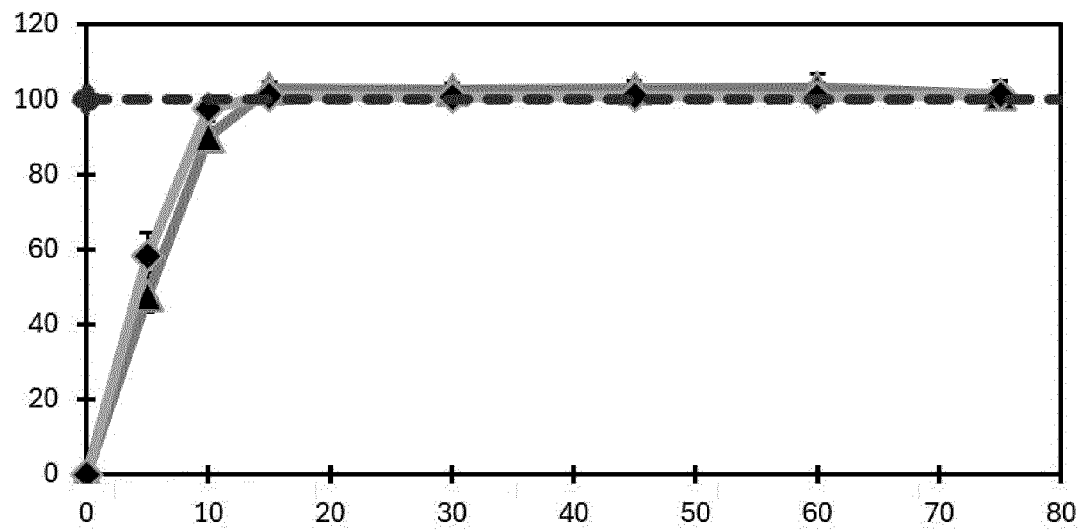


Fig. 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2024/058061

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

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

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

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

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

see additional sheet

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2024/058061

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D277/42 A61P35/00 A61K31/426 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) A61P 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 practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/214019 A1 (BAYER AG [DE] ; DEUTSCHES KREBSFORSCH [DE]) 28 October 2021 (2021-10-28) cited in the application page 354 - page 355; example 62.2 -----	1 - 26
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 August 2024		Date of mailing of the international search report 06/09/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2024/058061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 3180819 A1	28-10-2021
		CL 2022002919 A1	31-03-2023
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		CR 20220536 A	17-01-2023
		DO P2022000223 A	15-11-2022
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		PE 20230322 A1	22-02-2023
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		US 2023167103 A1	01-06-2023
		WO 2021214019 A1	28-10-2021
		WO 2021214020 A1	28-10-2021

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-23

Subject-matter relating to a microcrystalline form of the compound

2. claims: 24-26

Subject-matter not relating to a microcrystalline form of the compound
